THE EFFECTS OF PALATABLE INGESTA ON THE PERCEPTION OF THERMALLY- AND MECHANICALLY-INDUCED EXPERIMENTAL PAIN

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BY

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Abstract

Previous studies with animals and human infants have found that the ingestion of palatable sweet solutions produces a morphine-like analgesia (e.g., Blass, 1986; Blass & Hoffmeyer, 1991). This "sweet-induced analgesia" can be reversed by minimal doses of naltrexone, an opioid antagonist, suggesting that sweets operate through an endogenous opioid system (e.g., Blass, Fitzgerald, & Kehoe, 1987). This thesis investigated whether sweet-induced analgesia occurs in human adults. In the present experiments, subjects (330 university undergraduates) were exposed to cold water (Expt.1), pressure (Expts. 2a-2c), or contact heat (Expts. 3a-3b) and then assessed for pain sensitivity. Subjects then consumed either nothing (control group), or foods that they rated previously as unpalatable (e.g., black olives), neutral (e.g., rice cakes), or palatable (e.g., chocolate-chip cookies). Following a brief delay (approx. 5 min), subjects were exposed a second time to the cold water, pressure, or contact heat and again assessed for pain sensitivity. Pain sensitivity was assessed with four pain measures: pain threshold, pain tolerance, and visual analogue scale (VAS) ratings of pain intensity and unpleasantness. Tactile thresholds were also measured before and after treatment. Results showed that

sweet palatable foods appeared to produce significant increases in females' pain tolerance to contact heat and to pressure. However, pain thresholds, VAS measures, and tactile thresholds were not consistently affected by sweet intake. Gender differences in pain perception were also present; females reported lower pain thresholds and pain tolerances and rated the pain as more intense and more unpleasant than did males.

These data constitute the first demonstration that sweet-induced analgesia occurs in human adults. Sweet induced-analgesia is thought to operate through an endogenous opioid system whereby sweet consumption causes the release of opioids into the CNS, resulting in pain-inhibition. However, the present results also indicate that this sweet-induced analgesia is influenced by a number of factors, including the method of pain induction, the type of pain measure, and the gender of the subjects. Moreover, the palatability of the ingesta seems to be a critical factor in producing analgesia. Collectively, the present results suggest that a more accurate label for sweet-induced analgesia may be "palatability-induced analgesia".

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TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

TABLE OF CONTENTS (continued)

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES (continued)

FIGURE

LIST OF FIGURES (continued)

FIGURE

" My headaches become so severe sometimes that I find myself doing really weird things, such as banging my head against the wall, or going to the kitchen and eating spoonfuls of sugar. Somehow, this relieves the pain yet I have no idea why..."

Sandy Jefferson, 1992, chronic migraine sufferer.

CHAPTER 1: INTRODUCTION

OPIOIDS AND SWEET-INDUCED ANALGESIA

There has been an enormous expansion of interest in the study of pain and analgesia over the past 25 years. Researchers have been intrigued, not only with the physiology and anatomy of the vertebrate pain and analgesia systems, but also with the perception of pain and the factors which might influence it. Recent studies (e.g., Blass, Fitzgerald, & Kehoe, 1987; Holder, 1988; Miczek, Thompson, & Shuster, 1982; Teskey, Kavaliers, & Hirst, 1984) have demonstrated that certain environmental stimuli, such as stress or the consumption of palatable foods, can substantially alter a rat's responsivity to experimentally-induced pain. For example, following intraoral infusions of a sucrose solution, rats placed on a hot-plate increased the latencies at which they removed their paws (Blass, Fitzgerald, & Kehoe, 1987). Similarly, the ingestion of a sucrose solution reduced the crying of human infants undergoing painful hospital procedures (Blass & Hoffmeyer, 1991). This thesis is a first attempt to determine the modulatory effects of sweet intake on the perception of pain in human adults. In order to better understand the possible relationship between pain perception and sweet consumption in humans, it is important to review vertebrate pain

systems. The following sections will summarize the pharmacological and anatomical evidence for endogenous pain-modulatory systems in vertebrates, particularly the opioid analgesic system, as well as the behavioral evidence for the interaction between sweets, opioids, and analgesia.

1.1: The Intrinsic Pain-Modulatory Systems of Vertebrates

Although the definition and operationalization of pain has varied, there have been many intriguing developments in the area of pain and analgesia. One of the most exciting advancements was the discovery of an intrinsic pain-modulatory system in the central nervous system (CNS) of vertebrates. The first empirical support for an endogenous pain-modulatory system was the finding that electrical stimulation of specific brain areas could effectively suppress rats' perception of pain (Mayer, Wolfe, Akil, et al., 1971; Reynolds, 1969). The neural mechanisms involved in this phenomenon, labelled stimulation-produced analgesia (SPA), paralleled those of opiate analgesia (OA) and was therefore, thought to involve an endogenous opiate-like substance. This hypothesis was soon supported by the discovery that opioid receptors and endogenous opioid peptides (EOPs) were present in the central nervous system (CNS) of vertebrates (Hughes, 1975; Hughes, Smith, Kosterlitz, et al., 1975; Pert & Snyder, 1973). Further

studies of SPA and the mechanisms of OA revealed a number of similarities in the neural circuitry of SPA and OA. First, cells within the medial brainstem [specifically, the periaqueductal gray (PAG) and the periventricular gray (PVG)] are effective sites for both SPA and OA (Mayer and Price, 1976). Second, both types of pain modulation are mediated partly by fibers descending from the medial brainstem to the spinal cord dorsal horn (Basbaum, Marley, O'Keefe, & Clanton, 1977; Murfin, Bennett & Mayer, 1976). Third, the primary inhibition of the transmission of pain both by SPA and OA occurs in the neurons of the spinal dorsal horn (Bennett & Mayer, 1979). Finally, SPA appears to depend on endogenous opioid peptides (EOPs) in that a) SPA can be reversed or blocked by the specific opiate antagonist, naloxone (Akil, Mayer, & Liebeskind, 1976); b) tolerance can develop to the analgesia produced by either opiates or stimulation (Mayer & Hayes, 1975); c) SPA and OA show cross-tolerance (Mayer & Hayes, 1975); and d) only subanalgesic doses of morphine are required for pain inhibition when combined with subanalgesic levels of brain stimulation (Samanin & Valzelli, 1971, cited in Mayer & Watkins, 1984).

Although vertebrates possess a central endogenous opioid system (EOS) whose major function is to modulate pain, not all intrinsic mechanisms of pain suppression rely

on these opioid neural pathways. There is also evidence for an opioid-hormonal system (see Mayer & Watkins, 1984) as well as nonopioid pain-modulatory systems (see Cannon, Prieto, Lee, & Liebeskind, 1982). A major way in which the opioid and nonopioid systems are distinguished is in their responses to opiates and opioid antagonists. Opioid-modulated analgesia is reversible by opioid antagonists (e.g., naloxone), develops tolerance, and shows cross-tolerance with morphine analgesia. Nonopioid-modulated analgesia is naloxone-insensitive, does not develop tolerance, and shows no cross-tolerance with morphine analgesia. Therefore, there are probably multiple endogenous pain-modulatory systems within the vertebrate CNS whose primary function is to reduce pain by modulating transmission in pain pathways and/or by modifying the emotional reaction to the pain. Mayer and Watkins (1984) propose that there are as many as four systems of analgesia, two of which are nonopioid (neural-nonopioid and hormonal-nonopioid) and probably mediated by serotonergic and/or noradrenergic pathways, and two more which are mediated by endogenous opioid peptides (neural-opioid and hormonal-opioid). This thesis will focus mainly on the neural pathways and mechanisms underlying only the neural-opioid system because this system is involved in the interaction between sweet intake and analgesia (Blass et al., 1987; Dum,

Gramsch, & Herz, 1983; Kehoe & Blass, 1986).

1.2: A General Overview of the Endogenous Opioid System

Opioid-mediated analgesia involves direct action on the CNS. Like stimulation-produced analgesia, opioid analgesia is produced by opioids acting directly on the spinal cord or on the descending inhibitory systems which originate in the brainstem and terminate on nociceptive neurons in the spinal cord. The opioid-mediated descending pathway is located within the dorsolateral funiculus (DLF) and has three major components: the periaqueductal gray (PAG) of the midbrain, the rostroventral medulla (RVM), and the superficial laminae of the dorsal horn. The PAG receives afferents from the frontal cortex and the hypothalamus which are thought to play a critical role in activating these descending analgesia systems. Neurons in the periaqueductal (PAG) and periventricular (PVG) gray matter make excitatory connections in the rostroventral medulla (RVM), a region that includes the serotonergic nucleus raphe magnus (NRM) and the adjacent nucleus reticularis paragigantocellularis (NRP). Stimulation of these RVM neurons activates a descending projection through the DLF to the dorsal horn of the spinal cord. There it makes inhibitory connections with the neurons of laminae I, II, and V, including the spinothalamic tract neurons which respond to noxious

stimulation. These dorsal horn laminae are also the site of termination of nociceptive afferent neurons. Local circuits within the dorsal horn mediate the modulatory role of the descending pathways. The descending projections modulate pain either directly by inhibiting dorsal horn neurons or indirectly by stimulating the release of opioids from enkephalin-containing interneurons (ENK) in the superficial layers of the dorsal horn, which in turn inhibit the dorsal horn neurons. In addition, the ENK exert both presynaptic and postsynaptic inhibitory actions at primary afferent synapses (for reviews, see Fields & Basbaum, 1989; Jessell & Kelly, 1991; Schneider & Tarshis, 1986).

Endogenous opioid peptides (EOPs) are naturally-produced, morphine-like peptides which are thought to function as neurotransmitters or neuromodulators (Kosterlitz & Hughes, 1975). There are three major classes of EOPs, namely the enkephalins, the beta-endorphin-related peptides, and the dynorphin-related peptides (Cox, 1982). Each type is derived from one of three genes: the proenkephalin, pro-opiomelanocortin (POMC), and prodynorphin genes (e.g., Khachaturian, Lewis, Schafer, & Watson, 1985). These three classes of EOPs are thought to exist in two different pools, one in the peripheral blood which is synthesized by the pituitary, and a second in the central nervous system (CNS) which is synthesized directly by peptidergic neurons in the

brain (Fraioli, Moretti, Paolucci, Alicicco et al., 1980).

Members of each class are located at sites both within and outside the CNS which are associated with the modulation of nociception (Jessell & Kelly, 1991). Enkephalin- and dynorphin-containing neuronal cell bodies and nerve terminals are found in the periaqueductal gray, the rostroventral medulla, the hypothalamus, and the dorsal horn of the spinal cord, particularly in laminae I and II. In contrast, the endorphinergic cells are located primarily in the pituitary and project to the hypothalamus and dorsal midbrain. In turn, hypothalamic neurons project to the thalamus, to the periaqueductal gray matter in the midbrain, and to the noradrenergic nuclei in the brainstem (Herz & Millan, 1988; Jessell & Kelly, 1991) .

Beta-endorphins are produced in the anterior pituitary, in the hypothalamus (particularly the arcuate nucleus), and in the nucleus tractus solitarius of the medulla (Akil, Watson, Young et al., 1984; Bronstein, Schafer, Watson, & Akil, 1992; Guillemin, Vargo, & Rossier, 1977). They are also present in the thalamus, the midbrain, the amgydala, the sympathetic nervous system, the cerebrospinal fluid, the male reproductive tract, the placenta, and the gastro-intestinal tract. The location of the enkephalins is much more diffuse, with the highest concentrations in the adrenal medulla, the gastrointestinal tract, the brain and the

spinal cord. Areas of particularly high levels of met-enkephalin include the posterior hypothalamus, amygdala, globus pallidus, striatum (caudate putamen), nucleus accumbens, and olfactory tubercle. Low levels of met-enkephalin circulate in the plasma and may be secreted by the adrenal gland. The dynorphins are found in the posterior pituitary, hypothalamus, hippocampus, midbrain, brainstem, and spinal cord (Herz, Holz, & Gramsch, 1982; Herz & Millan, 1988).

Extensive biochemical, pharmacological, and behavioral evidence from rats indicates that the actions of these three classes of EOPs are mediated by at least four opioid receptor classes: mu, delta, epsilon, and kappa (for reviews, see Goldstein, 1988; Snyder, 1984; Zukin & Zukin, 1981). The sigma receptor is no longer considered an opioid receptor (opioceptor) type because it is not blocked by naloxone (Goldstein, 1988; Zukin & Zukin, 1984). The different types of EOPs have varying selectivities for one or more of these opioid receptor types (for a review, see Akil et al., 1984). Beta-endorphin binds chiefly to the epsilon receptor but can also bind strongly with the mu and delta receptors, and possibly with the kappa receptors. Met-enkephalin and particularly leu-enkephalin bind primarily to the delta receptors, secondly to the mu receptors, and have only a small affinity for the kappa

receptors. Dynorphin appears to bind exclusively with the kappa receptors.

Consistent with the fact that the EOPs are widely distributed throughout the CNS and the periphery, opioid receptors are also located both within and outside the CNS (Chang, Cooper, Hazum, & Cuatrecases, 1979; Lutz & Pfister, 1992; Tempel & Zukin, 1987). Mu receptors are widely distributed throughout the brain with the highest densities in the neocortex, caudate-putamen, nucleus accumbens, thalamus, hippocampus, amygdala, inferior and superior colliculi, nucleus tractus solitarius, and spinal cord. A moderate density of mu receptors are located in the periaqueductal gray, and raphe nuclei (Mansour, Khachaturian, Lewis, Akil, & Watson, 1988; Tempel & Zukin, 1987). Delta receptors are less widely distributed and of highest density in forebrain structures such as the neocortex, striatum, amygdala, and the olfactory areas (Mansour et al., 1988; Yaksh, 1984). Kappa (and sigma) receptors are localized mainly in the preoptic area, caudate-putamen, nucleus accumbens, and posterior pituitary (Goodman & Snyder, 1982; Mansour et al., 1988; Tempel, Gardner, & Zukin, 1985; Yaksh, 1984). Kappa receptors also have high densities within feeding sites such as the nucleus tractus solitarius, the thalamus and hypothalamus, the amygdala, the median eminence, the stria terminalis, and the

olfactory tubercle (Lynch, Watt, Krall, & Paden, 1985; Mansour et al., 1988). Epsilon receptors have been isolated only in the rat vas deferens (Shulz, Wuster, & Herz, 1981; Garzon, Schulz, & Herz, 1985, cited in Goldstein, 1988). It is still unclear as to whether they exist in the CNS (Ronai, 1983).

1.3: The Association Between EOPs and Both the Reward and Pain-Modulatory Systems

EOPs were once thought to serve only a pain-modulatory role. However, more recent observations suggest that there is a relationship between central opioid mechanisms and both the pain-modulatory and reward systems (Le Magnen, Marfaing-Jallat, Miceli, & Devos, 1980). Firstly, opiates (e.g., morphine, heroin), which are the most powerful drugs for the relief of pain (analgesia), are known to have strong abuse potential[1] (reward) (Franklin, 1989; Jaffe, 1990; Melzack, 1990). Secondly, there are at least two sites at which opioids induce a rewarding effect: the ventral tegmental area (VTA) and the nucleus accumbens (ACC; Bozarth & Wise, 1981; Mucha & Iversen, 1986; Olds, 1982). Moreover, the lateral hypothalamus (LH), the periaqueductal gray (PAG), and even the hippocampus may contain opioid reward sites as well (Franklin, 1989; Wise, 1989). Thirdly, stimulation of "rewarding" brain areas (e.g., PAG) produces analgesia

(Dubuisson & Dennis, 1977; Rose, 1974; Reynolds, 1969; Wise, 1987). Thus, there appears to be considerable overlap in the neural mechanisms involved in the systems of reward and analgesia. Le Magnen et al. (1980) hypothesize that the reward and pain-modulatory systems share a common single brain mechanism involving the EOPs. They also suggest that these brain rewarding systems, in which opio-peptidergic neurons seem to be involved, may underlie the naturally rewarding aspect of certain sensory stimuli, such as the pleasure obtained from ingesting palatable foods. In fact, recent evidence suggests that the rewarding effects of consuming palatable foods may depend critically on the activation of EOSs (Cooper, 1983; Siviy & Reid, 1983).

1.4: Evidence For a Link Between EOPs and Sweet Ingestion

In addition to the correlational and anatomical evidence for an interaction between reward and analgesia systems, behavioral and biochemical studies show that activation of the endogenous opioid system (EOS) produces changes in the pleasure obtained from sensory stimuli as well as changes in the perception of noxious stimuli. In particular, there is strong evidence that the EOS modulates both analgesia and food ingestion. Increased opioid activity has been shown to affect pain responsivity and consummatory behavior, especially the ingestion of

palatable sweet foods (for reviews, see Levine & Billington, 1989; Levine, Morley, Gosnell et al., 1985; Morley, 1980; Morley & Levine, 1982; Morley, Levine, Yim, & Lowy, 1983; Reid, 1985). For example, following the administration of morphine, an opioid agonist, rats consume greater amounts of sweet substances (Cooper & Turkish, 1989; Le Magnen et al., 1980; Lynch & Libby, 1983; Lynch, 1986; Rockwood & Reid, 1982). This increase in sweet consumption is best explained by an increased preference for sweets following the morphine injection[2] (Lynch & Libby, 1983). Conversely, rats who are administered an opioid antagonist, such as naloxone, reduce their preference and intake of palatable sweet substances (Le Magnen et al., 1980; Levine, Murray, Kneip et al, 1982; Lynch, 1986; Rockwood & Reid, 1982). Similarly, with humans, naltrexone, another opioid antagonist, has been shown to reduce the intake (Fullerton, Swift, Getto, & Carlson, 1986; Marks-Kaufman, 1982), the hedonic ratings (Fantino, Hosotte, & Apfelbaum, 1986) and the perceived pleasantness (Lynch, 1986) of sweets. Moreover, following prolonged morphine treatment, morphine-dependent rats reduce their consumption of preferred saccharin solutions, up to five days following the last injection (Lieblich, Yirmiya, & Liebeskind, 1991; Yirmiya, Lieblich, Lewis, & Liebeskind, 1986). The authors suggest that prolonged morphine reduces sweet intake because cross-tolerance develops between the

morphine and the opioid-mediated hedonic effects of sweets (Lieblich et al., 1991; Yirmiya et al., 1986). However, this explanation is unlikely given that under most circumstances, tolerance to opiate's rewarding effects appears to be minimal (e.g., Bechara & Van der Kooy, 1992; Di Chiara & North, 1992; Esposito & Kornetsky, 1977). Alternatively, these findings may be explained by the fact that chronic morphine produces an up-regulation of opioid receptors (Holaday, Hitzemann, Curell et al., 1982). Conversely, withdrawl from chronic morphine produces a down-regulation of opioid receptors (Snell, Moses, & Hughes, 1984). This may explain why incarcerated heroin addicts report increased preferences and cravings for sweet foods during heroin withdrawl (Weiss, 1988).

In summary, the EOS appears to mediate both pain modulation and reward. Increased opioid activity produces both analgesia and increased sweet consumption. Moreover, sweet intake increases opioid activity. The first biochemical evidence that sweet consumption modulates opioid activity was the finding that consumption of either candy or chocolate milk by non-deprived rats caused an immediate release of beta-endorphin from the lateral hypothalamus (Dum et al., 1983). It was later demonstrated that the intake of glucose, sucrose, and aspartame by humans elevated plasma beta-endorphin concentrations (Getto, Fullerton, & Carlson,

1984; Getto, Swift, Carlson, & Fullerton, 1986; Melchior, Rigaud, Colas-Linhart et al., 1991). Therefore, the relationship between sweet intake and opioid activity appears to be bidirectional; opioid activity modulates sweet intake, and sweet intake modulates opioid activity.

1.5: Evidence For a Link Between Sweet Intake and Analgesia

Given the evidence that sweet intake modulates opioid activity, it is not surprising that behavioral studies have demonstrated that sweet consumption also modulates opioid-mediated analgesia. For example, compared to rats given water, rats chronically exposed to sweet solutions showed attenuation to the analgesic effects of morphine (e.g., Gogas, Kirtland, & Cannon, 1985). More specifically, when placed on a hot-plate, rats exposed to sweets and morphine showed decreased paw-lift latencies compared to rats exposed to water and morphine (Bergmann, Lieblich, Cohen, & Ganchrow, 1985; Cohen, Lieblich, & Bergmann, 1984; Holder, 1988; Lieblich, Cohen, Ganchrow et al., 1983). Moreover, the magnitude of the attenuation increased as the exposure to the sweet solution was increased (to the point that the analgesic properties of morphine were almost eliminated). Holder & Belger (1988) compared the effects of chronic versus acute sweet ingestion on analgesia to a hot-plate and found that chronic exposure to a sweet (dextrose/saccharin)

solution lowered rats paw-lift latencies whereas acute (shorter duration) sweet exposure was shown to produce morphine-like analgesia in rat pups by increasing their paw-lift latencies. The authors suggested that acute exposure to sweets may release EOPs and/or increase the binding affinity of the EOPs to the opioid receptors whereas chronic exposure may result in a down-regulation of the opioid receptors in response to the initial sweet-stimulated elevation of EOP levels. Short-duration intraoral infusions of a sucrose solution also produced analgesia in rat pups, as indicated by increased paw-lift latencies and a marked (approx. 50%) reduction in distress vocalization induced by isolation (Blass et al., 1987). These effects of sucrose on analgesia were reversed by minimal doses of naltrexone, suggesting that sucrose operates through an opioid system[3] (Blass et al., 1987; Kehoe & Blass, 1986). Furthermore, "high-affect" rats bred to drink more sweet solutions have higher pain thresholds than either "low-affect" rats or "high-affect" rats bred on water (Lieblich et al., 1983). This effect also was found to be naloxone-reversible. Therefore, sweets, like opiates, ease social distress and decrease pain responsivity in rats (Blass et al., 1987; Kehoe & Blass, 1986).

Recently, Blass and his colleagues demonstrated an interaction between sweet intake and analgesia with human

infants (e.g., Blass, Fillion, Rochat et al., 1989). As little as 0.2 ml of sucrose immediately stopped crying in 1- to 3-day-old newborns, and this quieting persisted well after the termination of sucrose delivery (Smith, Fillion, & Blass, 1990). Furthermore, Blass & Hoffmeyer (1991) demonstrated that the sweet taste of sucrose can serve as a potent antinociceptive during standard painful hospital procedures. They reported that 2 ml of a 12% sucrose solution markedly reduced crying in normal and preterm infants during both circumcision and blood collection from the heel. This sweet-modulated analgesia is produced by the pleasant taste of the sweets rather than by the chemical composition of the sweets or by any post-ingestive factors (Smith et al., 1990).

1.6: The Present Experiments

In summary, recent evidence suggests that the consumption of palatable sweet foods increases opioid activity resulting in analgesia. The opioids which are released by sweet palatable tastes become available to those systems involved in coping with pain and distress (Blass et al., 1987). This sweet intake-analgesia relationship has been demonstrated in human infants (e.g., Blass & Hoffmeyer, 1991; Blass, Jackson, & Smotherman, 1991) and in rats (e.g., Blass et al., 1987; Holder & Bolger, 1988). However, a

relationship between sweet intake and analgesia has yet to be demonstrated with human adults. This thesis attempts to determine whether sweet consumption suppresses the perception of experimental pain experienced by human adults as it does in animals and human infants. If a sweet-analgesia relationship does hold for human adults, this finding could have value in the clinical treatment of pain. If palatable sweet foods can be used to activate our EOS, then it may be possible to reduce the dosage of opiates required to relieve certain types of acute pain, thereby reducing the adverse side effects (e.g., constipation, nausea, vomiting, tachycardia) that normally accompany the use of high dosages of opiates.

Furthermore, the present research should prove to be useful scientifically as well as clinically. First, the results of this thesis should help us to better understand the role of our EOS in both pain-modulation and reward, specifically the pleasure obtained from consuming palatable foods. Moreover, if there is a relationship between sweet intake and analgesia, this will indicate that it is the opioid pathways (rather than the nonopioid pain-modulatory pathways) that are mediating this interaction. Previous studies (e.g., Bergmann et al., 1985; Holder, 1988) have shown that sweet-induced analgesia is naloxone-reversible and shows cross-tolerance to morphine. Secondly, the use of

human adults as subjects should allow us to determine exactly which aspect(s) of pain, if any, is(are) modulated by sweet intake. A problem with previous studies that have used either animals or human infants is that their procedures rely on behavioral data that provide only "yes-no" type answers. In other words, previous research has ascertained only whether or not sweet-induced analgesia occurs, but it has not determined exactly which aspect of pain is affected. For example, the dependent measures used with rats (e.g., paw-lift latency on a hot-plate) and with human infants (e.g., the cessation of crying during a painful hospital procedure) are somewhat limited. The only conclusion that can be made from these rat or infant studies is that sweet intake appears to reduce pain. However, the perception of pain induced by a noxious stimulus is a multidimensional experience that involves sensory processes (e.g., intensity, duration) as well as an affective response (unpleasantness) (Melzack, 1973).

The importance of the sensory-affective distinction is underscored in studies with human adults that have evaluated different pain treatments. For example, opiates and tranquilizers appear to modulate only the affective dimension of pain and to have little effect on the sensory dimension (e.g., Price, Harkins, Rafii, & Price, 1986). Results of studies that have used visual analogue scales

(VAS, see Appendix D) indicate that intensity and unpleasantness are independent measures of experimentally-induced pain (Price, McGrath, Rafii, & Buckingham, 1983; Price, Von der Gruen, Miller, Rafii & Price, 1985). For example, lower doses of morphine significantly reduced affective (unpleasantness) but not sensory intensive VAS responses (Price et al., 1985). Similarly, diet (e.g., sweets), like analgesics and other pain treatments, may affect one component of pain but not another. In order to determine which aspect(s) of pain is(are) modulated by sweet intake, it is necessary to study the sweet-analgesia relationship in human adults because they can communicate verbally. Thus, the present experiments with human adults used VASs to evaluate separately the effects of sweets on both the intensity and unpleasantness of pain.

In addition to VAS pain measures, both pain threshold and pain tolerance were measured in the present thesis. Pain threshold is defined as the point at which a person first perceives a noxious stimulus to be painful whereas pain tolerance is defined as the point at which a person perceives the noxious stimulus as being too painful to allow the experimenter to continue its delivery (Kitchell & Erickson, 1983). Harris and Rollman (1983) argue that threshold and tolerance judgements are not the same and therefore both should be obtained in studies evaluating

experimental pain. They state that threshold judgements emphasize discrimination of nociceptive quality and tolerance judgements emphasize an unwillingness to receive more intense stimuli.

In addition to using multiple pain measures, this thesis also employed multiple pain induction techniques. Numerous studies (e.g., Greenspan, Vierck, & Ritz, 1986; Landis, Robinson, Helms, & Levine, 1989; Oliveras, Maixner, Dubner et al., 1986; Rainville, Feine, Bushnell, & Duncan, 1993) assessing the efficacy of various analgesic manipulations in both animals and humans have found that experimental manipulations have different analgesic effects depending on the method of pain induction (e.g., electric shock, muscle ischemia, cold water immersion, contact heat). This may also hold true for the analgesic effects of sweets; sweets may modulate experimental pain induced in one way but not in another. Therefore, to evaluate more comprehensively the effects of sweets on the multiple dimensions of pain perception (i.e., on threshold, tolerance, intensity and unpleasantness), the present research utilized three different types of noxious stimuli: cold-water immersion and contact heat (both thermal stimuli), and pressure (a mechanical stimulus). All three types of stimuli have been used previously with animals and humans (e.g., Bodnar, Kelly, & Glusman, 1979; Duncan, Bushnell, & Lavigne, 1989;

Hapidou & De Catanzaro, 1988; Rainville et al., 1993; Whipple & Komisaruk, 1988). Moreover, contact heat was the method of pain induction used in studies demonstrating sweet-induced analgesia in rats (e.g., Blass et al., 1987; Holder, 1988).

The present research uses multiple sensory modalities and multiple measures of experimental pain for two purposes. First, it should lead to a clearer understanding of the multiple endogenous pain-modulatory systems present in vertebrates. For instance, if the results of this thesis show that one type of pain (e.g., contact heat) is modulated by sweet intake but another type (e.g., cold-water pressor) is not, this may suggest that the pain induced by contact heat activates an opioid-neural pathway whereas the pain induced by cold-water pressor activates either a nonopioid pathway or an opioid-hormonal pathway. Secondly, this research should provide insight into the different facets of pain experiences. In this regard, the following experiments should help determine: 1) whether pain induced by cold water is perceived differently than pain induced by contact heat or by pressure; and 2) whether humans differentiate between the sensory (intensity) and affective (unpleasantness) components of pain similarly for different modalities. For example, for one type of pain (e.g., contact heat), subjects may rate the pain as more unpleasant than intense whereas

for another type of pain (e.g., pressure), the reverse may hold true. Moreover, the use of multiple pain measures will help determine which, if any, of the measures are modulated by sweet intake.

In summary, the goals of this thesis are: 1) to determine which aspects of human pain, if any, are modulated by sweet ingestion, 2) to compare the effects of sweet intake on pain in human adults (present results) with those found previously with human infants and other animals, and 3) to better understand our intrinsic pain-inhibitory systems and the environmental stimuli which activate these systems. In addition to scientific importance, improved knowledge of human pain-modulatory systems has the potential to provide new and more effective approaches to the therapeutic treatment of pain.

CHAPTER 2: GENERAL METHODOLOGY AND EXPERIMENT 1

This chapter describes the general methods shared by all of the experiments, and provides the rationale for choosing the various procedures. Each experiment in the thesis includes a detailed methods section.

2.1: Subjects

The subjects were 330 right-handed, non-smoking, undergraduate university students who reported that they were currently free of any physical pain. To recruit subjects, signs were posted on campus bulletin boards. Each sign stated, "Subjects (right-handed, non-smokers only) needed for a psychology experiment. Pay is $4.75/hour. The study will evaluate subjective discomfort in response to pressure, heat, or cold water, followed by a personal questionnaire (anonymous). Please sign up at the Psychology office." Subjects were then contacted by phone and given the following instructions. First, they were told to abstain from alcohol and analgesics during the test day (usually the following day). Moreover, subjects were told to abstain from eating or drinking anything for at least 1 hour (Experiments 1, 2a, and 2b) or 2 hours (Experiments 2c, 3a, and 3b) prior to the experimental session. This duration for food deprivation was used so that subjects did not consume sweets or any other palatable foods prior to

baseline testing. Longer deprivation periods were not used in an attempt to avoid deprivation-induced analgesia (see Gambert, Garthwaite, Pontzer, & Hagen, 1980; Majeed, Lason, Przewlocka, & Przewlocki, 1986; McGivern, Berka, Berntson, Walker, & Sandman, 1979; Przewlocki, Lason, Konecka, Gramsch, Herz & Reid, 1983; Reid, Konecka, Przewlocki, Millan, & Herz, 1982; Vaswani & Tejwani, 1986). Smokers were excluded from the studies because smoking is known to reduce pain sensitivity (Pomerlau, Turk, and Fertig, 1984). Because left limbs show greater pain sensitivity than right limbs regardless of hand preference (Murray & Hagan, 1973), and because the subject's preferred hand needed to be free to mark the visual analogue scales (VASs), only right-handed subjects were chosen.

2.2: General Procedure

Subjects came individually to the laboratory. In Expts. 1 and 2a, subjects were pre-assigned to one of three groups, either a group in which they consumed sweets (the experimental group), water (control group-1), or nothing (control group-2). In Expts. 2b, 2c, 3a and 3b, subjects were pre-assigned to one of four groups in which they consumed either a sweet palatable food, a neutral food, or an unpalatable food (3 experimental groups), or nothing (a control group). After a brief introduction, each subject

was instructed to place either his left hand and forearm in ice water (Expt. 1), his/her left fingers in a pressure algometer (Expts. 2a, 2b and 2c), or his/her left forearm on a hot-plate (Expts. 3a and 3b). [See Appendices A, B & C for detailed subject instructions.] Hands were used instead of feet because previous work with rats has shown that discomfort to fore limbs, but not hind limbs, is opioid-modulated (Watkins & Mayer, 1982).

Cold water, contact heat, and pressure were chosen as methods of inducing pain because previous studies with humans have shown that these methods are sensitive to various treatments, such as stress, naloxone, or pleasurable stimulation (Jungkunz, Engel, King, & Kuss, 1983; Price et al, 1985; Whipple & Komisaruk, 1985).

The experimental protocol was approved by Memorial University of Newfoundland's Faculty of Science Ethics Committee.

2.3: Measures

In each experiment, three classes of measures were used to determine the effects of food intake on pain perception and touch sensitivity. First, each subject's pain responsivity was assessed using two latency measures, pain threshold and pain tolerance. During this procedure, each subject was asked to inform the experimenter when s/he first

feels pain (threshold), and then to remove her/his forearm/finger when the pain became too uncomfortable to be continued (tolerance). If the subject failed to withdraw his/her arm from the pain apparatus upon reaching a previously determined duration (5 minutes for cold water, 30 seconds for pressure, or after the hot-plate reached 48°C], the experimenter instructed the subject to remove her/his arm to ensure against tissue damage.

Second, each subject's perception of pain was assessed with two visual analogue scales (VASs): an intensity VAS and an unpleasantness VAS. Each scale was a 10 cm linear, vertical line consisting of twenty 0.5 cm divisions (see Appendix D), thus yielding scores ranging from 0 to 20. The endpoints of the subjective intensity scale were labelled, "No sensation" and "Most intense that one can imagine". The endpoints of the subjective unpleasantness scale were labelled, "Not bad at all" and "Most unpleasant that one can imagine". At the beginning of each laboratory session, the experimenter described the conceptual distinction between the intensity and unpleasantness of pain using the instructions and auditory analogy described by Price et al. (1983). Then, at specific points during the session, each subject was instructed to use the VASs to rate both the subjective intensity and unpleasantness of either the cold water, contact heat, or

pressure. These four pain measures (pain threshold, pain tolerance, subjective intensity and unpleasantness) were chosen because they are standard measures known to be sensitive to different aspects of human pain systems (see Duncan et al., 1989).

Third, following the measurement of a subject's pain perception, his/her tactile sensitivity was measured using a graded series of calibrated nylon monofilaments (von Frey fibers). These fibers were applied to the area between the thumb and index finger on the dorsal side of the right hand and tactile thresholds were measured. Tactile thresholds, defined as the minimal force required for the subject to detect a fiber on three consecutive trials, were measured for control purposes. Tactile sensitivity was assessed because it is important to distinguish whether the experimental manipulation modulates the pain system exclusively or other systems as well (see Whipple & Komisaruk, 1988).

After testing was complete, all subjects completed a brief questionnaire (see Appendix E) intended to provide information about each subject's experience with factors which have been shown to modulate pain responsivity (e.g., smoking, menstruation, recent alcohol consumption, medication, exercise) [see Hapidou & De Catanzaro, 1988; Pomerlau et al., 1984].

2.4: Design

In all of the present experiments, a within-subjects design was used. In some of the experiments (Expts. 2c, 3a, & 3b), pain and touch sensitivity were measured three times (familiarization, pre-treatment, and post-treatment trials) while in others (Expts. 1, 2a, & 2b), pain and touch sensitivity were measured only twice (pre-treatment and post-treatment trials). During the familiarization and pre-treatment trials, subjects were exposed to cold water (Expt.1), pressure (Expts. 2a-2c), or contact heat (Expts. 3a-3b), and this was followed by testing with the monofilaments. Subjects then consumed either a liquid, a food, or nothing. In the post-treatment phase, subjects were again exposed to cold water, pressure, or contact heat, followed by the monofilaments. An advantage of the within-subjects design is that we can compare the measurements of a given subject following sweet consumption with the subject's own baseline measurements, thus minimizing individual differences. Moreover, the baseline (or familiarization) trial allows the subject to become familiar with the procedure and with the pain measures. This results in fewer subjects having to be discarded due to experimental errors. A disadvantage of the within-subjects design is that the familiarization trial may change the subjects' responses on the second exposure to the cold water, contact heat, or

pressure. For example, previous studies have found that exposure to noxious stimuli and/or certain environmental stressors can activate endogenous pain-inhibitory systems, producing analgesia (e.g., Hayes, Bennett, Newlon, & Mayer, 1978; Madden, Akil, Patrick, & Barchas, 1977; Melzack, 1975). This phenomenon has been termed stress-induced analgesia. Therefore, the initial pain or stress experienced during the pre-treatment trial could activate intrinsic pain-modulatory systems (either opioid or nonopioid), thereby reducing sensitivity to pain during the post-treatment trial. Statistical procedures were used to determine whether stress-induced analgesia had occurred.

2.5: Data Analyses

Although some of the experiments (Expts. 2c, 3a, and 3b) in this thesis employed three trials (familiarization, pre-treatment, and post-treatment) while others (Expts. 1, 2a, and 2b) used only two trials (pre- and post-treatment), all analyses of treatment effects were performed on the data from the pre- and post-treatment trials only. In the three-trial experiments, the first trial called the familiarization trial was omitted from the treatment analyses for the following reasons: 1) the familiarization trial was added to the experiments only to provide the subjects with a practice trial in which they become familiar

with the pain procedure (as the two-trial experiments indicated that subjects showed an adaptation or practice effect); and 2) analyses of the control groups' data showed that there was a practice or "warm-up" effect, as pain sensitivity was greater during the familiarization trial than during either the pre- or post-treatment trials (see Results sections of Expts. 2c-3b).

For between-groups comparisons, one-way analyses of covariance (ANCOVAs) were used to analyze the data of each gender separately. Between-groups ANCOVAs comparing the groups at post-treatment (the pre-treatment trial served as the covariate) were performed on each of the four pain measures (threshold, tolerance, intensity, and unpleasantness) and tactile thresholds. The primary rationale for using ANCOVAs rather than either ANOVAs for difference scores or ANOVAs for repeated measures was that subjects could not be randomly assigned to treatment groups (see General Discussion). Moreover, an additional problem with the use of difference scores is the potential for ceiling or floor effects. ANCOVA minimizes these problems by equating the experimental groups (i.e., by adjusting group means to what they would be if all subjects scored identically on the covariate or pre-treatment measure). In other words, ANCOVA removes the influence of baseline group differences from the treatment group analyses.

The rationale for analyzing the data of males and females separately is three-fold. First, evidence suggests that males and females show differences in pain sensitivity. On average, males report higher pain thresholds and tolerances than do females (e.g., Rollman & Harris, 1984). Second, there is some evidence which suggests that males and females may differ in their taste sensitivity and taste preferences. For example, females display a greater preference for sweets than males (Valenstein, Kakolewski, & Cox, 1967). Third, because males appear to be more influenced by experience with experimental pain than do females (Feine, Bushnell, Miron, & Duncan, 1991), they may show larger intertrial differences than females. Because each of these three factors likely influences the effects of sweets on pain, analyses of the combined data (i.e., of males and females together) might obscure any sweet-induced analgesia that might occur if the genders were analyzed separately.

To compare males and females on each of these factors (i.e., baseline pain sensitivity, food palatability, and trial differences), one-way analyses of variance (ANOVAs) were used. Group baseline differences were analyzed with one-way ANOVAs also.

To determine if there was an influence of stress-induced analgesia, correlated t-tests were used to compare

the control groups' familiarization, pre-treatment and post-treatment means. And finally, Pearson product-moment correlations were utilized to determine: 1) whether any of the subject variables (e.g., alcohol use, amount of sleep, phase of menstrual cycle; see Appendix E) were related to any of the pain measures; 2) whether the two latency pain measures (threshold and tolerance) were related to each other, and the two VAS pain measures (intensity and unpleasantness) were related to each other; and 3) whether VAS ratings of food palatability and hunger were related to changes (from pre-to post-treatment) in any of the pain measures.

CHAPTER 2.6: EXPERIMENT 1. COLD-WATER PRESSOR

Previous research with rats (e.g., Bergman et al., 1985; Holder, 1988) and human infants (e.g., Blass et al., 1989, 1991) has shown that sweet intake produces analgesia. This effect has yet to be studied in human adults. In the present study, a within-subjects design was used to assess the effects of sweet intake on the perception of pain induced by a cold-water pressor. To help eliminate variability associated with hormonal cyclicity, only male university students were tested in this preliminary study. Previous studies have shown that female pain perception is influenced by the phase of the menstrual cycle (Goolkasian, 1980), the presence or absence of dysmenorrhea or painful menstruation (Goolkasian, 1983; Hapidou & De Cantanzaro, 1988), and the use of oral contraceptives (Goolkasian, 1980; Gracely, Taylor, Schilling, & Wolskee, 1984).

In the present study, male subjects immersed their left arm in a cold-water bath and their pain sensitivity was assessed with measures of pain threshold and pain tolerance as well as with VAS ratings of pain intensity and unpleasantness. Subjects then ingested either an 8% sucrose solution, water, or nothing (control), and were again exposed to the cold-water pressor. If the sweet intake produced analgesia to the pain induced by cold water, then

subjects receiving the sucrose should show elevated pain thresholds and/or tolerances, and/or decreased VAS ratings of pain intensity or unpleasantness, relative to subjects receiving water or nothing.

Method

Subjects. Thirty male university students participated in the experiment. All subjects met the criteria outlined in the General Methodology section of this thesis.

Apparatus. 1) **Cold-Water Pressor.** The cold-water pressor consisted of a 45.5 x 24.5 x 21 cm Plexiglas tank (a modified rat laboratory cage) filled with ice water (depth = 15 cm). A wire mesh screen divided the tank so that one section (45 x 6.5 x 21 cm) contained crushed ice and the other section (45.5 x 18 x 21 cm) contained ice-free water. The water temperature was monitored prior to each arm immersion with a digital display thermometer, and the water was circulated continuously with a submersible aquarium water pump (120 V; output = 480 l.p.h.) in order to maintain a water temperature between 0 and 1.5° C (M = 0.83; SD = 0.28).

2) **Esthesiometer.** A Von Frey fiber kit (Stoelting, Co., Wood Dale, IL) was used to determine tactile thresholds. These fibers are a series of 20 force-calibrated nylon monofilaments of equal length but

increasing diameters (therefore, varied stiffness). The force needed to bend each fiber ranges from below the normal threshold of detection (.005 grams) to forces which, if not detected, indicate a severe sensitivity deficit (448.0 grams).

Procedure. The male volunteers were contacted by phone and debriefed about the experimental procedure. In this debriefing, subjects were informed that their arm would be submersed in cold water, and therefore, they would experience some pain. The subjects were then randomly assigned to one of three groups that differed on whether they were to consume an 8% sucrose solution (sucrose mixed with filtered tap water), filtered tap water, or no solution (control). A sucrose solution was chosen for the experimental treatment in order to replicate the procedure used previously with both rats and human infants. Upon arrival at the laboratory, each subject was seated next to a table. On the table was a tank that contained ice water. The tank was positioned so that the subject could comfortably place his forearm at the bottom of the tank. First, the subject was asked to rate his current level of discomfort using the pain intensity and unpleasantness VASs. This was to familiarize the subject with the VASs and to ensure that the subject was not experiencing any discomfort prior to the experiment. The subject was then asked to

immerse his left hand and forearm in the cold-water pressor and his discomfort was assessed with measures of pain threshold, pain tolerance, and subjective intensity and unpleasantness. Following the cold-pressor procedure, tactile sensitivity of the right hand (the non-exposed hand) was measured with the monofilaments.

Next, if the subject was in the control (nothing) group, he was instructed to sit and read a selected passage from a psychology textbook for 15 minutes. If he was in either of the solution groups, he was given the 8% sucrose solution or the tap water (both served at room temperature), using the following standardized procedure. Every 2 minutes the subject was instructed to take all of the solution from one of five premeasured cups and swish the solution around in the mouth for 1 minute prior to swallowing it. Each cup contained 20 ml of the solution for a total of 100 ml. Immediately after the fifth and final ingestion of the solution (or after 15 minutes of reading if the subject was in the control group), each subject was asked again to place his left forearm and hand in the cold-water pressor. Measures of pain threshold, pain tolerance, intensity and unpleasantness were again assessed, followed by a second measurement of tactile sensitivity. At the end of the session, each subject was instructed to complete a personal questionnaire (see Appendix E). [For procedural details, see

Appendix A.]

Results

Baseline Comparisons.

Treatment Group Differences: Table 2.6.1 shows for each group, the pre-treatment means for each pain measure: pain threshold, pain tolerance, intensity ratings, and unpleasantness ratings. One-way ANOVAs revealed no significant differences among the three groups at pre-treatment for any of the pain measures (all ps > 0.05).

Insert Table 2.6.1 about here

Treatment Effects on Pain Perception.

Figures 2.6.1 to 2.6.4 show, for each group, the ANCOVA adjusted post-treatment means of each of the four pain measures: threshold, tolerance, intensity, and unpleasantness, respectively. One-way ANCOVAs performed on

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Insert Figures 2.6.1 to 2.6.4 about here

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each of the four post-treatment pain measures revealed a significant group (or treatment) difference for pain tolerance [$F(2,26) = 3.84$, $p = .035$]. Post-hoc comparisons

Table 2.6.1

Experiment 1: Pre-treatment and ANCOVA Adjusted Post-treatment Means (and Standard Errors) for **Males** (n=30) in each Treatment Group.

Group	Pre-treatment Measures				Post-treatment Measures			
	Thr (s)	Tol (s)	Int	Unp	Thr (s)	Tol (s)	Int	Unp[1]
Nothing	46 (22)	86 (31)	10.8 (1.8)	9.8 (2.0)	16 (9)	63 (18)	13.1 (1.6)	11.9 (1.9)
Water	16 (3)	101 (33)	11.9 (1.1)	11.2 (1.4)	17 (3)	**103** (35)	12.5 (1.1)	13.1 (1.3)
Sucrose	23 (6)	71 (24)	11.3 (1.4)	11.5 (1.8)	18 (4)	57 (8)	13.7 (0.6)	14.8 (1.1)
Grand Mean	28 (8)	86 (17)	11.6 (1.4)	11.1 (1.8)	17 (4)	74 (14)	13.1 (0.7)	13.3 (0.9)

Bold-faced #s = Group which differs from the other groups in that column ($p < .05$).

[1] Thr = Threshold, Tol = Tolerance, Int = Intensity, Unp = Unpleasantness

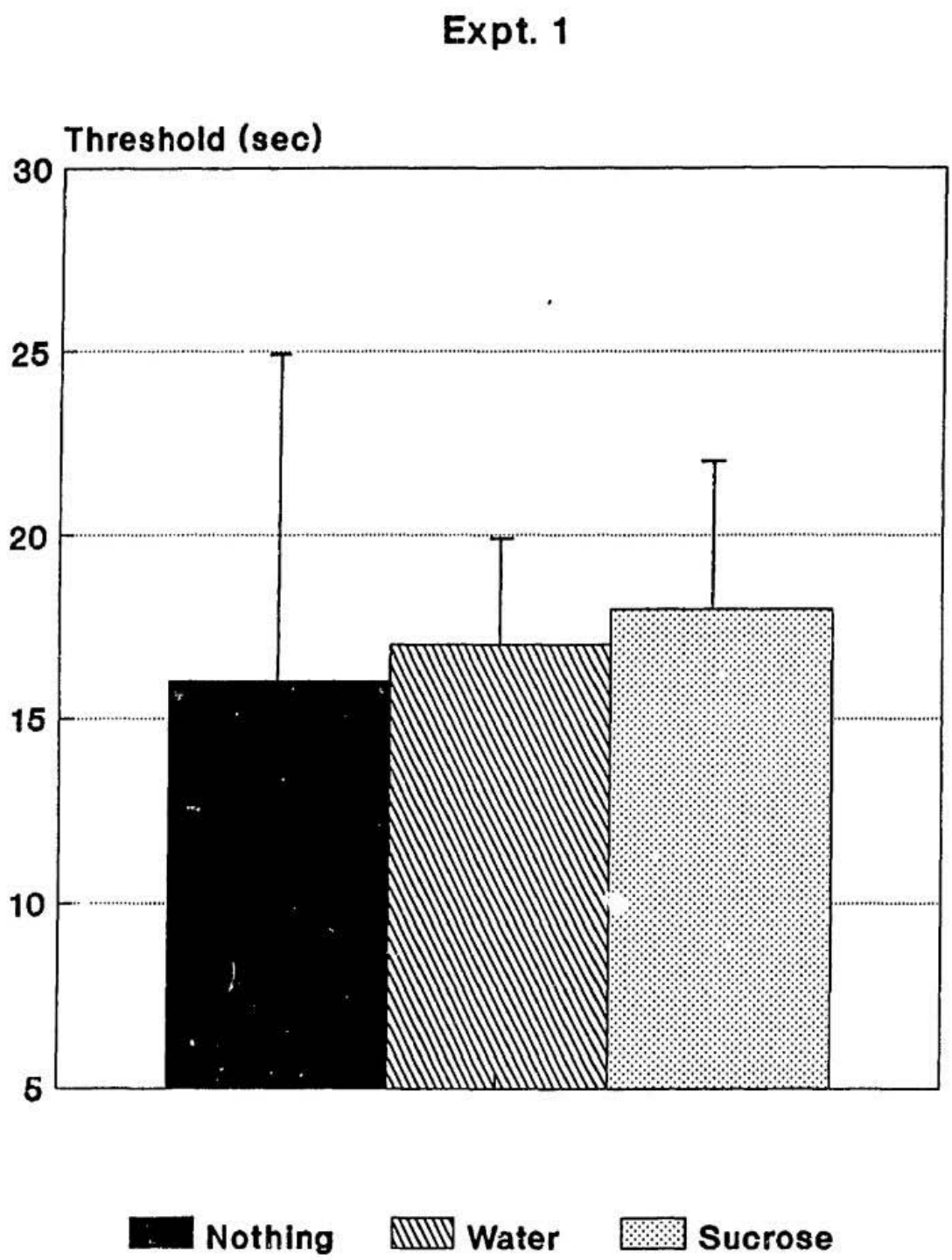

Figure 2.6.1. Post-treatment mean pain thresholds (sec) to the cold water pressor for **males** (n=40) in each treatment group.

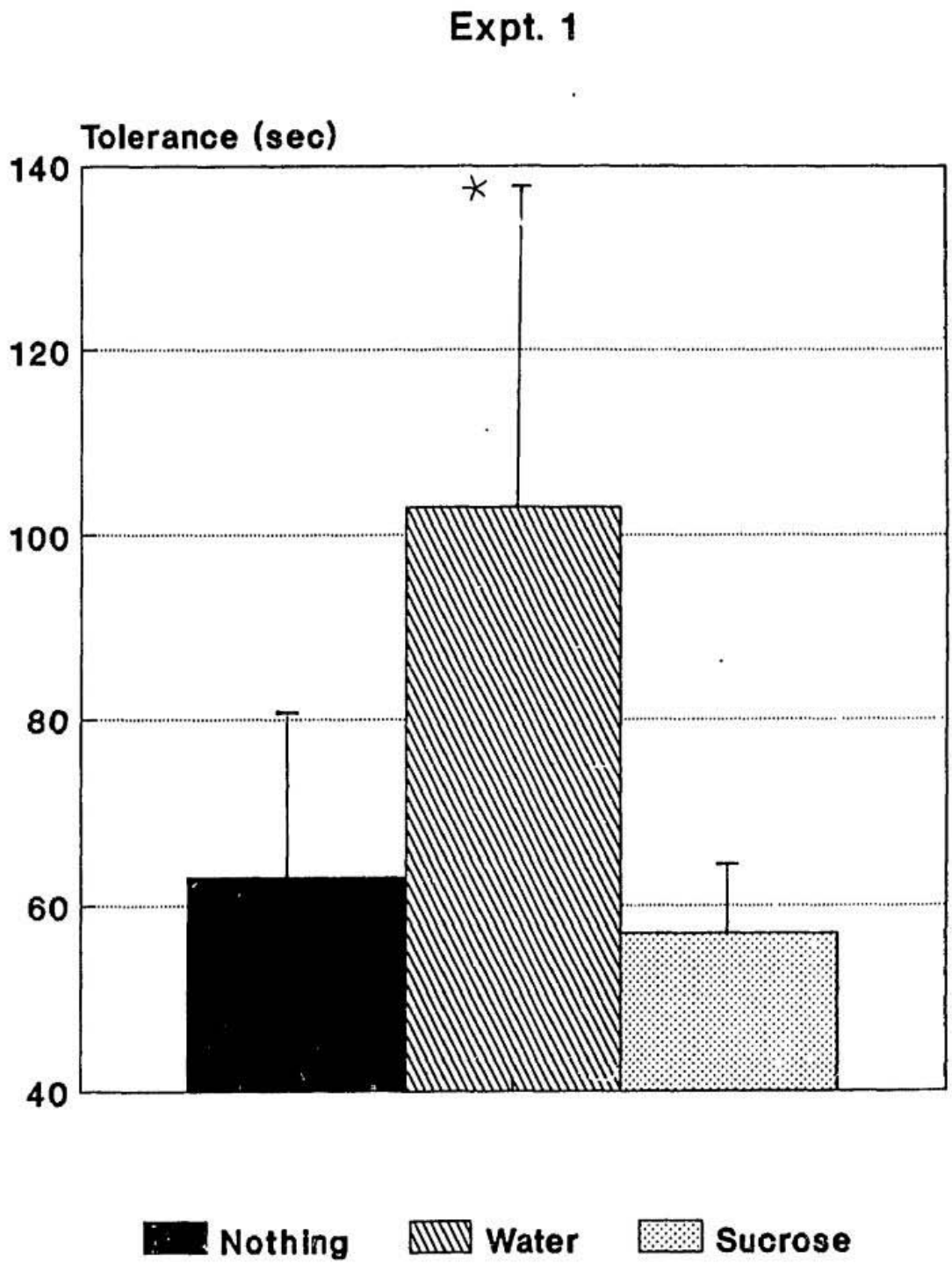

Figure 2.6.2. Post-treatment mean pain tolerances (sec) to the cold water pressor for males (n=40) in each treatment group. * indicates the treatment group that differs from the others at post-treatment.

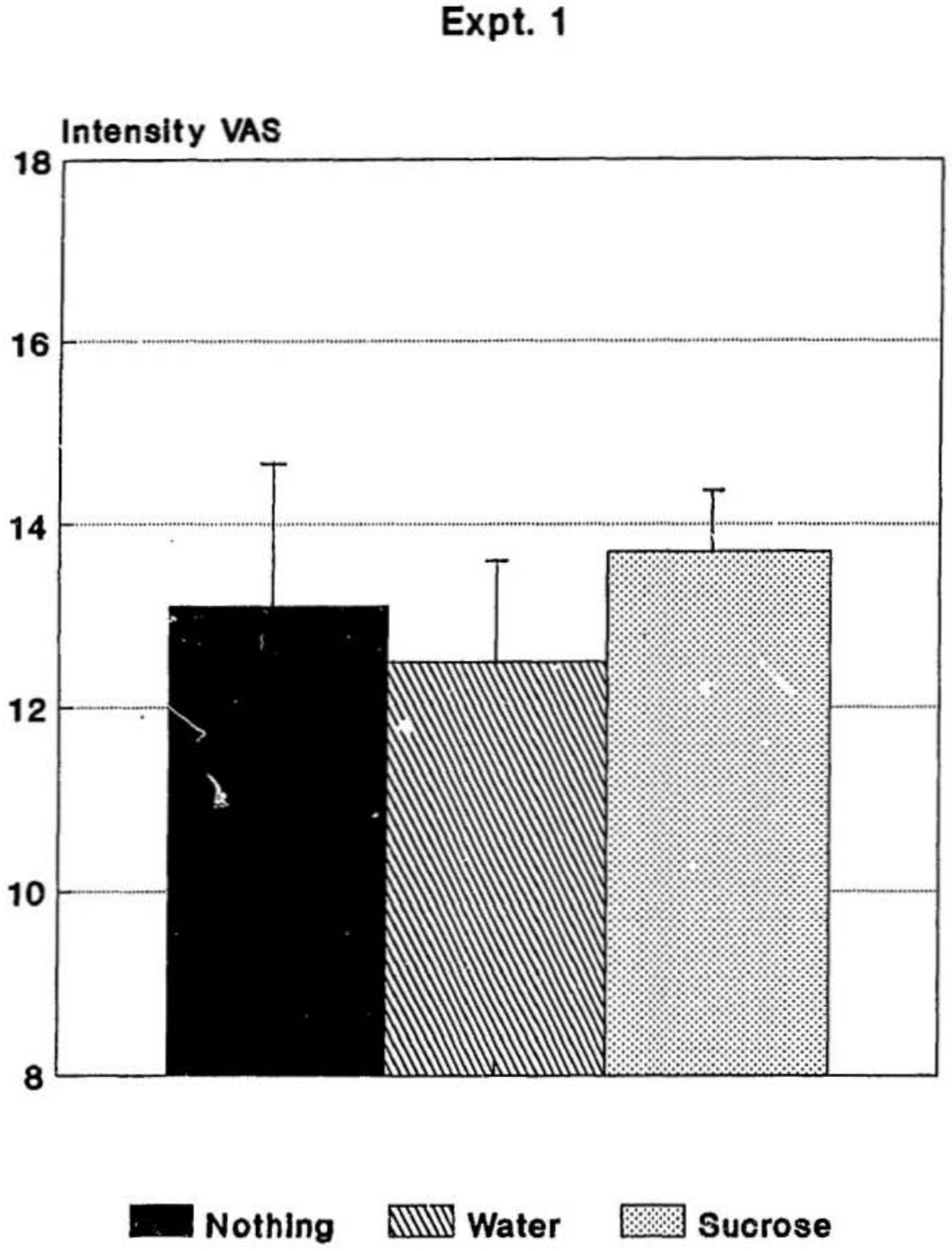

Figure 2.6.3. Post-treatment mean pain intensity ratings to the cold water pressor for **males** (n=40) in each treatment group.

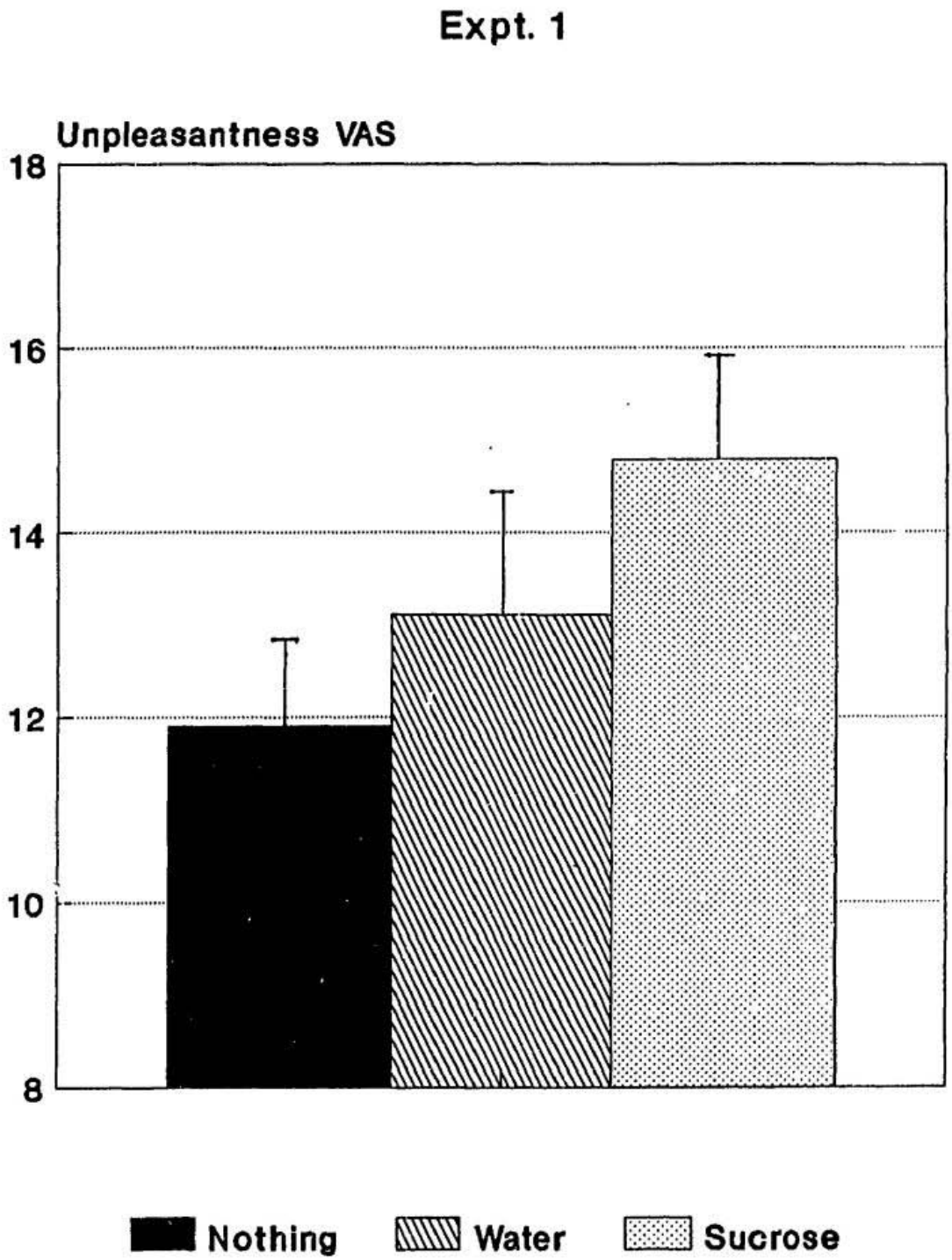

Figure 2.6.4. Post-treatment mean pain unpleasantness ratings to the cold water pressor for **males** (n=40) in each treatment group.

showed that the water group's post-treatment pain tolerance differed significantly from that of the other two groups (Newman-Keuls, $p < 0.05$). The groups did not differ significantly on any of the other pain measures (all ps > 0.05) [see ANCOVA adjusted post-treatment means, Table 2.6.1]. In summary, compared to the sucrose and control (nothing) groups, the water group showed increased analgesia. This result was contrary to expectation.

Trial Effects.

To test for the influence of stress-induced analgesia (SIA), the control group's (n=10) pre- and post-treatment means were compared for each pain measure. Correlated t-tests revealed significant trial effects for intensity [$t(9) = -2.43$, $p = .038$] and unpleasantness [$t(9) = -3.67$, $p = .005$] VAS ratings. However, both intensity and unpleasantness ratings increased from pre-treatment ($M_{int} = 10.8$; $M_{unp} = 9.8$) to post-treatment ($M_{int} = 12.7$; $M_{unp} = 11.0$), contrary to that expected for an influence of SIA.

For the first and second trials respectively, 30% and 36% of the subjects kept their hands immersed in the cold water for more than 60 seconds (the time at which, for most people, the pain reaches maximum intensity; Johnson, 1974). Moreover, two (6.7%) subjects kept their hands immersed in the water for the full five minutes.

Treatment and Trial Effects for Tactile Sensitivity.

The pre- and post-treatment mean tactile thresholds of each group are displayed in the first two columns of Table 2.6.2. Tactile thresholds did not differ among groups as confirmed by a one-way ANCOVA comparing the groups' means [$F(2,26) = 1.51$, $p = 0.239$]. However, an ANOVA for repeated measures showed a significant trial effect [$F(1,27) = 4.92$, $p = .035$] with all groups displaying an increase in tactile threshold (i.e., a decrease in touch sensitivity) from pre- [M = 3.26] to post-treatment [M = 3.35].

Insert Table 2.6.2 about here

Correlations Between Subject Variables and Pain Measures.

To determine whether there were any relationships between the latency pain measures (threshold and tolerance) between the VAS pain measures (intensity and unpleasantness), or between the four pain measures and each of the recorded subject variables (e.g., body weight, amount of exercise, amount and quality of sleep; see Appendix E), Pearson product-moment correlations were conducted. Intensity and unpleasantness measures were highly correlated at pre-treatment ($r = 0.77$, $p < 0.05$) as were measures of threshold and tolerance ($r = 0.46$, $p < 0.05$). There were no

Table 2.6.2

Mean Tactile Thresholds at Pre- and Post-Treatment for each Treatment Group (No = Nothing, Un = Unpalatable, Ne = Neutral, Pa = Palatable, M = Overall Mean) for **All** Experiments.

	Expt.1		**Expt.2a**		**Expt.2b**		**Expt.2c**		**Expt.3a**		**Expt.3b**	
	1	2	1	2	1	2	1	2	1	2	1*	2*
No	3.23	3.31	3.22	3.30	3.14	3.20	3.24	3.40	3.18	3.22	3.24	3.24
Un					3.14	3.28	3.44	3.34	3.14	3.23	3.23	3.27
Ne	3.34	3.45	3.28	3.27	3.26	3.21	3.42	3.30	3.22	3.22	3.22	3.27
Pa	3.22	3.30	3.27	3.30	3.16	3.38	3.38	3.42	3.26	3.25	3.26	3.21
M	3.26	3.35	3.26	3.29	3.18	3.27	3.37	3.36	3.20	3.23	3.24	3.25

* 1 = Pre-treatment, 2 = Post-treatment

significant correlations between the pain measures and any of the subject variables (all ps > 0.05).

Discussion

The results from the present study failed to support the hypothesis that sweet consumption would produce analgesia to cold-pressor pain. Instead, relative to the consumption of a 8% sucrose solution (sucrose mixed with filtered tap water) or nothing, the consumption of the filtered tap water alone produced increased pain tolerance. There are several possible explanations for these results. First, because the 8% sucrose solution was served at room temperature and was very sweet-tasting, it may not have tasted very palatable. If the sucrose solution was not palatable, it may not have elicited the release of opioids and, therefore, would not have produced analgesia. In fact, because the subjects were slightly water-deprived, and because they may have been nervous about participating in an experiment involving pain, the subjects may have found the water to be more palatable or more rewarding than the sucrose solution. This may explain why the water group, but not the sucrose or nothing group, showed increased pain tolerance.

Secondly, the temperature of the water in which the hand was immersed may have been too low. Studies with rats

have shown that severe (lower temperature, longer duration) cold-water swims produce nonopioid-modulated analgesia whereas lower severity (higher temperature, shorter duration) cold-water swims produce opioid-modulated analgesia (e.g., Terman, Morgan, & Liebeskind, 1986). In the present experiment, the water temperature of the cold-water pressor was between 0 and +1.5° C, and the maximum duration of exposure was 5 min., an exposure period which is considered severe by most researchers of animal pain. These severe conditions may have activated a nonopioid, rather than an opioid, pain-modulatory system and there is little evidence to suggest that sweets are capable of modulating a nonopioid-mediated analgesia system. This explanation is supported by recent findings that intraoral sucrose solutions did not produce analgesia to a 0° C cold pressor in adults (unpublished data, cited in Miller, Barr, & Young, 1994), but did increase pain thresholds to a warmer, much less severe, 10° C cold pressor in 8-11 year-old children (Miller et al., 1994).

A further problem with the method of cold-water immersion may originate from the nature of cold-water pain. It has been reported that 8% of males and 4% of females adapt to the numbing effect of cold without reporting pain (Johnson, 1974). This may be explained by the fact that a cold pressor activates nociceptive as well non-nociceptive

afferent nerve fibers (Houle, McGrath, Moran, & Garrett, 1988; Miller et al., 1994). Moreover, it is generally agreed that the pain induced by cold water is cyclical; a person whose hand is immersed in cold water (</= 4° C) first experiences a dull, diffuse, aching pain which increases to a maximum intensity after approximately 60 sec. The intensity slowly subsides, and then increases again at various intervals (Wolf & Hardy, 1941), thus making discomfort measures taken after 60 seconds difficult to interpret. In the present study, over 30% of the subjects kept their hand immersed in the cold water for more than 60 seconds, and 6.7% of subjects kept their hand immersed in the cold water for the maximum 5 minutes. Collectively, the above arguments suggest that any analgesic effects may have been obscured by ceiling effects, resulting either from the high pain tolerance scores or from the cyclical nature of cold-water pain.

In summary, although the cold-water pressor has been an effective method for measuring general features of human pain sensitivity (Murray & Hogan, 1973), its cyclical nature and its potential for producing ceiling effects appears to make it a poor candidate for the precise and accurate measurement of analgesic effects.

CHAPTER 3: PRESSURE-ALGOMETRY STUDIES, EXPTS 2A, 2B AND 2C

CHAPTER 3.1: EXPERIMENT 2A

Experiment 1 showed that consumption of a sucrose solution did not produce analgesia to cold-pressor pain. The present experiment improved upon the previous one in three ways: 1) because of the cyclical nature of pain induced by cold water as well as the possibility that cold-pressor pain may be mediated by nonopioid pathways, this experiment employed a different method to induce pain, namely pressure algometry; 2) to improve the palatability of the solution consumed by the sweet group, rather than ingesting a room temperature 8% sucrose solution (which the subjects in Expt. 1 may not have found palatable), the subjects in the present study ingested a refrigerated, carbonated soft drink; and 3) because male subjects tend to show high pain thresholds and tolerances, thus increasing the likelihood of ceiling effects, female subjects were also tested in the present experiment. Several parameters were changed simultaneously in this follow-up study because the main objective of this thesis was to determine whether sweet-induced analgesia **can** be demonstrated in human adults. Thus, these three major modifications to the present experiment were an attempt to maximize the likelihood of

observing sweet-induced analgesia in human adults.

Testing of both sexes also allows for the assessment of gender differences. Previous studies which have used various pain inducers have found that pain thresholds and/or tolerances are lower for females than for males (e.g., Buchsbaum, Davis, Coppola & Naber, 1981; Otto & Dougher, 1985; Sherman, 1943), and that subjective ratings of pain are higher for females than for males (Dubreuil & Kohn, 1986; Feine, Bushnell, Miron, & Duncan, 1991; Zeltzer, Fanurik, & LeBaron, 1989). Moreover, recent studies employing pressure algometry have found that pressure-pain thresholds (PPT) are 30-70% higher in males than in females (Brennum, Kjeldsen, Jensen, & Jensen, 1989; Fischer, 1987). Therefore, the present study used both sexes to assess whether intake of sweets, specifically non-diet soft drinks, produces analgesia to pain induced by finger pressure.

Method

Subjects. Sixty (30 male and 30 female) university students served as subjects.

Apparatus. **1) Pressure Algometer.** An Ugo-Basile (Milan, Italy) analgesia meter was used to apply pressure to the subjects' four finger tips. Over time, the instrument gradually increases compressive force (0-1250 g) at a constant rate (approximately 80 grams/second) by

electrically driving four weights along a pivoted beam to which is attached a blunt cone-shaped point, 1.5 mm in diameter. Under this blunt point is a small base on which the subject places his/her finger tip. An operator depresses a pedal-switch to start or stop the mechanism. The forces applied are continuously monitored by a pointer moving along a linear calibrated scale containing twenty-five 1 cm divisions. These 25 divisions are clearly marked and are easily read, thus providing accurate measures of pain threshold and pain tolerance.

2) **Von Frey Fibers** (see description in Expt. 1)

Procedure. Because the procedure was similar to that of Experiment 1, only the differences will be emphasized here. First, in order to test for gender differences, both male and female subjects were used. Second, mechanical pressure rather than cold water was used to induce pain. Pressure was applied to each finger of the subject's left hand starting with the index finger. For all four fingers, threshold and tolerance measures were obtained. Each subject was instructed to say "pain" (threshold) when she/he first felt pain and to say "stop" (tolerance) when the pain became too uncomfortable to continue, at which time the operator released the pedal and removed the subject's finger. In addition, during testing of the fourth finger, the subject was given two VASs and was asked to rate the

intensity and unpleasantness of his/her finger discomfort, just prior to saying "stop". In the case of subjects who did not say "stop" before 30 seconds had elapsed, they were told to remove their finger and to rate the intensity and unpleasantness of the discomfort. Third, the subjects in the experimental group consumed a can of caffeine-free, non-diet carbonated soft drink (either Coke or Sprite, whichever they preferred) rather than a 8% sucrose solution. Fourth, the carbonated soft drink and the water were served cold (refrigerated) rather than at room temperature. Fifth, rather than swishing 100 ml of solution in a standardized procedure, the subjects were given a glass and 355 ml of either soft drink or water and instructed to "drink as much as you want". At the end of the experiment, the subjects in the experimental group were asked to rate the palatability of the chosen soft drink using a 10-point VAS with the endpoints labelled "Strongly Dislike" and "Strongly Like" (See Appendix B for procedural details).

As mentioned above, pain thresholds and pain tolerances were measured for each finger. Pilot work revealed that there may be differences in pain sensitivity among the four fingers; the index finger (and sometimes the second finger) appeared to be less sensitive than the other fingers. This is consistent with anatomical evidence which indicates that there are differences among fingers in the

number of nociceptors that each contains, especially between the index and the other three fingers (Penfield & Rasmussen, 1950, cited in Jessell & Kandel, 1991). Thus, in the present study, finger differences were analyzed and, to minimize ceiling effects, the least sensitive finger(s) was (were) excluded from the between-groups analyses.

Results

Baseline Comparisons.

Treatment Group Differences. Tables 3.1.1 (females) and 3.1.2 (males) show, for each group, the pre-treatment means for each pain measure. One-way ANOVAs performed on

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Insert Tables 3.1.1 and 3.1.2 about here

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each of the four pre-treatment pain measures revealed a significant group difference for the intensity ratings of males [$F(2,27) = 7.25$, $p = .003$]. Post-hoc comparisons showed that the pre-treatment intensity ratings of the control (nothing) group ($M = 8.3$) were significantly lower than those of the soft drink ($M = 13.4$) group (Newman-Keuls, $p < 0.05$).

Gender Differences. One-way ANOVAs were performed on each of the pain and tactile pre-treatment measures to determine whether males and females differed in their

Table 3.1.1

Experiment **2a**: Pre-treatment and ANCOVA Adjusted Post-treatment Means (and Standard Errors) for **Females** (n=30) in each Treatment Group.

Group	**Pre-treatment Measures**				**Post-treatment Measures**			
	Thr (cm)	Tol (cm)	Int	Unp	Thr (cm)	Tol (cm)	Int	Unp[1]
Nothing	9.6 (1.3)	16.9 (2.2)	12.3 (1.1)	12.3 (1.2)	9.0 (1.2)	14.1 (1.9)	11.6 (1.4)	10.4 (1.5)
Water	9.9 (4.1)	15.2 (1.5)	14.6 (0.9)	12.9 (1.3)	9.7 (1.4)	**16.9** (1.8)	**13.9** (1.0)	**13.7** (1.0)
Soft Drink	8.9 (1.0)	15.5 (1.4)	13.9 (0.9)	12.1 (1.4)	10.5 (1.1)	**16.2** (1.5)	**14.4** (0.9)	**13.2** (1.5)
Grand Mean	9.5 (0.7)	15.9 (1.0)	13.4 (0.6)	12.4 (0.7)	9.8 (0.7)	15.7 (1.0)	13.3 (0.7)	12.4 (0.8)

Bold-faced #s = Groups which differ from the other group in that column ($p < .05$).

[1] Thr = Threshold, Tol = Tolerance, Int = Intensity, Unp = Unpleasantness

Table 3.1.2

Experiment 2a: Pre-treatment and ANCOVA Adjusted Post-treatment Means (and Standard Errors) for Males (n=30) in each Treatment Group.

	Pre-treatment Measures				Post-treatment Measures			
Group	Thr (cm)	Tol (cm)	Int	Unp	Thr (cm)	Tol (cm)	Int	Unp[1]
Nothing	14.0 (2.0)	25.9 (3.0)	8.3 (0.7)	10.0 (1.0)	14.8 (3.0)	24.0 (2.2)	11.7 (0.9)	11.3 (0.9)
Water	13.2 (1.5)	23.7 (2.6)	10.8 (1.1)	10.4 (1.3)	14.7 (1.7)	24.4 (2.8)	12.0 (1.2)	11.2 (1.3)
Soft Drink	14.2 (1.1)	24.3 (2.3)	13.4 (1.0)	11.8 (1.3)	13.3 (1.4)	24.3 (3.1)	12.0 (1.1)	12.8 (1.4)
Grand Mean	13.8 (0.9)	24.6 (1.5)	10.8 (0.6)	10.7 (0.7)	14.3 (0.9)	24.2 (1.5)	11.9 (0.7)	11.8 (0.7)

Underlined #s = Groups in that column which differ from each other ($p < .05$).

[1] Thr = Threshold, Tol = Tolerance, Int = Intensity, Unp = Unpleasantness

sensitivity to pain or touch. Significant gender differences were found for pre-treatment threshold [$F(1,57) = 9.17$, $p = .004$], tolerance [$F(1,57) = 16.95$, $p = .0001$], and intensity [$F(1,57) = 9.98$, $p = .0025$] measures with females showing (or reporting) greater sensitivity to pressure pain (see pre-treatment means, Tables 3.1.2 and 3.1.2). In other words, males took longer to report pain (threshold was 36-44% higher), withstood more pressure (tolerance was 41-45% higher) and reported the pain to be less intense (VAS ratings were 26% lower) than did females. There was not a significant gender difference for unpleasantness [$F(1,57) = 2.93$, $p = .09$] or for tactile thresholds [$F(1,57) = 0.40$, $p = .53$].

Finger Differences. As discussed in the procedure, it is important to determine which fingers are relatively insensitive to pain. Mean thresholds and tolerances for each finger were compared for the subjects of the control (nothing) group only ($n = 20$). Figures 3.1.1 and 3.1.2 depict the means of the pre- and post-treatment trials across each finger for threshold and tolerance, respectively. Two-way ANOVAs [4(Finger) x 2 (Trial)] revealed significant finger differences for both mean threshold [$F(3,54) = 8.02$, $p = .0002$] and mean tolerance [$F(3,54) = 12.28$, $p < .0001$]. Post-hoc multiple comparisons showed that mean threshold and tolerance were higher for the

first and second fingers relative to the third and fourth digits [Newman-Keuls, $p < 0.05$].

Insert Figures 3.1.1 and 3.1.2 about here

Treatment Effects on Pain Perception.

Because the first and second fingers were less sensitive than the last two fingers, between-groups analyses were performed on the combined data from the third and fourth fingers only. Moreover, because of gender differences in pain sensitivity (see above), the data of males and females were analyzed separately.

Figures 3.1.3 to 3.1.6 plot the adjusted post-treatment means for each pain measure. One-way ANCOVAs performed on

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Insert Figures 3.1.3 to 3.1.6 about here

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the post-treatment data of females showed group differences for measures of pain tolerance [$F(2,27) = 5.19$, $p = .013$], intensity [$F(2,27) = 5.16$, $p = .013$], and unpleasantness [$F(2,27) = 4.17$, $p = .027$], but not for pain threshold ($p > 0.05$). Post-hoc comparisons showed that, on all three pain measures, the female water and soft drink groups differed significantly from the nothing group (Newman-Keuls, $p <$

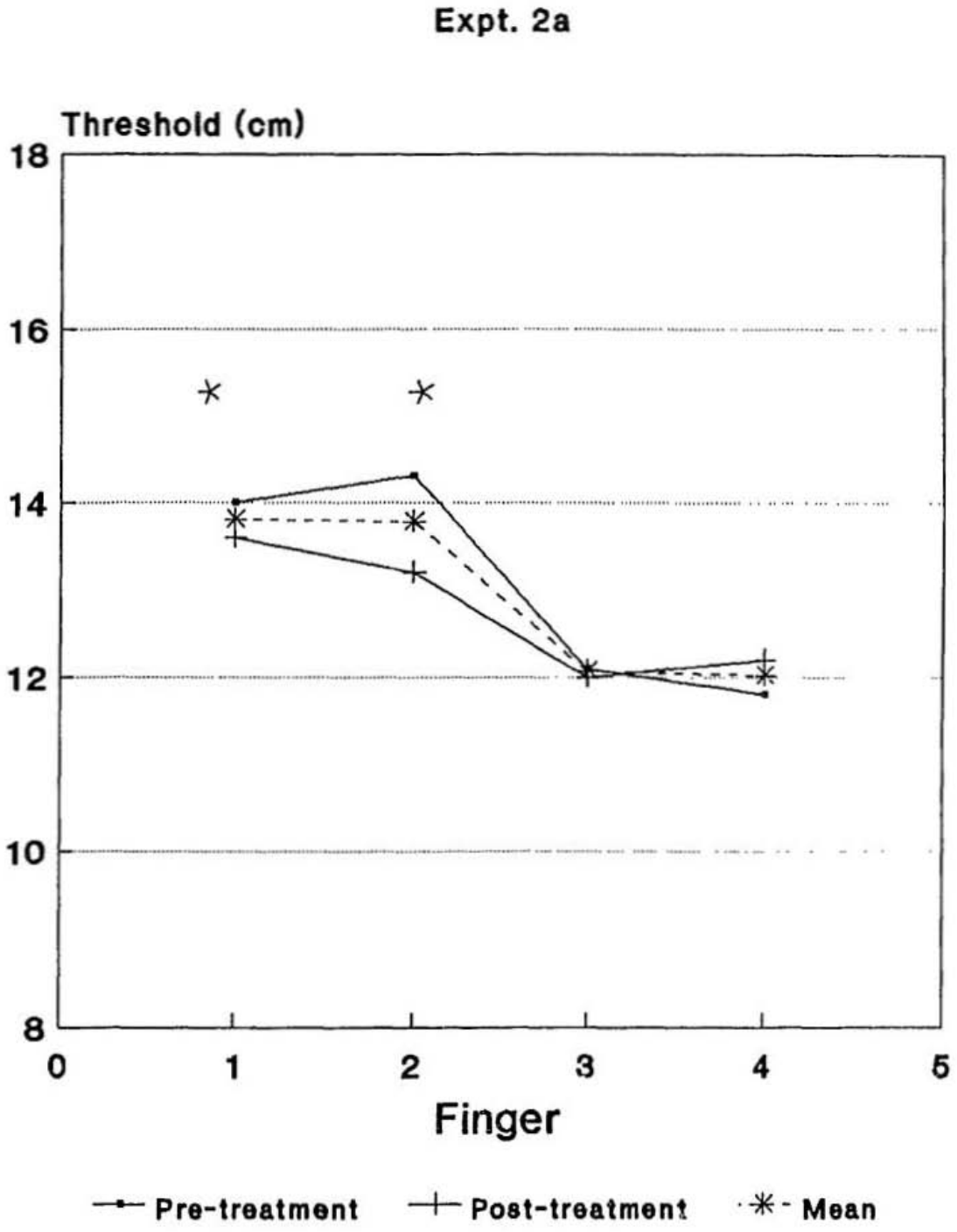

Figure 3.1.1. Mean pain thresholds to pressure for each finger at pre- and post-treatment for subjects (n=20) in the nothing group only. Note that the dashed line represents the mean of the two trials. * indicates the fingers which differ from the other fingers.

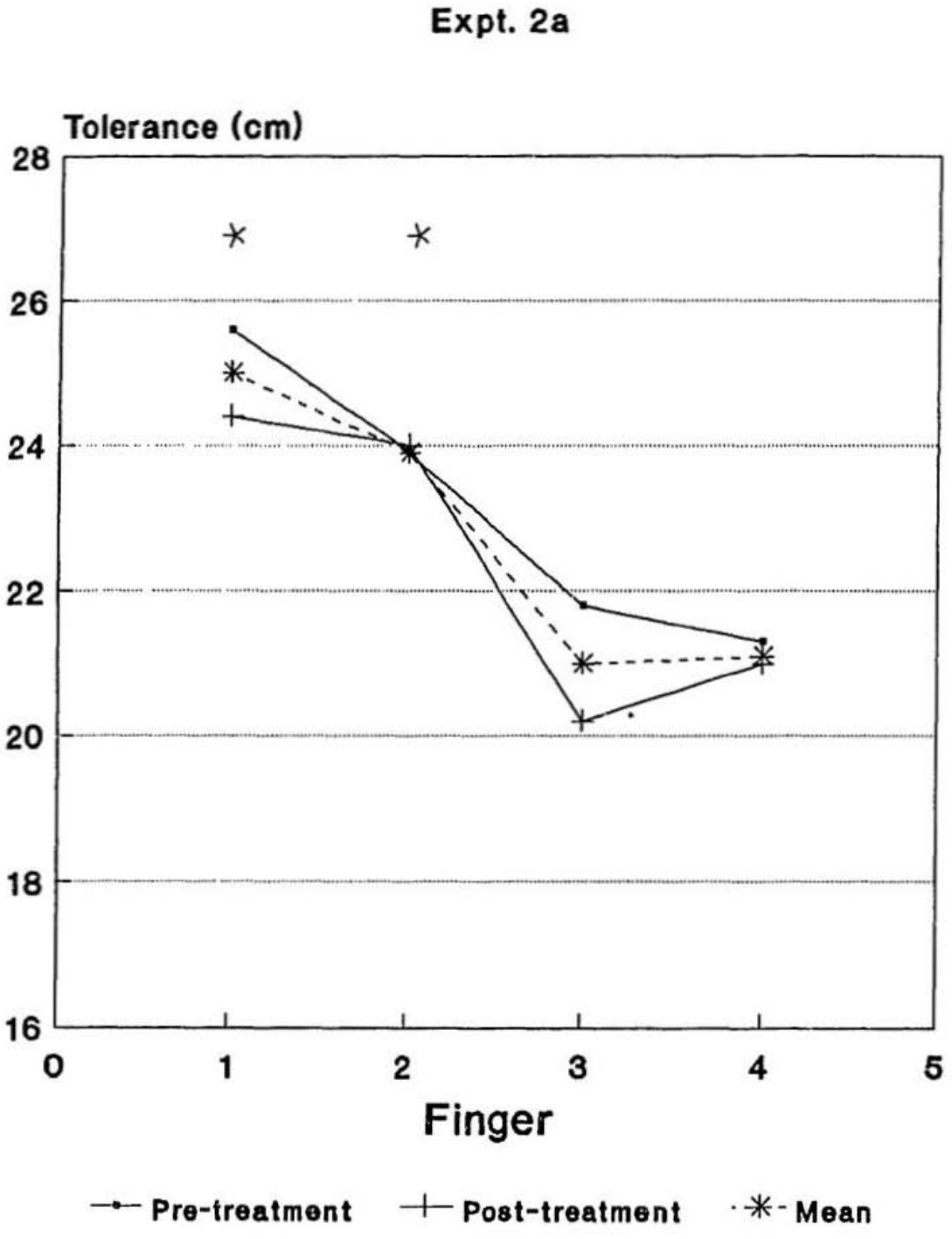

Figure 3.1.2. Mean pain tolerances to pressure for each **finger** at pre- and post-treatment for subjects (n=20) in the nothing group only. Note that the dashed line represents the mean of the two trials. * indicates the fingers which differ from the other fingers.

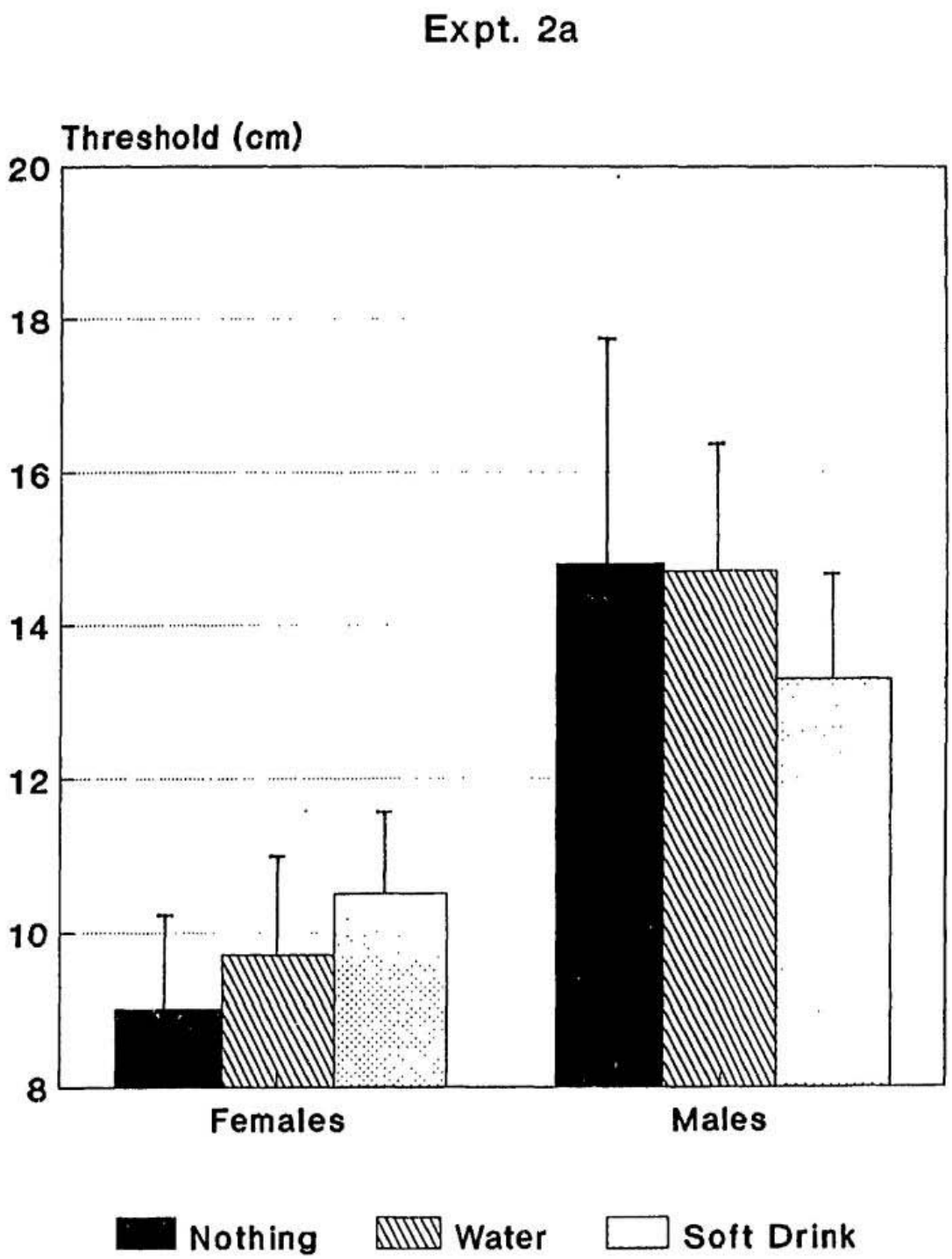

Figure 3.1.3. Post-treatment mean pain thresholds to pressure for females (n=30) and males (n=30) in each treatment group.

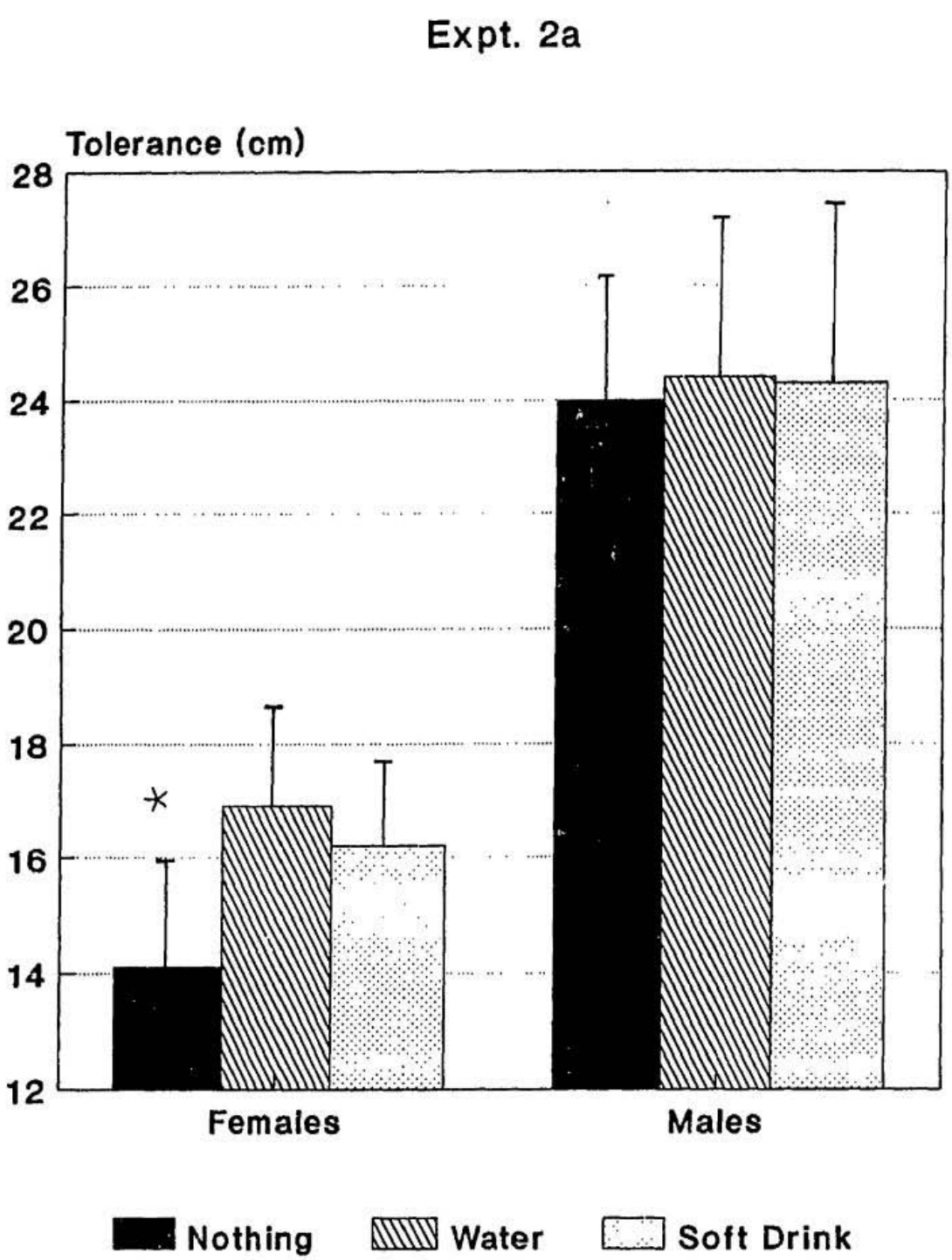

Figure 3.1.4. Post-treatment mean pain tolerances to pressure for females (n=30) and males (n=30) in each treatment group. * indicates the group that differs from the others at post-treatment.

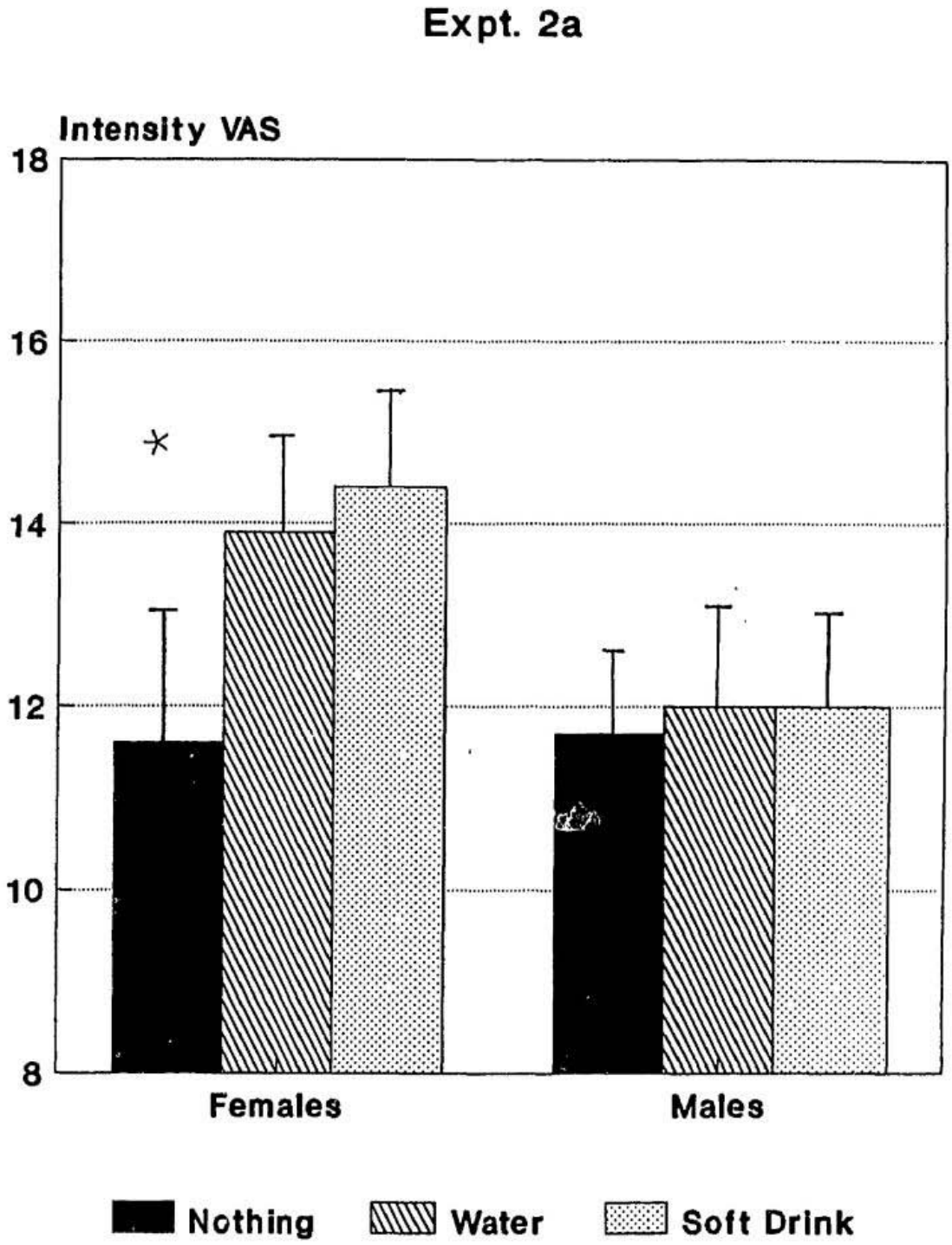

Figure 3.1.5. Post-treatment mean pain intensity ratings to pressure for females (n=30) and males (n=30) in each treatment group. * indicates the group that differs from the others at post-treatment.

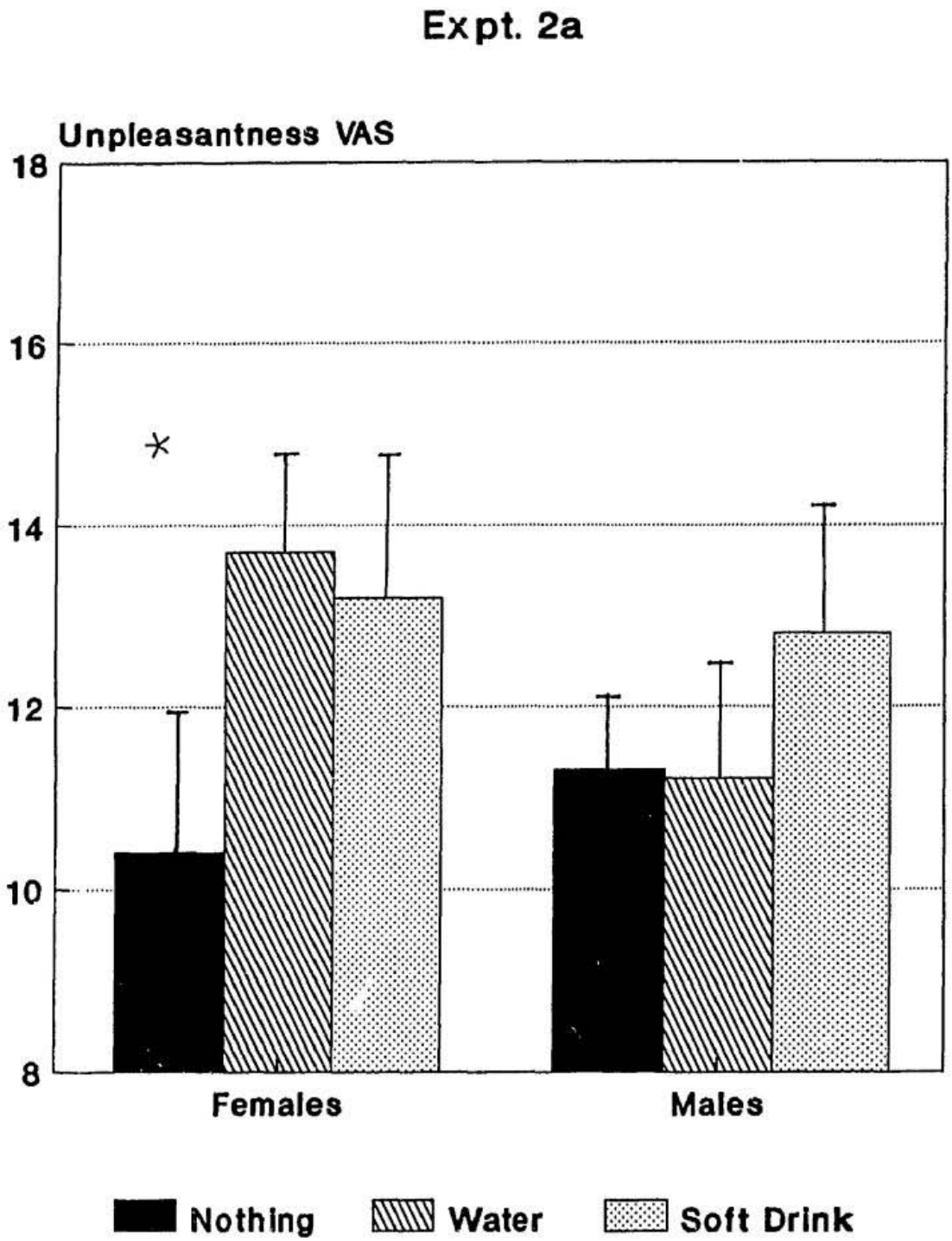

Figure 3.1.6. Post-treatment mean pain unpleasantness ratings to pressure for females (n=30) and males (n=30) in each treatment group.
* indicates the group that differs from the others at post-treatment.

0.05). In contrast, no significant group differences were found within the male data (all ps > 0.05). In summary, females who received either water or soft drink (i.e., treatment) appeared to show increased analgesia relative to those receiving nothing (i.e., no treatment).

Trial Effects.

Correlated t-tests performed on the data of subjects in the control group only (n=20) showed no significant differences between pre- and post-treatment means for any of the pain measures (all ps > 0.05). This absence of trial effects suggests that: 1) experience with the pressure pain did not change subjects' pain responsivity, and 2) stress-induced analgesia was minimal.

For both the first and second trials, 47% (14/30) of males and 10% (3/30) of females kept their fingers in the pressure algometer for the maximum amount of pressure (i.e., 1250 g, or the 25th and last division on the algometer's scale).

Soft Drink Palatability and Consumption.

Of the 10 subjects who were in the soft drink group, five chose Sprite and five chose Coke. All subjects in this group consumed at least half of the soft drink. The 10-point VAS palatability ratings of the consumed soft drinks

ranged from 1 to 10 (M = 7.1, S.E.M. = 0.51). Males (M = 7.6, S.E.M. = 0.86) and females (M = 7.0, S.E.M. = 0.62) did not differ in their palatability ratings of the soft drinks [$t(18) = 0.52$, $p = .61$].

To determine whether palatability ratings were correlated with changes (from pre- to post-treatment) in any of the pain measures, Pearson product-moment correlations were conducted. There were no significant correlations found between the palatability ratings and the pain measures for either males or females (all ps > 0.05).

Treatment and Trial Effects for Tactile Sensitivity.

Mean tactile thresholds of each group are reported in columns three and four of Table 2.6.2. Touch sensitivity did not differ among treatment groups [ANCOVA, $F(2,56) = 0.22$, $p = 0.807$] nor between trials [ANOVA, $F(1,57) = 3.13$, $p = .0822$].

Correlations Between Subject Variables and Pain Measures.

To determine whether there were any relationships between the latency pain measures (threshold and tolerance), between the VAS pain measures (intensity and unpleasantness), or between the four pain measures and each of the recorded subject variables (e.g., body weight, amount of exercise, amount and quality of sleep; see Appendix E),

Pearson product-moment correlations were conducted. Intensity and unpleasantness measures were highly correlated at pre-treatment (r = 0.63, p < 0.05) as were measures of threshold and tolerance (r = 0.71, p < 0.05). There were no significant correlations between the pain measures and any of the subject variables (all ps > 0.05).

Discussion

The results of the present experiment suggest that females who consumed soft drinks or water showed increased analgesia relative to those receiving nothing. More specifically, females who consumed soft drinks or water endured more pain (as shown by increased pain tolerances), yet rated the pain as more intense and unpleasant than they had before treatment. The somewhat paradoxical intensity and unpleasantness results may be explained in several ways. First, it may be that treatment modulates only our responsivity (e.g., tolerance) to pain but not our perception of pain (e.g., intensity and unpleasantness ratings) [see General Discussion for elaboration]. Because females left their fingers in the algometer for a longer period and therefore, withstood more pressure at post-treatment than at pre-treatment, one might expect the VAS ratings to be higher at post-treatment. Another possible explanation is that after experiencing something

pleasant, such as the taste of a soft drink, the pressure pain may be perceived more unfavourably because of a contrast effect. Given that the subjects were mildly water-deprived, consuming cold water may also have been pleasurable for the subjects. This may also explain why subjects of the water group showed increased pain tolerance at post-treatment.

Sweets (or water) did not appear to produce increased analgesia in males. However, the potential for analgesia in males may have been obscured by ceiling effects. Compared to females, males had higher baseline thresholds and tolerances, making it difficult for them to show increases in these measures following treatment. Forty-seven percent of males (including 3 of the 10 males in the sweet group), versus only 10% of females, left their fingers in the algometer for the maximum amount of pressure. Therefore, almost half of the subjects were virtually unable to show increased tolerances at post-treatment.

A second problem that makes interpretation of the results difficult is that the ratings of the soft drink palatability were not exceedingly high (**M** =7.1) and were variable (S.E.M = 0.51, range = 1-10). Many subjects in the sweet group did not find the soft drinks palatable. Only 4 of the 20 subjects gave the soft drink the maximum rating of 10. Studies suggest that it is the palatability of sweets

rather than the composition of sweets that increases opioid activity and induces analgesia (e.g., Smith et al., 1990). Therefore, it may be more advantageous for each subject to rate a number of foods prior to the laboratory session to ensure that subjects of the sweet group receive foods that taste palatable to them (see next experiment). Moreover, because there was so much variation among subjects in their ratings of the soft drinks, it may be better to choose a more commonly-liked food for the sweet condition. For example, a recent study suggests that sweet high-fat foods, such as chocolate-chip cookies, are universally regarded as highly palatable (Drewnowski, Krahn, Demitrack, Nairn, & Gosnell, 1992).

The finding that females and males differ in their reporting of pressure pain is consistent with results from previous experiments. Studies using various pressure techniques have reported that women show lower pain thresholds and/or tolerances than do men (Dubreuil & Kohn, 1986; Otto & Dougher, 1985; Woodrow, Friedman, Siegelaub, & Collen, 1972). For example, two separate pressure algometry studies found that pressure-pain thresholds (PPT) were 30-70% higher in males than in females (Brennum et al., 1989; Fischer, 1987). The present experiment found that both PPT and tolerance was 36-45% higher for males than females. These gender differences in pain sensitivity may be due to

either sensory factors or to reporting factors (see General Discussion for elaboration).

The finding that the first two fingers tested (the index and second finger) were less sensitive to pressure pain than the third and fourth fingers was an expected result (see procedure). This finding is consistent with anatomical evidence showing that the index finger is very extensively innervated and is represented in a relatively large proportion of the somatosensory cortex (Penfield & Rasmussen, 1951, cited in Kandel & Jessell, 1991). Because the index finger is so important for tactile discrimination, it likely contains very small, dense, receptive fields for touch, and therefore fewer nociceptors.

Alternatively, there may be finger differences because of the order in which the fingers were tested. The first two fingers may differ from the last two fingers because the subject was unfamiliar with the pain procedure during testing of the first fingers. If the little finger had been tested first, we may have found this finger to be less sensitive than the others. However, this explanation is unlikely because pilot work investigating these order effects demonstrated that the first and second fingers were always less sensitive than the other two fingers, regardless of the order in which they were tested.

CHAPTER 3.2: EXPERIMENT 2B

The results of Expt. 2a showed that females' perception of pain induced by finger pressure was affected by the ingestion of sweets (i.e., a soft drink), and surprisingly, by the ingestion of water as well. In an attempt to improve upon the previous experiment, and to examine further the nature of sweet-induced analgesia, the present pressure-algometry study incorporated several changes. First, because the soft drinks used in Expt. 2a did not taste palatable to all subjects, the present study used as its sweet substance, a sweet universally-liked food, namely a chocolate-chip cookie (Drewnowski et al., 1992). Note also that all subjects who ingested a cookie had rated it highly prior to the experiment. This ensured that the sweets tasted palatable to the subjects consuming them. Second, the present study used a number of foods of differing palatability which allowed us to evaluate more directly the influence of palatability on food-induced analgesia. Specifically, subjects in the different groups were given food that they previously rated as either "strongly liked" (chocolate-chip cookies), "neutral" (rice cakes), or "strongly disliked" (black olives). Finally, only females were tested in the present study. Males were not tested here because the results from the previous experiment

indicated that the pressure-algometry procedure may not be suitable for the assessment of analgesia in male subjects. In summary, the present study compared the effects of a palatable sweet food, a neutral food, and an unpalatable food on females' perception of pain induced by finger pressure.

Method

Subjects. Subjects were 40 females: 14 senior high school students participating in the Women In Science & Engineering (WISE) summer program, and 26 university students. An additional 16 subjects were tested but not included in the final sample; 12 because it was later discovered that they did not meet the experiment's criteria (e.g., they smoked, were in pain, or were not appropriately food-deprived), and 4 because they did not follow proper procedural instructions (e.g., they did not say "pain" or "stop" during the pre- or post-treatment trials).

Apparatus. The apparatus (the pressure algometer and von Frey fibers) was the same as in Expt. 2a. The foods consumed by the subjects in the three treatment groups were a Mr. Christie Chunky Chips Ahoy cookie (palatable group), a bottled Gattuso black olive (unpalatable group), or a Dominion generic brand rice cake (neutral group).

Procedure. In a group session, which occurred

approximately one week prior to the individual laboratory sessions, the subjects were shown 30 slides of different food types and were asked to rate each of these foods on 10-point VASs. The endpoints of the VASs were labelled "Strongly Dislike" and "Strongly Like". Based on their palatability VAS ratings, they were then assigned to one of three treatment groups: "unpalatable" (those who gave the black olives a VAS rating of 1 or 2), "neutral" (VAS ratings of 4-6 for the rice cakes), "palatable" (VAS ratings of 8-10 for the chocolate-chip cookies). Subjects who satisfied none of these criteria were placed in the nothing (control) group. The remainder of the experiment proceeded exactly as in Experiment 2a with the exception that two different experimenters were used in the present study. One experimenter (Experimenter 1), a senior high school student, tested the 14 high school students, and the other experimenter (Experimenter 2), the present author, tested the 26 university students.

Results

Baseline Comparisons.

Treatment Group Differences. Table 3.2.1 shows for each group the pre-treatment means for each pain measure. One-way ANOVAs revealed no significant differences among the four groups at pre-treatment for pain threshold, pain

tolerance, or for VAS ratings of pain intensity and unpleasantness (all ps > 0.05).

Insert Table 3.2.1 about here

Finger Differences. Mean threshold and tolerance for each finger were compared for subjects in the control group only (n = 10),. Figures 3.2.1 and 3.2.2 depict the means of the pre- and post-treatment trials across each finger for threshold and tolerance, respectively. Two-way ANOVAs [4(Finger) x 2 (Trial)] showed finger differences for mean tolerance [$F(3,24) = 4.69$, $p = 0.01$], but not for mean threshold ($F(3,24) = 0.21$, $p = .89$]. Post-hoc multiple comparisons showed that mean tolerance for the first finger was significantly higher than mean tolerances for each of the other three fingers [Newman-Keuls, $p < 0.05$].

Insert Figures 3.2.1 and 3.2.2 about here

Treatment Effects on Pain Perception.

Because the first finger appears to be less sensitive than the other three fingers, between-groups analyses were performed on the data from the second, third, and fourth fingers only.

Table 3.2.1

Experiment 2b: Pre-treatment and ANCOVA Adjusted Post-treatment Means (and Standard Errors) for **Females** (n=40) in each Treatment Group.

Group	Pre-treatment Measures				Post-treatment Measures			
	Thr (cm)	Tol (cm)	Int	Unp	Thr (cm)	Tol (cm)	Int	Unp[1]
Nothing	11.1 (1.2)	18.2 (2.0)	12.7 (1.1)	12.1 (1.6)	9.9 (1.2)	16.5 (1.9)	14.0 (1.3)	14.2 (1.4)
Unpalat	10.6 (1.1)	18.4 (1.4)	13.9 (1.0)	13.7 (0.8)	10.3 (1.1)	16.7 (1.6)	14.1 (0.7)	12.6 (0.9)
Neutral	10.6 (0.9)	17.2 (1.1)	12.9 (1.1)	11.8 (1.3)	9.9 (1.0)	17.2 (1.2)	13.2 (1.2)	13.2 (1.6)
Palatab	10.8 (1.5)	18.5 (2.2)	14.4 (1.2)	13.3 (1.2)	11.8 (1.4)	**19.1** (2.4)	15.4 (1.0)	14.6 (1.3)
Grand Mean	10.8 (0.6)	18.0 (0.8)	13.5 (0.5)	12.7 (0.6)	10.4 (0.6)	17.4 (0.9)	14.2 (0.5)	13.7 (0.7)

Bold-faced #s = Group which differs from the other groups in that column ($p < .05$).

[1] Thr = Threshold, Tol = Tolerance, Int = Intensity, Unp = Unpleasantness

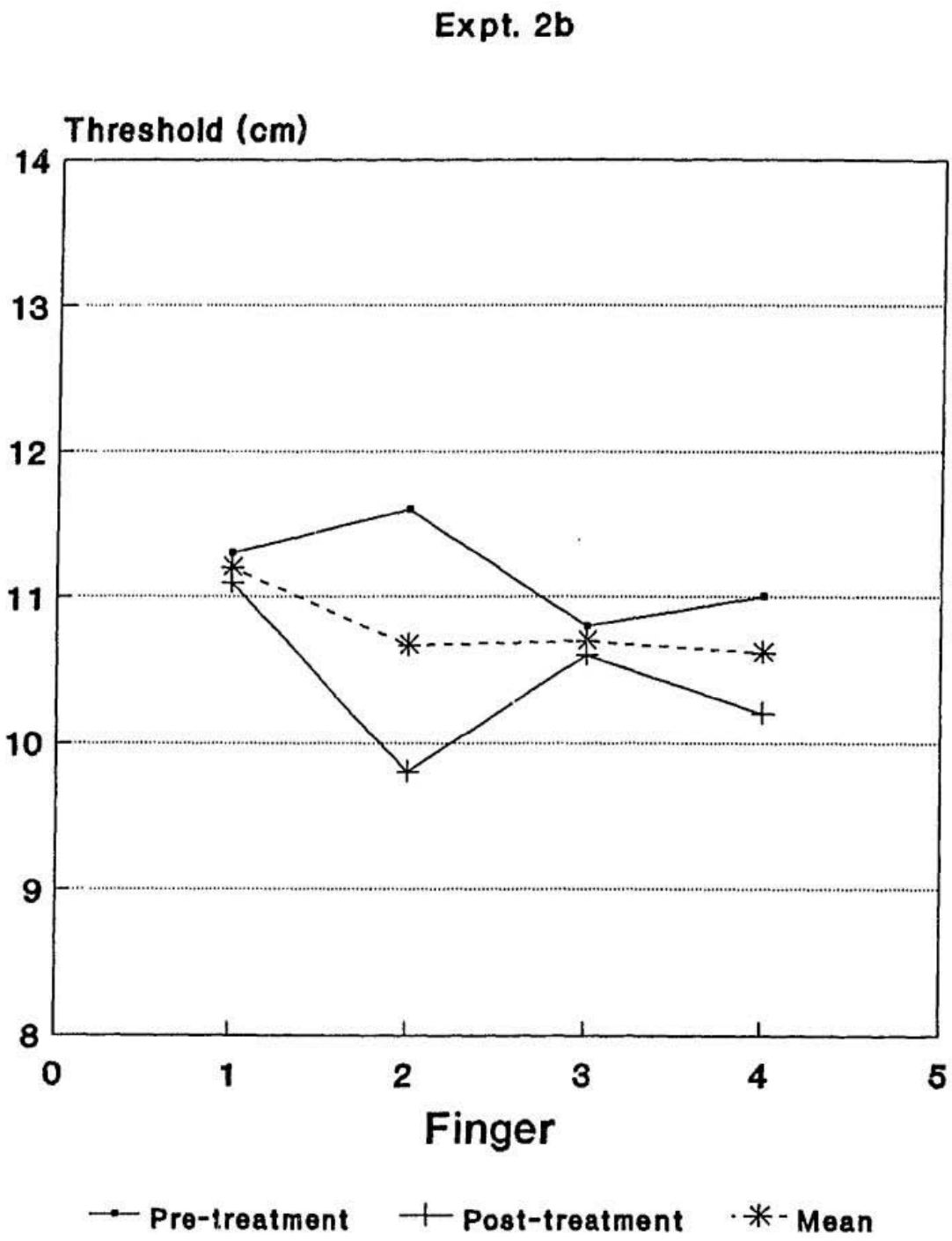

Figure 3.2.1. Mean pain thresholds to pressure for each **finger** at pre- and post-treatment for **females** (n=10) in the nothing group only. Note that the dashed line represents the mean of the two trials.

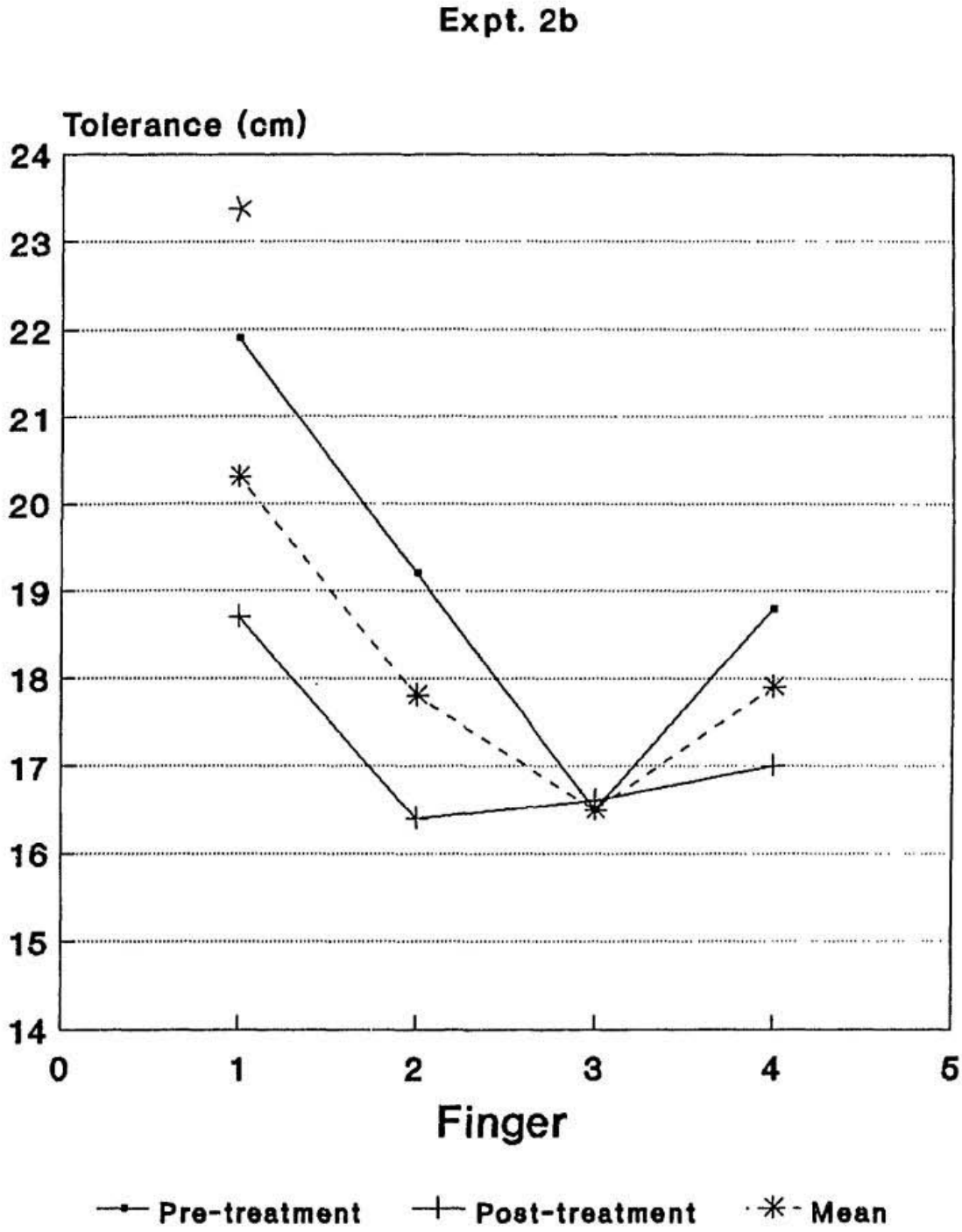

Figure 3.2.2. Mean pain tolerances to pressure for each finger at pre- and post-treatment for females (n=10) in the nothing group only. Note that the dashed line represents the mean of the two trials. * indicates the finger which differs from the other fingers.

Figures 3.2.3 to 3.2.6 plot the adjusted post-treatment

Insert Figures 3.2.3 to 3.2.6 about here

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means for each of the four pain measures. One-way ANCOVAs revealed significant group differences for mean tolerance [$F(3,35) = 3.25$, $p = .0332$] only. Newman-Keuls analyses revealed that post-treatment mean tolerance of the palatable sweet group differed significantly from those of the other three groups ($p < .05$). Groups did not differ on mean threshold, or on intensity and unpleasantness ratings (all $ps > .05$). Thus, compared to the unpalatable food, neutral food, or nothing, the sweet palatable food produced increased pain tolerance.

Trial Effects.

To analyze for stress-induced analgesia, the control group's (n=10) pre- and post-treatment means were compared for each pain measure. Correlated t-tests revealed significant trial effects for both intensity [$t(9) = -2.45$, $p = .037$] and unpleasantness [$t(9) = -3.54$, $p = .006$] VAS ratings. However, both intensity and unpleasantness increased from pre-treatment ($M_{int} = 12.7$; $M_{unp} = 12.1$) to post-treatment ($M_{int} = 13.5$; $M_{unp} = 13.7$), contrary to that expected for an influence of stress-induced analgesia.

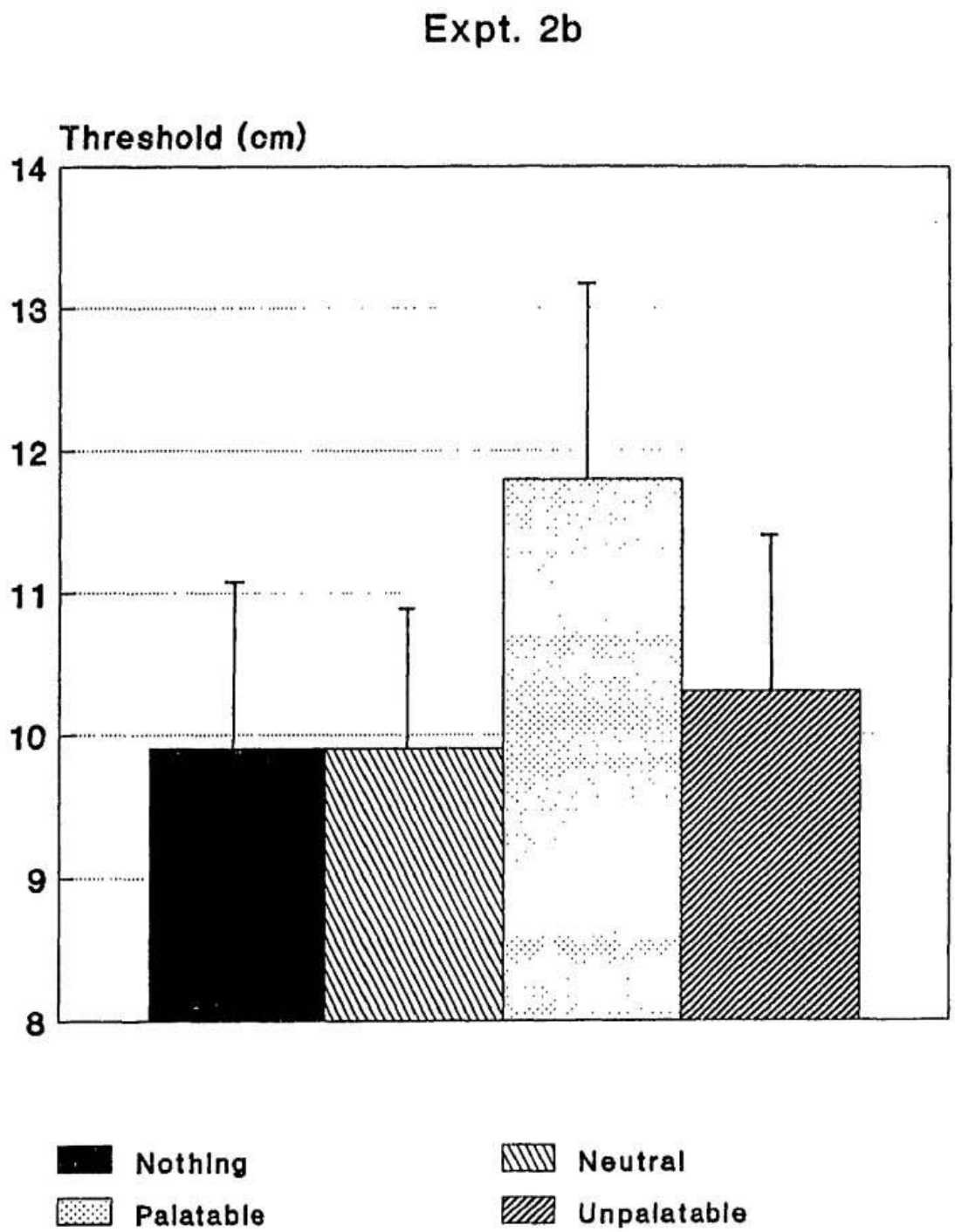

Figure 3.2.3. Post-treatment mean pain thresholds to pressure for females (n=40) in each treatment group.

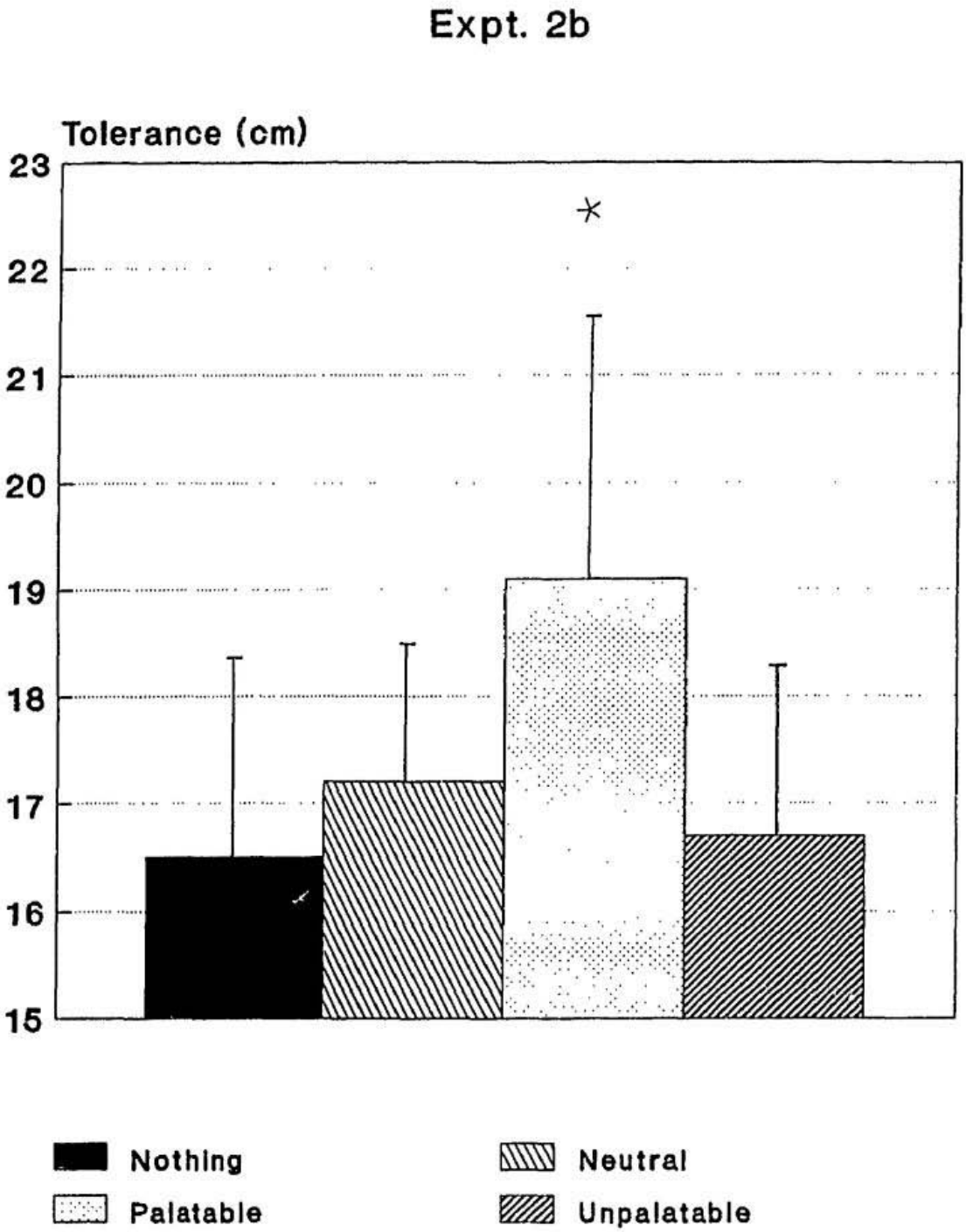

Figure 3.2.4. Post-treatment mean pain tolerances to pressure for **females** (n=40) in each treatment group. * indicates the group that differs from the others at post-treatment.

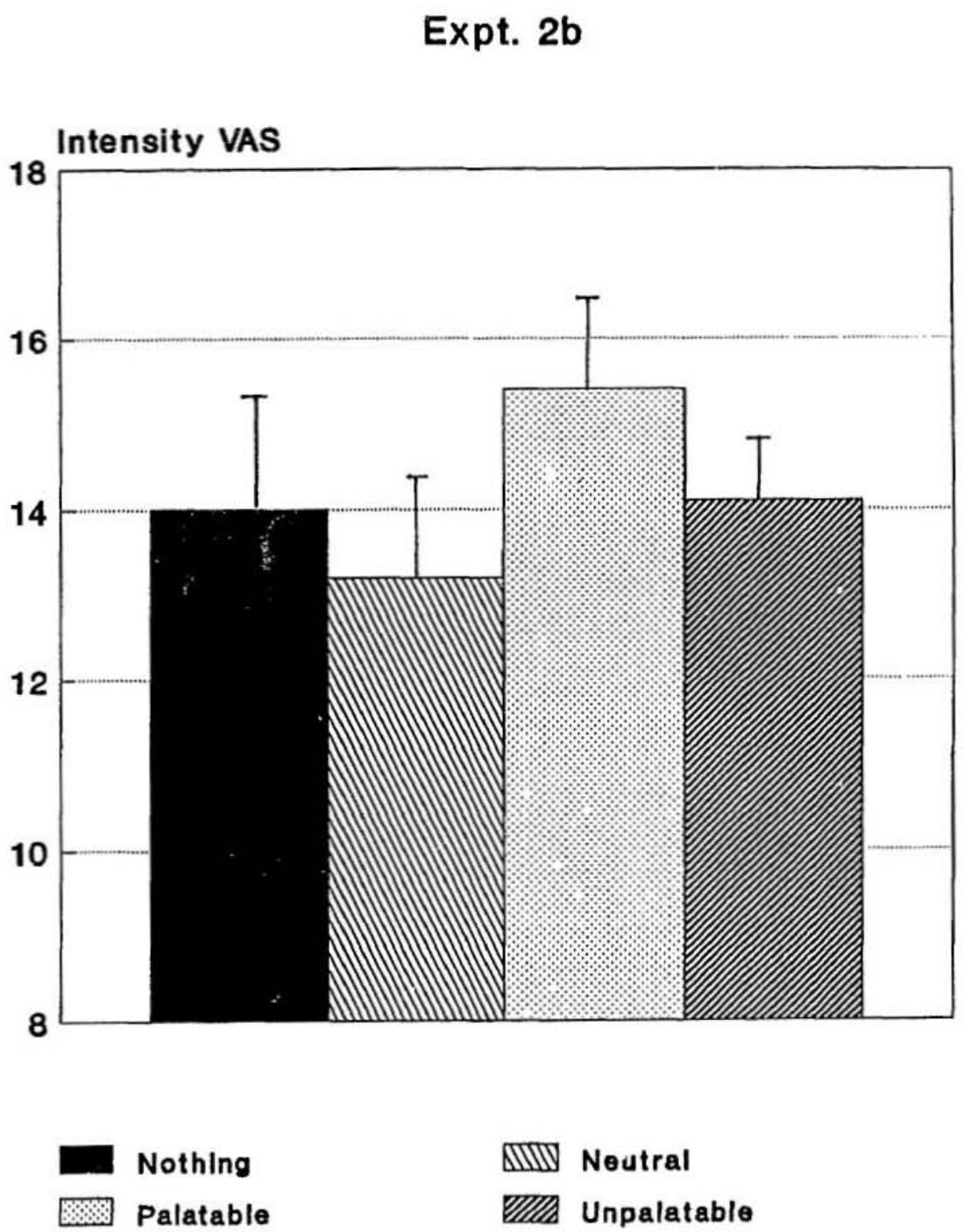

Figure 3.2.5. Post-treatment mean pain intensity ratings to pressure for **females** (n=40) in each treatment group.

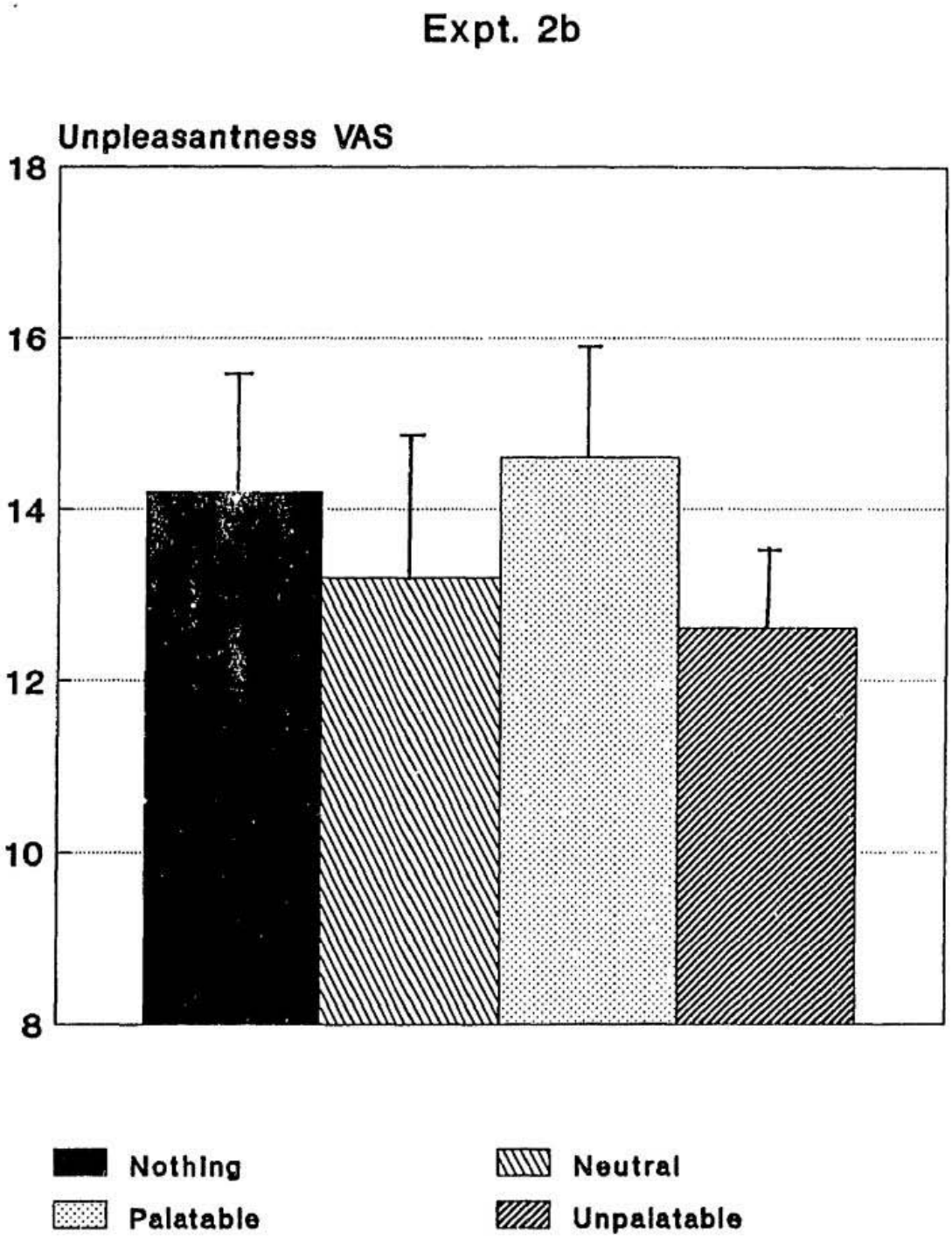

Figure 3.2.6. Post-treatment mean pain unpleasantness ratings to pressure for **females** (n=40) in each treatment group.

At pre- and post-treatment respectively, the percentages of subjects who withstood the maximum amount of pressure (i.e., 1250 g) were 27.5% and 12.5% for the first finger, 15% and 5% for the second, 7.5% and 7.5% for the third, and 12.5% and 7.5% for the fourth finger.

Food Palatability.

Following consumption, the mean VAS rating for each of the treatment foods was 8.75 (S.E.M. = 0.35, range = 7-10) for the cookies, 4.90 (S.E.M. = 0.52, range = 3-8) for the rice cakes, and 0.25 (S.E.M. = 0.20, range = 0-2) for the black olives. These group differences in mean palatability ratings were highly significant (ANCOVA, $F(2,27) = 123.36$, $p < .0001$] with each group differing from all other groups (Newman-Keuls, $p < .05$).

Pearson product-moment correlations revealed that palatability ratings were positively correlated with changes (post-treatment minus pre-treatment) in pain tolerance (Pearson's $r = 0.43$, $p < 0.05$), but not with changes in any of the other pain measures (all $ps > 0.05$).

Treatment and Trial Effects for Tactile Sensitivity

The mean pre- and post-treatment tactile thresholds of each group are displayed in columns five and six of Table 2.6.2. There were no significant group differences in

tactile thresholds [ANCOVA, $F(3,35) = 1.98$, $p = .135$]. There was a significant trial effect [ANOVA, $F(1,36) = 7.83$, $p = .008$], with all groups displaying a decrease in sensitivity from pre- ($M_{pre} = 3.18$) to post-treatment ($M_{post} = 3.27$). Note that in this experiment, unlike the others in this thesis, two experimenters were used. An Experimenter X Trial ANOVA for repeated measures of the tactile thresholds revealed an Experimenter effect [$F(1,38) = 6.91$, $p = .012$], with Experimenter 1 showing larger mean trial differences than Experimenter 2 (E1 = -.20, E2 = -.03). Moreover, by omitting the data ($n = 14/40$) of Experimenter 1 (who was the more inexperienced tester), an ANOVA for repeated measures did not reveal a trial effect for tactile thresholds [$F(1,22) = 1.12$, $p = 0.30$]. (Note that an Experimenter effect was not found for any of the pain measures.)

Correlations Between Subject Variables and Pain Measures.

To determine whether there were any relationships between the latency pain measures, between the VAS pain measures, or between the four pain measures and each of the subject variables recorded (e.g., body weight, amount of exercise, amount of sleep), Pearson product-moment correlations were conducted. Intensity and unpleasantness measures were highly correlated at pre-treatment ($r = 0.57$, $p < 0.05$) as were measures of threshold and tolerance ($r =$

0.87, $p < 0.05$). There were no significant correlations between the pain measures and any of the subject variables (all $ps > 0.05$).

Discussion

The results of the present pressure experiment indicate that the ingestion of a palatable sweet food (a cookie) produced increased analgesia relative to the consumption of a neutral food, an unpalatable food, or nothing. Females who consumed sweets showed increased pain tolerance at post-treatment compared to females consuming an unpalatable food, a neutral food, or nothing. These results more strongly support the possibility of human sweet-induced analgesia than did the results of the previous pressure experiment (Expt. 2a). Here, only the sweet palatable food influenced analgesia whereas, in Expt. 2a, both water and sweet soft drink (both of which were relatively palatable) produced analgesia. Moreover, in the present study, palatability ratings were positively correlated with changes in pain tolerance from pre-to post-treatment. Collectively, these findings implicate the importance of palatability in producing sweet-induced analgesia.

The finding that sweet intake produced analgesia to pressure pain is consistent with the results of Expt. 2a. However, in both pressure experiments, only on the tolerance measure did subjects show evidence of analgesia. One

explanation as to why the other pain measures did not reveal analgesia may be that sweet-induced opioid modulation affects certain aspects of the pain experience (e.g., pain responsivity, or cognitive-affective dimensions of pain) more than others aspects (e.g., pain perception, or sensory-discriminative dimensions of pain). This explanation will be elaborated in the General Discussion in light of the findings from all of the experiments.

A second reason why sweet ingestion influenced only pain tolerance scores may be that the analgesic effects of sweets were not robust enough. Perhaps sweets' analgesic effects were limited or attenuated because the cookies did not taste very palatable to the subjects during testing (mean VAS rating = 8.75), even though subjects had earlier rated the picture of the cookies very highly (mean VAS rating = 10). To increase the palatability of the sweet food at the time of testing, maybe the subjects should have abstained from food (especially sweets) for a longer period (e.g., for 2 hours rather than 1 hour) prior to the laboratory session.

In summary, the collective results of the present study and Expt. 2a indicate that sweet-induced analgesia can be demonstrated in human adults, at least in females. Moreover, the results also imply that palatability may be a critical factor in mediating sweet-induced analgesia.

CHAPTER 3.3: EXPERIMENT 2C

The results of the two previous pressure experiments suggest that sweet consumption produces increased analgesia in females, and that palatability plays an important role. Moreover, of the four pain measures, pain tolerance appears to be the most sensitive to the analgesic effects of sweets. To replicate and extend the findings of Expt. 2b, the present experiment will repeat Expt. 2b, testing males as well as females.

Method

Subjects. Forty (20 male and 20 female) university students served as subjects. An additional 9 subjects were tested but not included in the final sample; 8 because it was later discovered that they did not meet the experiment's criteria (e.g., they smoked, were in pain, or were not appropriately food-deprived), and 1 because he did not follow proper procedural instructions (e.g., he did not say either "pain" or "stop" at the appropriate time during either the familiarization, pre-treatment or post-treatment trial).

Apparatus. The apparatus (the pressure algometer and von Frey fibers) and the treatment foods were the same as described in Expt. 2a.

Procedure. The procedure was similar to that of Experiment 2b with a few exceptions. First, another trial (called the familiarization trial) was added before any testing began. One possible weakness of the previous studies was that subjects were not given an opportunity to become familiar with the pain procedure prior to the first test trial. This may account for the trial effects found within subjects of the control (nothing) group. In other words, the measurements taken at pre-treatment may have been less than accurate because the subjects were not given a practice trial beforehand, in which they were exposed to the pressure in order to "get a feel" for the procedure. The addition of the familiarization trial may also serve to reduce the number of subjects eliminated due to procedural errors, and to perhaps better analyze for the potential effects of stress-induced analgesia.

Second, the period of deprivation prior to the laboratory session was increased from 1 to 2 hours. A two-hour deprivation period was chosen to increase (presumably) the palatability of the cookies, and to better ensure that subjects did not consume any sweets immediately prior to the experiment. A deprivation period longer than 2 hours was not chosen because previous research has shown that longer periods of food deprivation increase opioid (especially beta-endorphin) activity in the brain and pituitary of rats

(Bodnar et al., 1978; Gambert et al., 1980; Majeed et al., 1986; Przewlocki et al., 1983; Reid et al., 1982; Vaswani & Tejwani, 1986). Therefore, extensive food deprivation on its own can produce analgesia. To help determine the subjects' levels of hunger prior to treatment, and to separate the analgesic effects of sweets from those of food-deprivation, at the beginning of the laboratory session, subjects rated their current level of hunger using a 10-point VAS with the endpoints labelled "extremely hungry" and "not hungry at all".

Third, unlike Expt. 2b in which the experimenter met with the subjects prior to the laboratory session, the only pre-experiment contact in the present study was via the telephone. The experimenter listed the 10 foods over the phone and asked each subject to rate these foods on a scale of 1 to 10, as opposed to asking subjects to rate the color slides of 30 foods with VASs. Finally, subjects were asked to rate the intensity and unpleasantness of the pressure pain for each of the four fingers rather than for the last finger only.

Results

Baseline Comparisons.

Treatment Group Differences. Tables 3.3.1 (females) and 3.3.2 (males) report for each group, the pre-treatment

means for each pain measure. One-way ANOVAs revealed no

Insert Tables 3.3.1 and 3.3.2 about here

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significant differences between groups at pre-treatment for pain threshold, pain tolerance, or for VAS ratings of intensity and unpleasantness (all *p*s > 0.05).

Gender Differences. To determine whether males and females differed in their reporting of pain and touch, one-way ANOVAs were performed on the pre-treatment means for each pain measure and for tactile thresholds (see Tables 3.3.1 and 3.3.2 for pre-treatment means). Significant Gender differences were found for pre-treatment threshold [$F(1,38) = 10.72$, $p = .002$], tolerance [$F(1,38) = 19.37$, $p = .001$], intensity ratings [$F(1,38) = 7.76$, $p = .008$], and tactile thresholds [$F(1,32) = 5.17$, $p = .030$], with females showing greater sensitivity to pressure pain and to touch. In other words, compared to males, females reported pain earlier (as indicated by lower thresholds), showed lower pain endurance (as indicated by lower tolerances), but rated the pain as less intense. Genders did not differ on their ratings of unpleasantness (ANOVA, $F(1,38) = 0.71$, $p = .406$).

Finger Differences. For each pain measure, the means for each finger were compared for subjects in the control group only ($n = 10$). Figures 3.3.1 to 3.3.4 depict the

Table 3.3.1

Experiment 2c: Pre-treatment and ANCOVA Adjusted Post-treatment Means (and Standard Errors) for **Females** (n=20) in each Treatment Group.

Group	Pre-treatment Measures				Post-treatment Measures			
	Thr (cm)	Tol (cm)	Int	Unp	Thr (cm)	Tol (cm)	Int	Unp[1]
Nothing	10.4 (0.8)	15.6 (1.6)	11.7 (0.7)	10.0 (1.9)	8.9 (1.1)	14.4 (1.0)	12.3 (0.7)	10.6 (1.9)
Unpalat	9.2 (1.3)	12.8 (1.5)	12.? (1.3)	12.3 (1.4)	10.4 (1.9)	14.8 (2.0)	12.2 (1.3)	12.4 (1.9)
Neutral	12.0 (1.8)	18.1 (2.2)	11.1 (1.2)	12.7 (1.0)	9.6 (1.2)	15.4 (2.4)	11.0 (0.8)	10.7 (1.9)
Palatab	7.4 (1.3)	11.9 (1.2)	9.0 (2.1)	9.2 (2.1)	9.9 (1.5)	14.7 (1.6)	11.3 (1.8)	11.7 (2.1)
Grand Mean	9.7 (0.7)	14.8 (0.9)	11.0 (0.7)	11.0 (0.8)	9.7 (0.7)	14.8 (1.0)	11.7 (0.6)	11.4 (0.9)

[1] Thr = Threshold, Tol = Tolerance, Int = Intensity, Unp = Unpleasantness

Table 3.3.2

Experiment 2c: Pre-treatment and ANCOVA Adjusted Post-treatment Means (and Standard Errors) for **Males** (n=20) in each Treatment Group.

Group	Pre-treatment Measures				Post-treatment Measures			
	Thr (cm)	Tol (cm)	Int	Unp	Thr (cm)	Tol (cm)	Int	Unp[1]
Nothing	15.7 (2.4)	24.8 (3.0)	14.0 (0.8)	12.9 (2.2)	14.6 (2.5)	22.6 (2.1)	14.1 (1.2)	11.1 (1.9)
Unpalat	14.0 (1.4)	22.7 (3.0)	13.4 (0.6)	12.4 (1.0)	14.5 (1.7)	23.0 (3.6)	13.6 (0.5)	13.0 (1.0)
Neutral	12.1 (2.6)	23.0 (2.8)	13.0 (1.4)	11.9 (1.5)	12.8 (2.6)	20.9 (2.4)	13.8 (1.0)	12.5 (1.5)
Palatab	13.2 (1.9)	17.3 (1.3)	13.6 (1.6)	11.4 (1.4)	14.8 (2.4)	22.3 (1.6)	14.3 (1.6)	13.9 (1.6)
Grand Mean	13.8 (1.0)	22.0 (1.4)	13.5 (0.5)	12.1 (0.7)	14.2 (1.2)	22.2 (1.3)	13.9 (0.5)	12.6 (0.7)

[1] Thr = Threshold, Tol = Tolerance, Int = Intensity, Unp = Unpleasantness

means of the familiarization, pre-, and post-treatment trials across each finger for threshold, tolerance, intensity, and unpleasantness, respectively. Two-way ANOVAs [4(Finger) x 3 (Trial)] revealed finger differences for measures of pain tolerance, [$F(3,21) = 11.54$, $p = .0001$], intensity [$F(3,21) = 6.30$, $p = .003$] and unpleasantness [$F(3,21) = 6.41$, $p = .003$], but not for threshold [$F(3,21) = 1.78$, $p = .18$]. For tolerance, intensity, and unpleasantness, Finger 1 (the index finger) was significantly less sensitive than Fingers 2, 3, and 4 (Newman-Keuls, all $ps < 0.05$).

Insert Figures 3.3.1 to 3.3.4 about here

Treatment Effects on Pain Perception.

Because the index finger appeared less sensitive to pain than the other three fingers for three of the four pain measures, the between-groups analyses were performed on the combined data from the second, third, and fourth fingers only. Moreover, because of gender differences in pain sensitivity (see above), the data of males and females were analyzed separately.

The adjusted post-treatment means for each pain measure and gender are shown in Figures 3.3.5 to 3.3.8. One-way

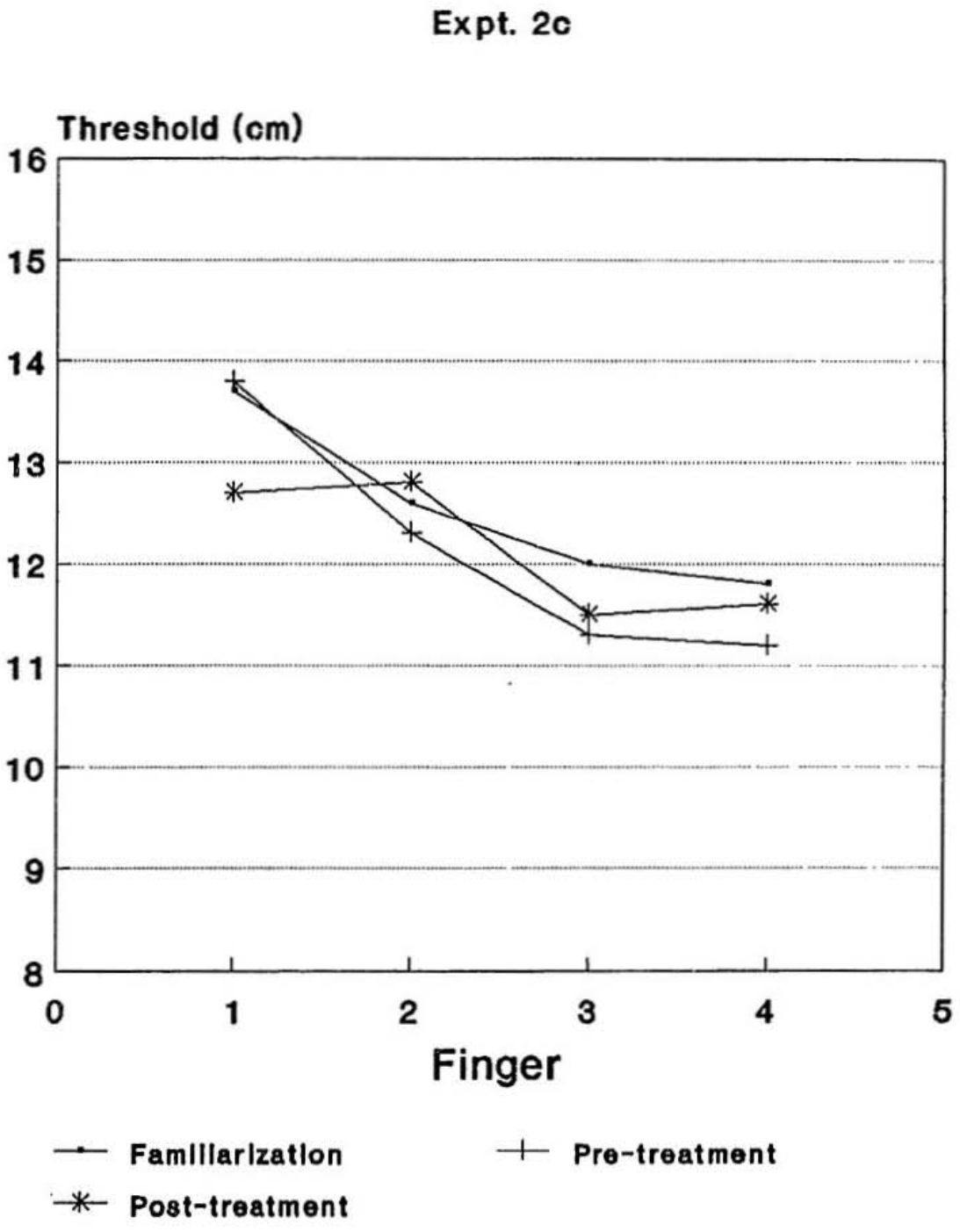

Figure 3.3.1. Mean pain thresholds to pressure for each finger at familiarization, pre-, and post-treatment for subjects (n=10) of the nothing group only.

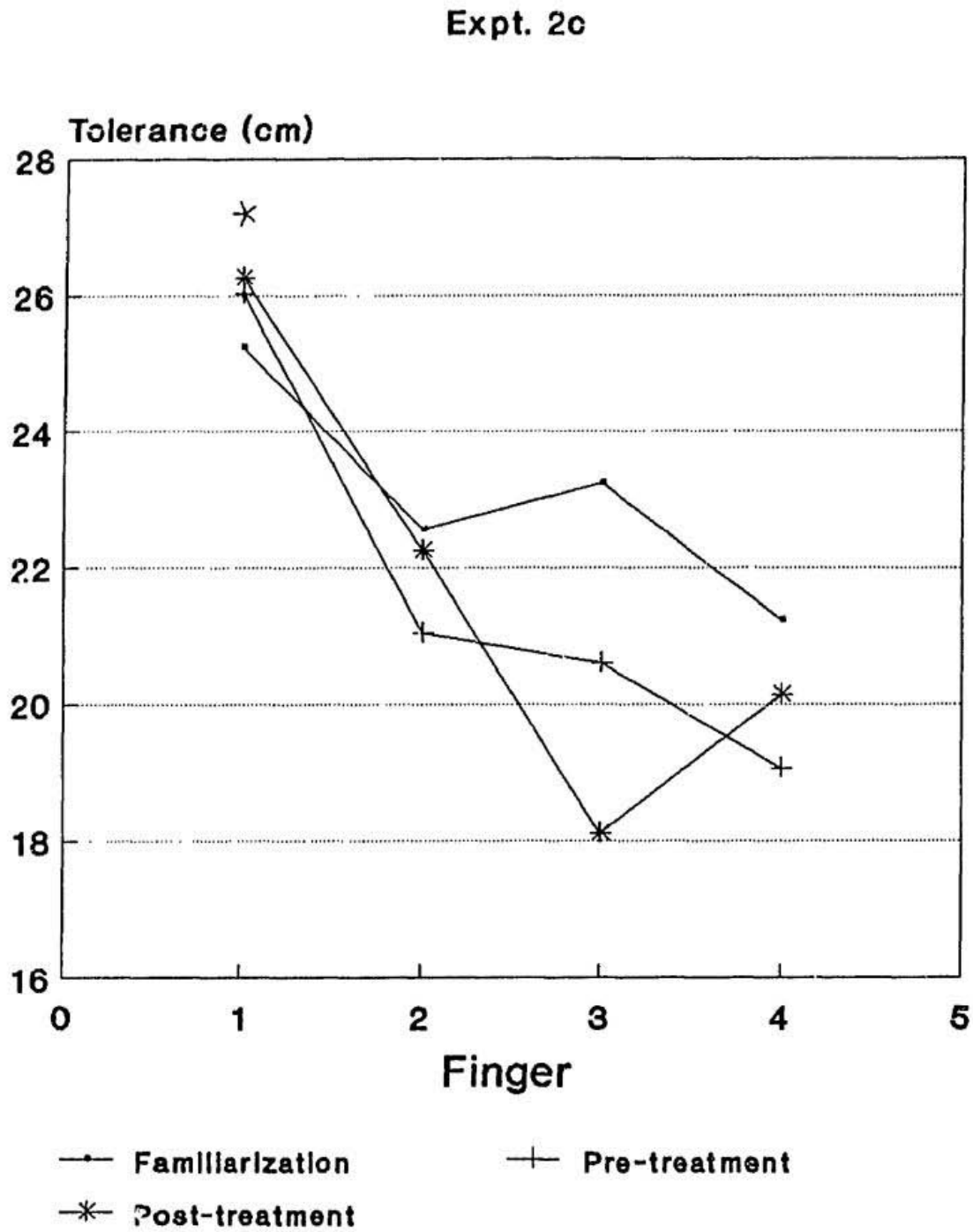

Figure 3.3.2. Mean pain tolerances to pressure for each finger at familiarization, pre-, and post-treatment for subjects (n=10) of the nothing group only. * indicates the finger which differs from the other fingers.

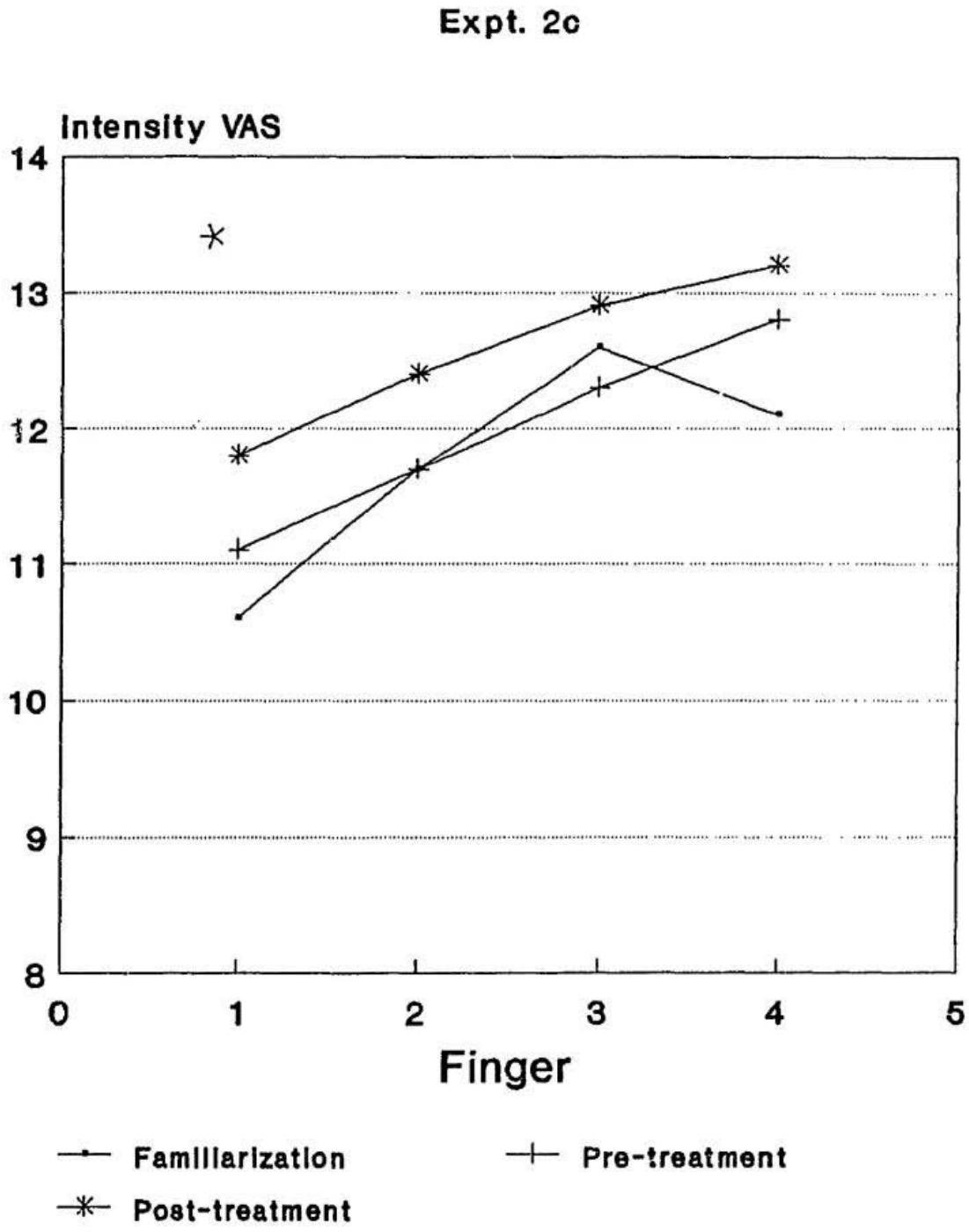

Figure 3.3.3. Mean pain intensity ratings to pressure for each **finger** at familiarization, pre-, and post-treatment for subjects (n=10) of the nothing group only. * indicates the finger which differs from the other fingers.

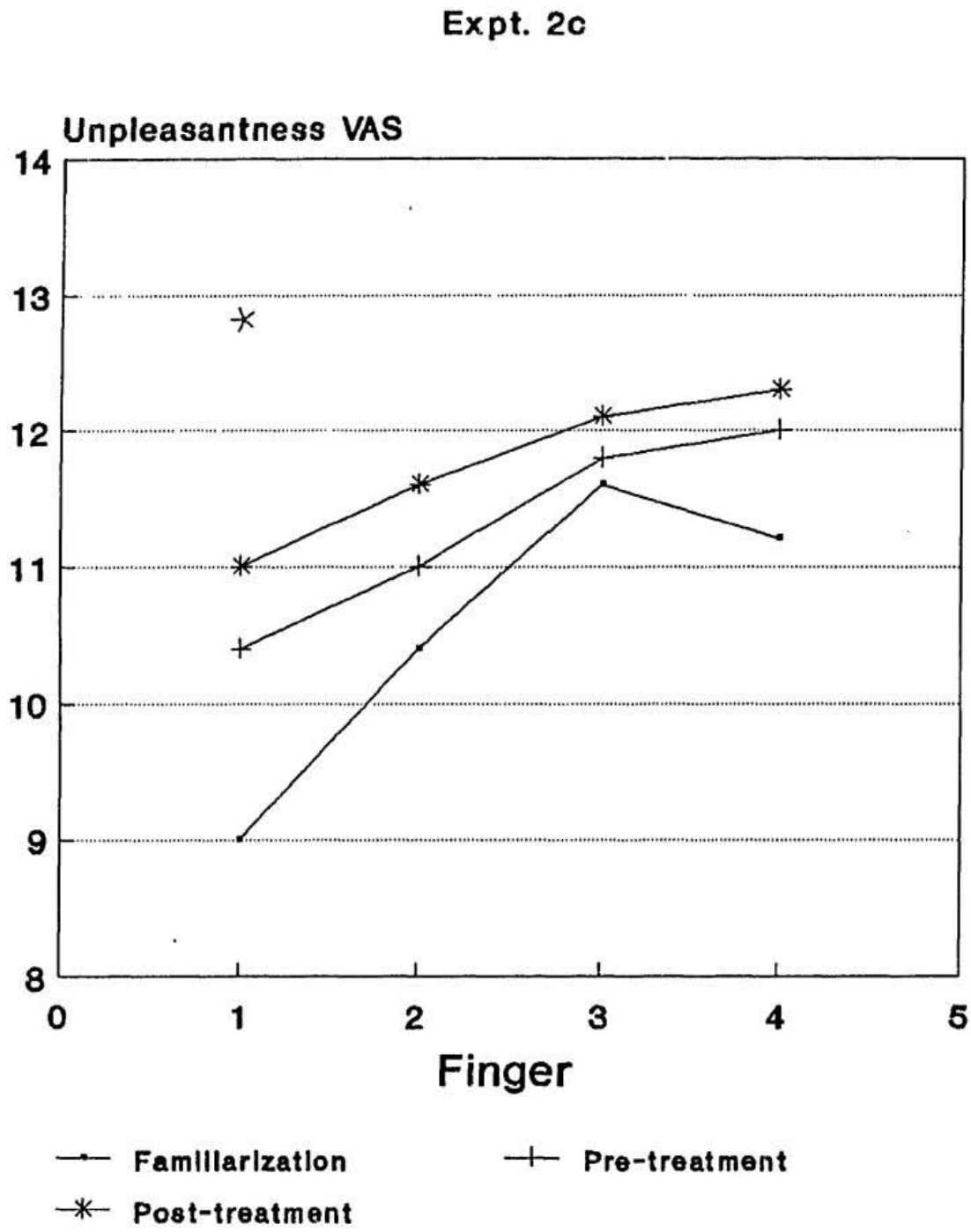

Figure 3.3.4. Mean pain unpleasantness ratings to pressure for each finger at familiarization, pre-, and post-treatment for subjects (n=10) of the nothing group only. * indicates the finger which differs from the other fingers.

ANCOVAs found no significant group effects for any of the pain measures for males or females (all ps > 0.05).

Insert Figures 3.3.5 to 3.3.8 about here

Trial Effects.

To analyze for stress-induced analgesia, two different analyses were performed. First, the familiarization and pre-treatment means, collapsed across groups, were compared with two-way ANOVAs [2 (Trial) x 2 (Gender)]. Significant trial effects were found for measures of tolerance [$F(1,38) = 7.24$, $p = 0.011$] and unpleasantness [$F(1,38) = 6.32$, $p = .016$]. However, mean tolerance decreased from familiarization (M = 20.9 cm) to pre-treatment (M = 19.4 cm,) and mean unpleasantness VAS ratings increased from familiarization (M = 10.6) to pre-treatment (M = 11.3), results contrary to that expected for an influence of stress-induced analgesia. A Trial x Gender interaction was found for unpleasantness ratings [$F(1,38) = 4.31$, $p = .045$] with males displaying increased ratings ($M_{fam} = 10.4$, $M_{pre} = 11.8$) between trials and females showing little change ($M_{fam} = 10.7$, $M_{pre} = 10.8$). This finding suggests that for males, but not for females, experience with the pressure pain at familiarization may have changed males' responsivity to pain

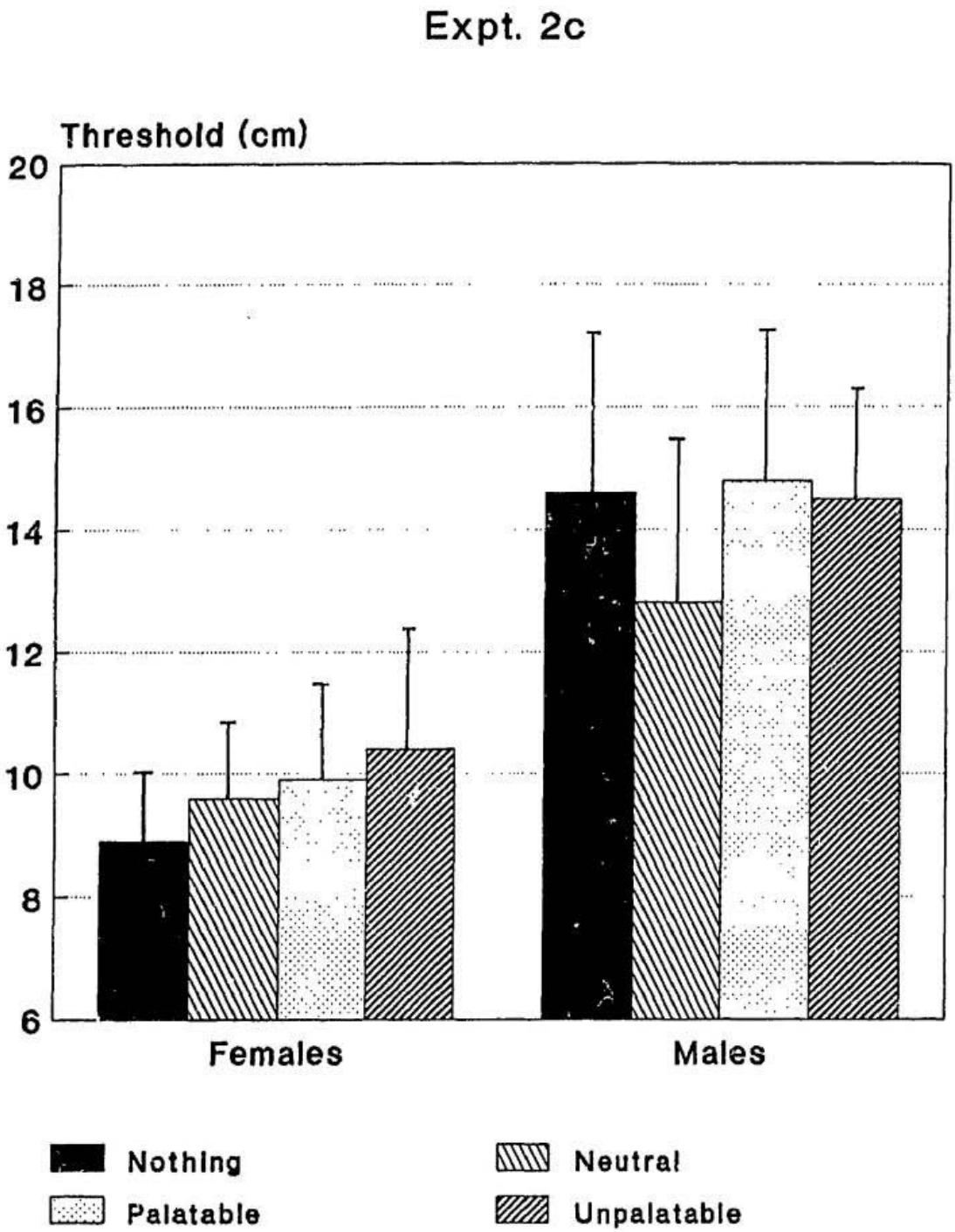

Figure 3.3.5. Post-treatment mean pain thresholds to pressure for females (n=20) and males (n=20) in each treatment group.

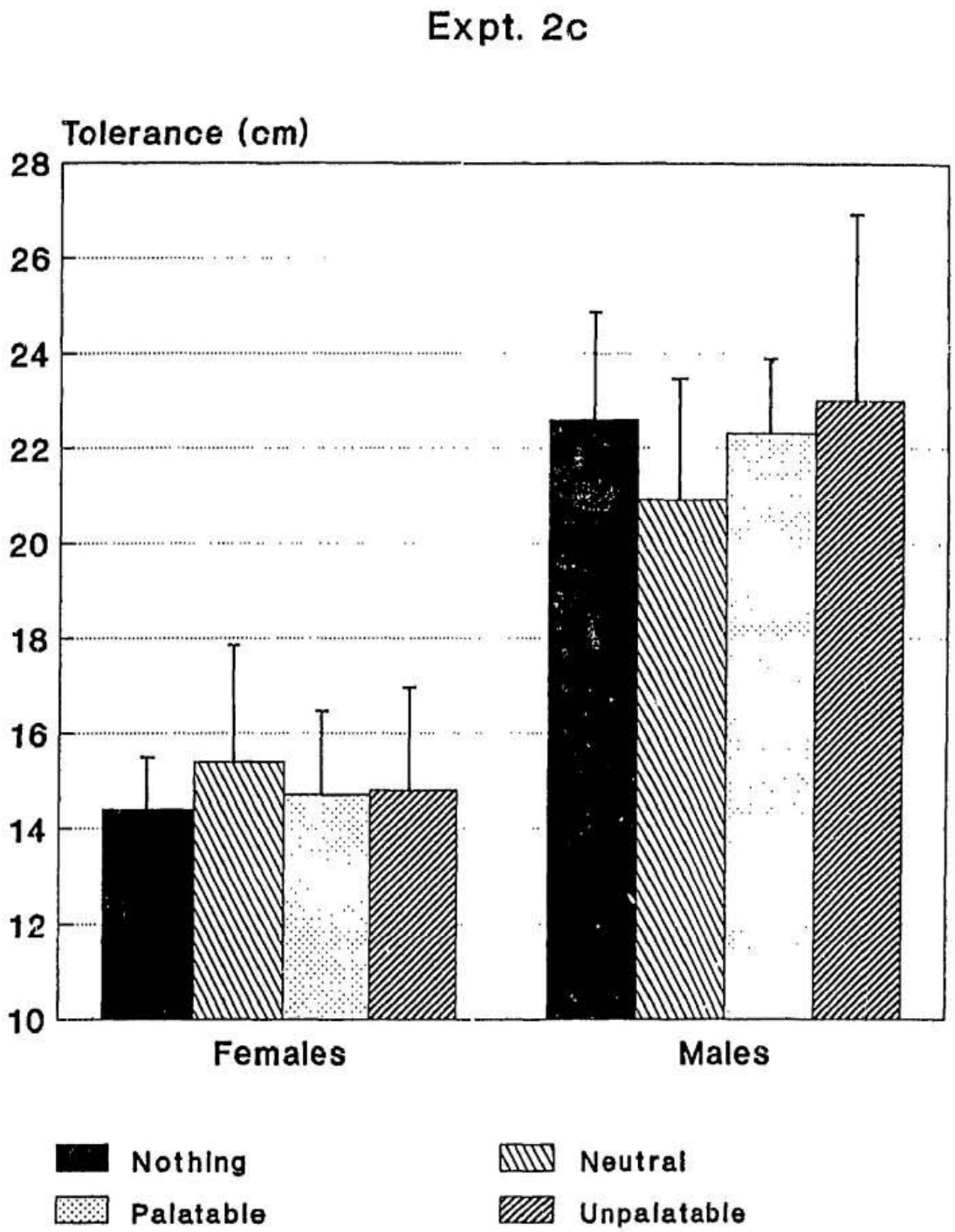

Figure 3.3.6. Post-treatment mean pain tolerances to pressure for females (n=20) and males (n=20) in each treatment group.

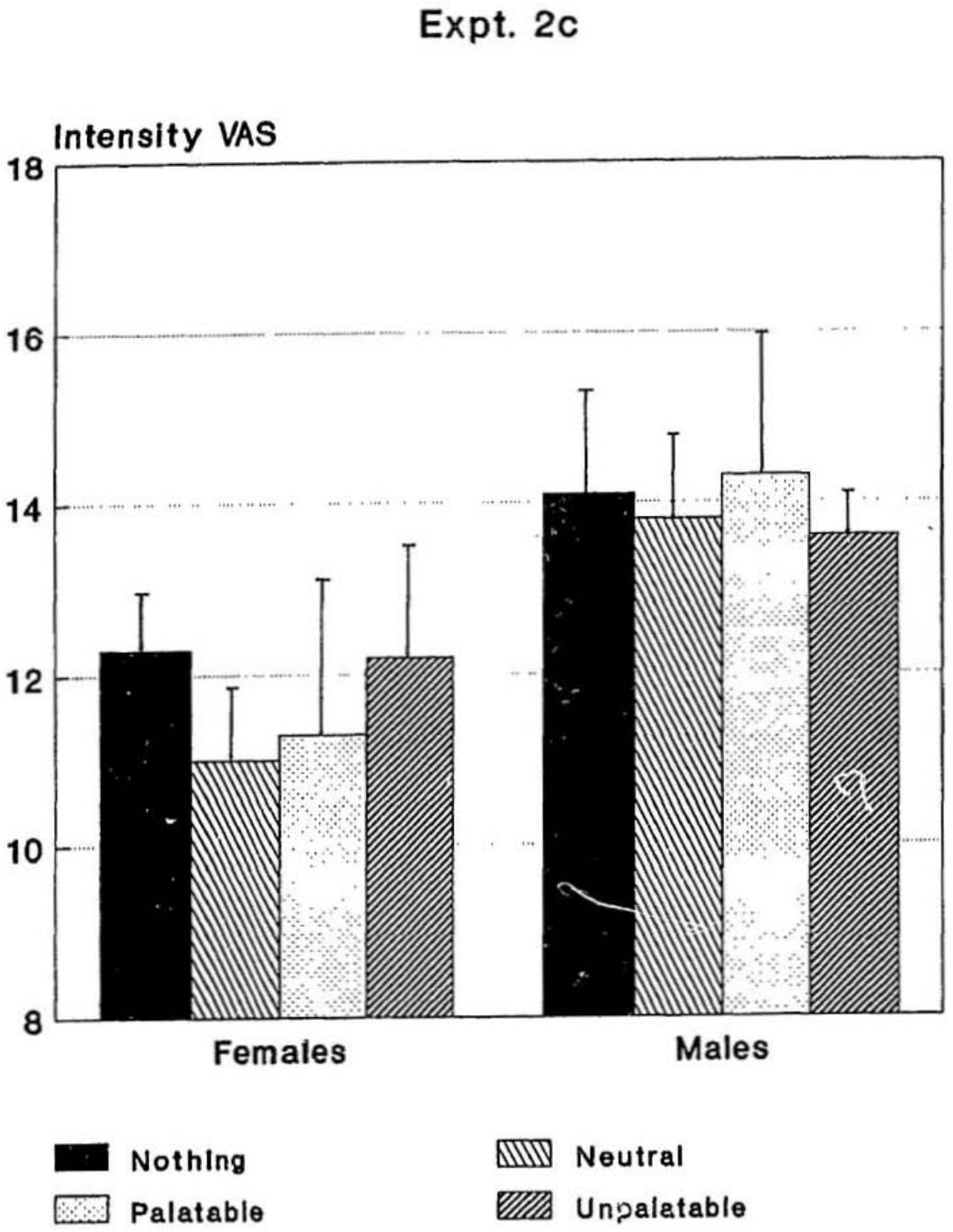

Figure 3.3.7. Post-treatment mean pain intensity ratings to pressure for females (n=20) and males (n=20) in each treatment group.

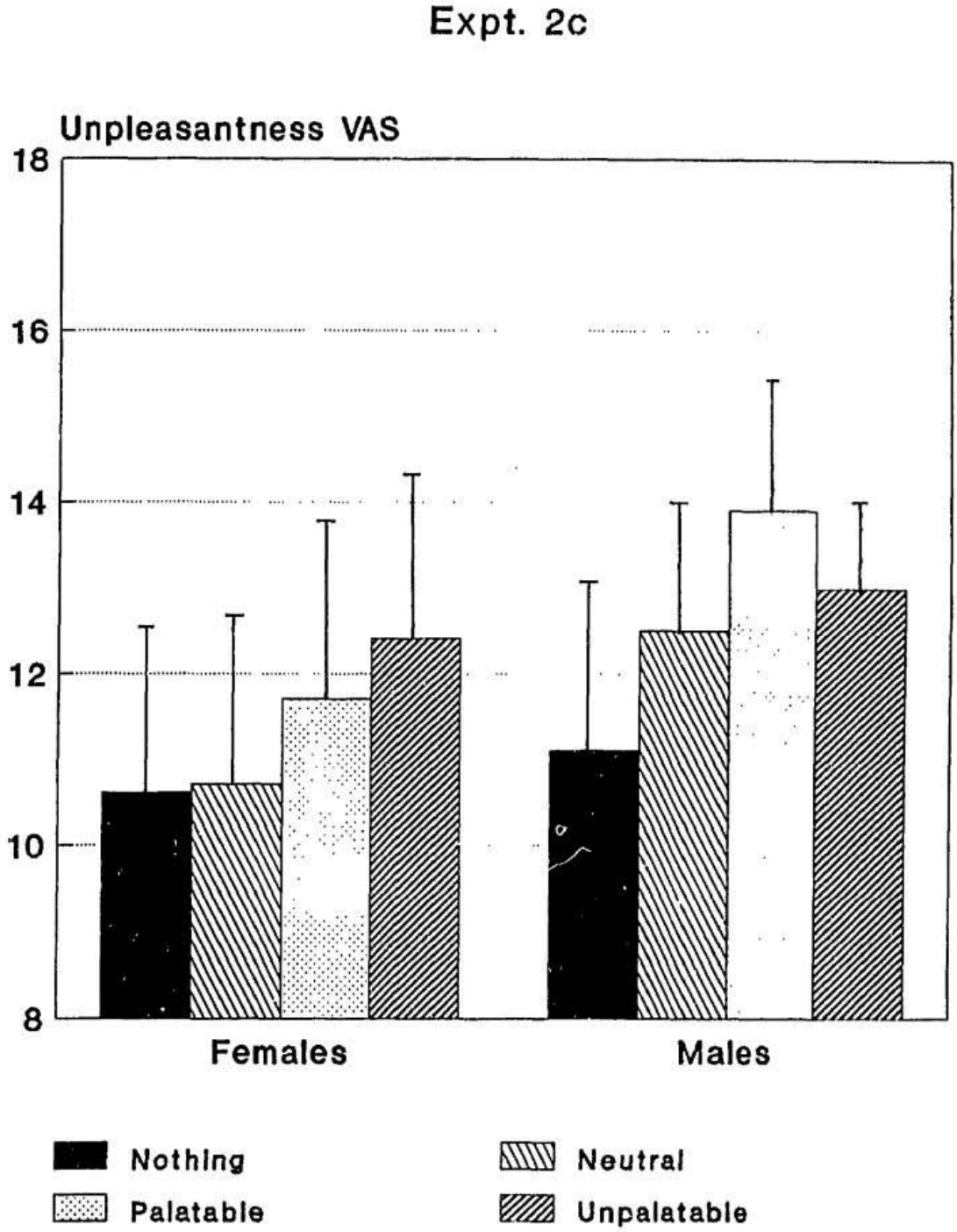

Figure 3.3.8. Post-treatment mean pain unpleasantness ratings to pressure for females (n=20) and males (n=20) in each treatment group.

at pre-treatment.

Second, the familiarization, pre-, and post-treatment means for subjects in the control (nothing) group only (n=10) were compared with correlated t-tests. No significant differences were found between familiarization and pre-treatment means, nor between pre-treatment and post-treatment means for any of the four pain measures (all ps > 0.05). Therefore, stress-induced analgesia was not evident.

At pre- and post-treatment respectively, the percentages of subjects who withstood the maximum amount of pressure (i.e., 1250 g) were 32.5% and 37.5% for the first finger, 22.5% and 22.5% for the second, 35% and 12.5% for the third, and 12.5% and 17.5% for the fourth finger. When tolerances were averaged across fingers for both pre- and post-treatment trials, 35% of males and 0% of females withstood the maximum amount of pressure.

Food Palatability and Hunger.

The mean palatability ratings for each treatment food and each gender are displayed in Table 3.3.3. A two-way ANOVA [4 (Treatment Group) x 2 (Gender)] performed on the palatability ratings showed a significant main effect for Treatment groups [$F(2,24) = 153.28$, $p < .0001$] with each group differing from all other groups (Newman-Keuls. $p < .05$). Although males and females did not differ on overall

palatability ratings [$F(1,24) = 4.01$, $p = .057$], females rated the chocolate-chip cookies more highly than did males [$t(8) = -2.31$, $p = .049$].

Insert Table 3.3.3 about here

Pearson product-moment correlations revealed no significant correlations between palatability ratings and changes (from pre- to post-treatment) in any of the pain measures for either male or female subjects (all $ps > 0.05$). Moreover, there was no evidence for deprivation-induced analgesia as hunger ratings were poorly correlated with changes in the pain measures from pre- to post-treatment (all $ps > 0.05$). Pearson product-moment correlations were also used to determine whether the hunger ratings taken at the beginning of the experiment were correlated with the palatability ratings taken after the foods were consumed. Hunger and palatability VAS ratings were not significantly correlated when each group was analyzed separately, nor when all groups were combined (all $ps > 0.05$).

Treatment and Trial Effects for Tactile Sensitivity.

Mean pre- and post-treatment tactile thresholds of each group are listed in columns seven and eight of Table 2.6.2. Touch sensitivity was not affected by treatment (ANCOVA,

Table 3.3.3

Experiment 2c: Mean Palatability Ratings (and Standard Errors) for each Treatment Food and Gender (n=30).

Gender / Food	Females Mean	Females Range	Males Mean	Males Range	Total Mean	Total Range
Chocolate-chip cookies	9.5 (0.3)	9-10	7.8 (0.7)	6-10	8.7 (0.4)	6-10
Rice cakes	4.6 (0.4)	3-5	3.8 (0.6)	2-5	4.2 (0.4)	2-5
Black olives	1.0 (0.0)	1	1.4 (0.2)	1-2	1.2 (0.2)	1-2
Total	5.0 (0.9)	1-10	4.3 (0.8)	1-10	4.7	1-10

$F(3,34) = .40$, $p = .75$) or by trial (ANOVA, $F(1,35) = 0.02$, $p = .88$).

Correlation Between Subject Variables and Pain Measures.

To determine whether there were any relationships between the latency pain measures, between the VAS pain measures, or between the four pain measures and each of the subject variables recorded (e.g., body weight, amount of exercise, amount of sleep), Pearson product-moment correlations were conducted. Intensity and unpleasantness measures were highly correlated at pre-treatment ($r = 0.41$, $p < 0.05$) as were measures of threshold and tolerance ($r = 0.82$, $p < 0.05$). There were no significant correlations between the pain measures and any of the subject variables (all ps > 0.05).

Discussion

Although the present experiment employed the same treatment foods and pain induction method as Expt. 2b, the present study failed to demonstrate sweet-induced analgesia in males or females. One explanation for these inconsistent and rather weak findings of the pressure-algometry experiments may be that pressure pain is not strongly modulated by sweet ingestion. Pressure pain, like cold-pressor pain, may activate a pain-modulatory system that is

not influenced by sweet ingestion (see General Discussion for elaboration). Alternatively, considerable adaptation or sensitization may occur over time to pain produced by pressure (Handwerker, 1984; Perkins, Grobe, Jennings, Epstein & Elash, 1992), a factor which may limit its usefulness when repeated measurements are involved. Other pain induction methods (e.g., contact or radiant heat) may not produce any sensitization, and therefore, may be more suitable for evaluating sweet-induced analgesia.

The present experiment, like the two preceding pressure studies, found differences among fingers for at least one pain measure. This finger effect was shown for both familiarization and pre-treatment trials, suggesting that the differences between fingers are true sensory differences, and not just the result of practice effects. In other words, the index finger, and likely the second finger, was less sensitive to pressure pain than were the other fingers because of physiological or anatomical differences. For example, the index finger may contain a smaller number/density of nociceptors than the other fingers.

Gender differences were found in both the present study and in Expt. 2a. In both experiments, females reported a greater sensitivity to pressure pain than did males. Males took longer to report pain (threshold), withstood more

pressure (tolerance) and, in one study (Expt. 2a), reported the pain to be less intense than did females. The finding that females are more sensitive to pain than are males is consistent with the results from previous pressure-algometry studies (Brennum et al., 1989; Dubreuil & Kohn, 1986; Fischer, 1987; Otto & Dougher, 1985; Woodrow et al., 1972). Interestingly, genders also differed in the palatability ratings of the chocolate-chip cookies. Females rated the cookies more highly than did males. This finding is consistent with previous findings that females display a greater preference for sweets than do males (e.g., Valenstein et al., 1967).

The present study was the first in this series of experiments to employ multiple trials. The addition of the familiarization trial provided the subjects with a practice trial, thereby reducing the number of subjects and data eliminated from the experiments due to procedural error. One concern of multiple trial pain experiments is stress-induced analgesia. However, in the present study, the analyses showed that stress-induced analgesia was minimal.

In summary, the results from the three pressure algometry studies were inconsistent, suggesting that pressure algometry may not be the most appropriate method of pain induction for evaluating sweet-induced analgesia in humans, especially in males.

CHAPTER 4: CONTACT-HEAT STUDIES. EXPTS. 3A and 3B.

CHAPTER 4.1: EXPERIMENT 3A

The results from the experiments in the previous chapter (Expts. 2a-2c) indicate that sweet-induced analgesia can be demonstrated in human females. However, the analgesic effect of sweets appears to be rather weak when pressure algometry is used as the method of pain induction. Therefore, to further evaluate sweet-induced analgesia, the present experiment employed a different method of pain induction, namely contact heat. Contact heat was chosen for two reasons: 1) contact heat (e.g., a hot-plate) has proven to be a successful technique for demonstrating sweet-induced analgesia in rats (e.g., Blass et al., 1987), and 2) whereas considerable adaptation or sensitization may occur over time to pain produced by cold water or pressure (Handwerker, 1984; Perkins, Grobe, Jennings, Epstein & Elash, 1992), under most conditions, adaptation to pain induced by heat stimulation does not occur (Lipman, Blumenkopf, & Parris, 1987).

In the present study, only female subjects were tested because two of the previous studies (Expt. 2a and Expt. 2c) suggest that the demonstration of sweet-induced analgesia in males may be constrained by ceiling effects. However, if

sweet-induced analgesia is demonstrated here with females, then another contact heat study will be conducted to test males.

The two previous pressure experiments showed that palatability may play an important role in sweet-induced analgesia in humans. The present study also evaluated the effects of palatability on analgesia by comparing the effects of palatable, neutral, and unpalatable foods on females' perception of pain induced by contact heat.

Method

Subjects. Forty female university students served as subjects. An additional 2 subjects were tested but not included in the final sample; 1 because she did not follow proper procedural instructions (i.e., she did not say "pain" at the appropriate time during either the pre- or post-treatment trials), and 1 because she kept her forearm on the hot-plate for the maximum temperature of 48° C during the pre-treatment trial (i.e., she showed maximum tolerance).

Apparatus. 1) **Hot-Plate** (Socrel, model DS37). The hot-plate consisted of a 20 x 20 cm metal plate connected to a variable DC power supply. The apparatus displays digitally, in 0.1° C increments, the surface temperature of the metal plate. Once the hot-plate is turned on, the temperature of the metal plate gradually increases at

approximately 1° C/15 s until it reaches 48° C.

2) **Von Frey Fibers** (same as in Expt. 1).

Procedure. The procedure was the same as that of Experiment 2c, with the exception that contact heat (i.e., a hot-plate), rather than pressure algometry, was used to induce pain. Once the hot-plate reached a temperature of 43° C, the subject placed her left forearm firmly on the hot-plate and the temperature counter was started. The temperatures at which the subject reported "pain" (threshold) and "stop" (tolerance) were recorded. If the subject did not say "stop" before the hot-plate's temperature reached 48° C, the subject was instructed to remove her arm from the hot-plate. In addition, immediately following the removal of her arm from the hot-plate, the subject used VASs to rate the intensity and unpleasantness of her forearm discomfort as she remembered it when she reported "stop".

Again, as in the previous study, there were three exposures to the hot-plate and to the von Frey fibers, and the first trial (the familiarization trial) was excluded from the data analyses. The familiarization trial served to warm up each subject's arm to a similar level prior to collecting data, as well as to give the subjects practice with the procedure and ensure that they understood all instructions.

Results

Baseline Comparisons.

Table 4.1.1 displays for each group, the pre-treatment means for each pain measure. One-way ANOVAs revealed no

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Insert Table 4.1.1 about here

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significant differences among the four groups for pre-treatment pain thresholds, pain tolerances, or VAS ratings of intensity and unpleasantness (all ps > 0.05).

Treatment Effects on Pain Perception.

Figures 4.1.1 to 4.1.4 plot for each group, the adjusted post-treatment means for threshold, tolerance, intensity, and unpleasantness. One-way ANCOVAs performed on

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Insert Figures 4.1.1 to 4.1.4 about here

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each of the four post-treatment pain measures revealed Group effects for pain tolerance [$F(3,35) = 4.71$, $p = .007$] and unpleasantness [$F(3,35) = 2.98$, $p = .044$]. Post-hoc comparisons showed that the mean tolerance of the palatable sweet group was significantly greater than that of the unpalatable group (Newman-Keuls, $p < 0.05$). Post-hoc comparisons of the mean unpleasantness ratings revealed that

Table 4.1.1

Experiment **3a**: Pre-treatment and ANCOVA Adjusted Post-treatment Means (and Standard Errors) for **Females** (n=40) in each Treatment Group.

Group	**Pre-treatment Measures**				**Post-treatment Measures**			
	Thr (deg. C)	Tol (deg.C)	Int	Unp	Thr (deg.C)	Tol (deg.C)	Int	Unp[1]
Nothing	44.1 (0.2)	45.3 (0.3)	10.2 (1.0)	11.6 (1.6)	44.8 (0.3)	45.6 (0.2)	11.5 (1.4)	11.6 (1.5)
Unpalat	44.7 (0.3)	45.5 (0.3)	12.5 (1.5)	12.2 (1.7)	44.4 (0.3)	<u>45.3</u> (0.3)	12.1 (1.5)	12.6 (1.8)
Neutral	44.9 (0.3)	45.9 (0.2)	11.6 (0.9)	12.2 (1.1)	44.8 (0.2)	45.6 (0.1)	13.3 (1.0)	**13.6** (1.1)
Palatab	44.5 (0.2)	45.3 (0.3)	12.8 (1.6)	12.9 (1.8)	44.9 (0.2)	<u>45.8</u> (0.3)	13.5 (1.6)	**14.0** (1.8)
Grand Mean	44.6 (0.1)	45.5 (0.1)	11.8 (0.6)	12.2 (0.8)	44.7 (0.1)	45.5 (0.1)	12.6 (0.7)	13.0 (0.8)

Bold-faced #s = Groups in that column which differ from the nothing group ($p < .05$).

Underlined #s = Groups in that column which differ from each other ($p < .05$).

[1] Thr = Threshold, Tol = Tolerance, Int = Intensity, Unp = Unpleasantness

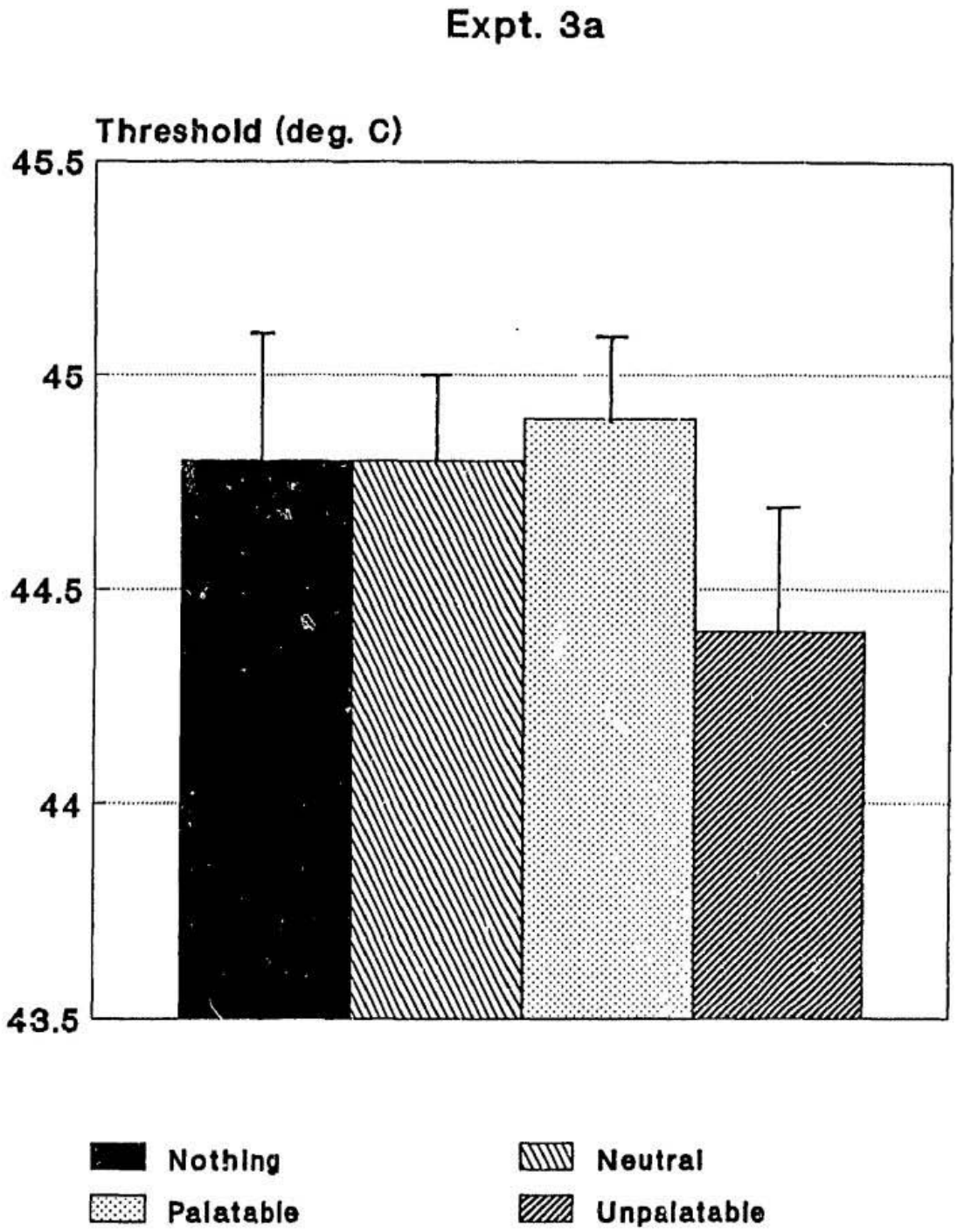

Figure 4.1.1. Post-treatment mean pain thresholds (deg. C) to contact heat for **females** (n=40) in each treatment group.

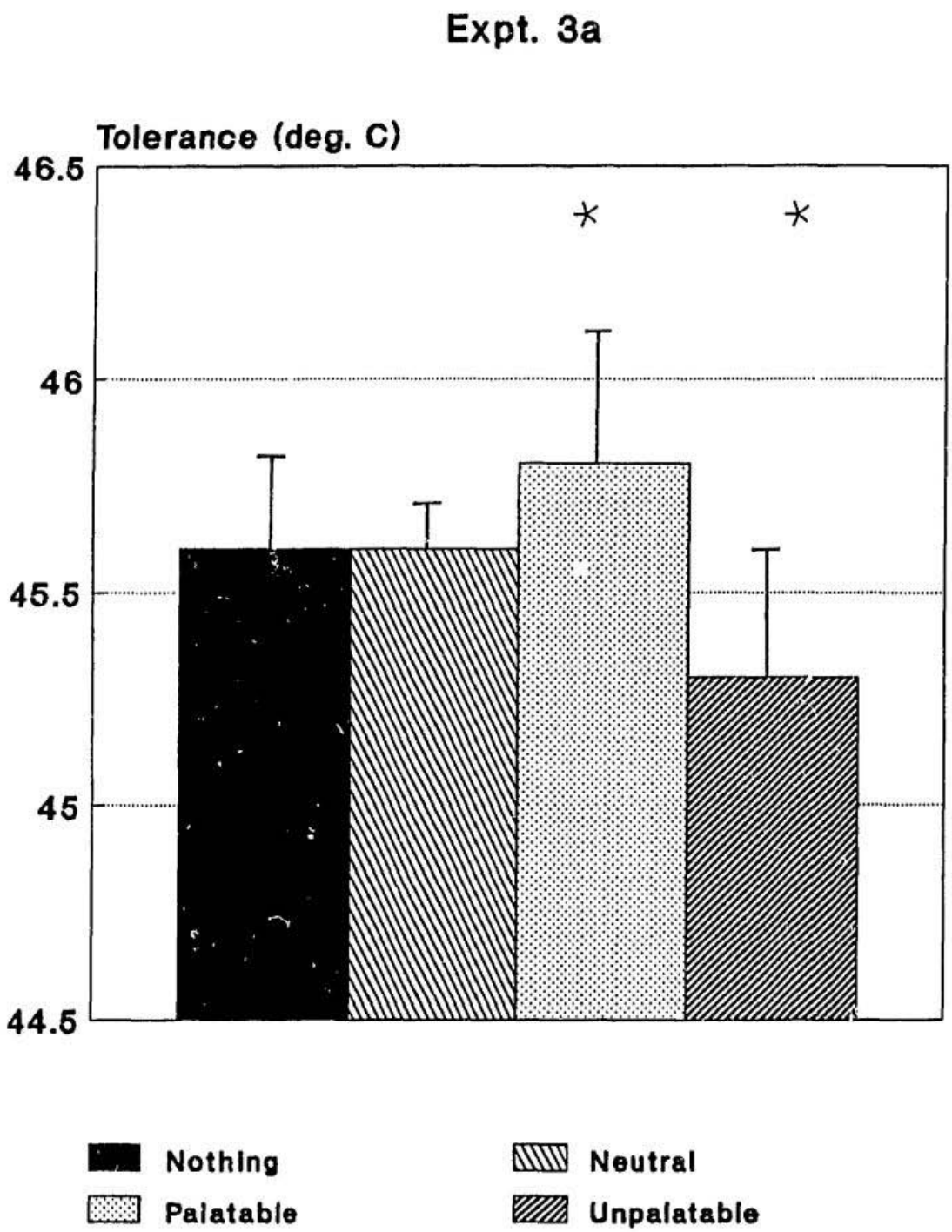

Figure 4.1.2. Post-treatment mean pain tolerances (deg. C) to contact heat for **females** (n=40) in each treatment group. * indicates the groups that differ from each other at post-treatment.

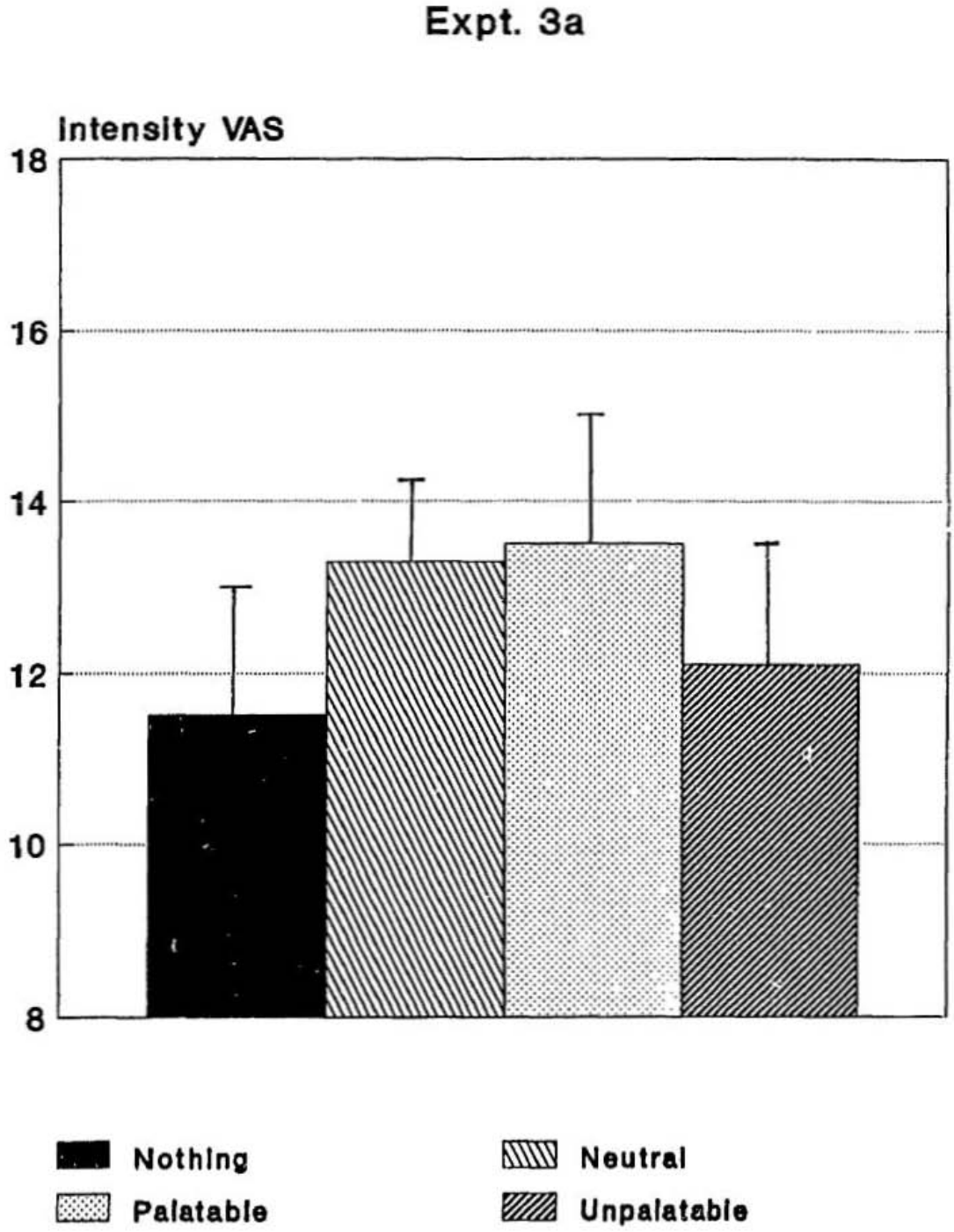

Figure 4.1.3. Post-treatment mean pain intensity ratings to contact heat for females (n=40) in each treatment group.

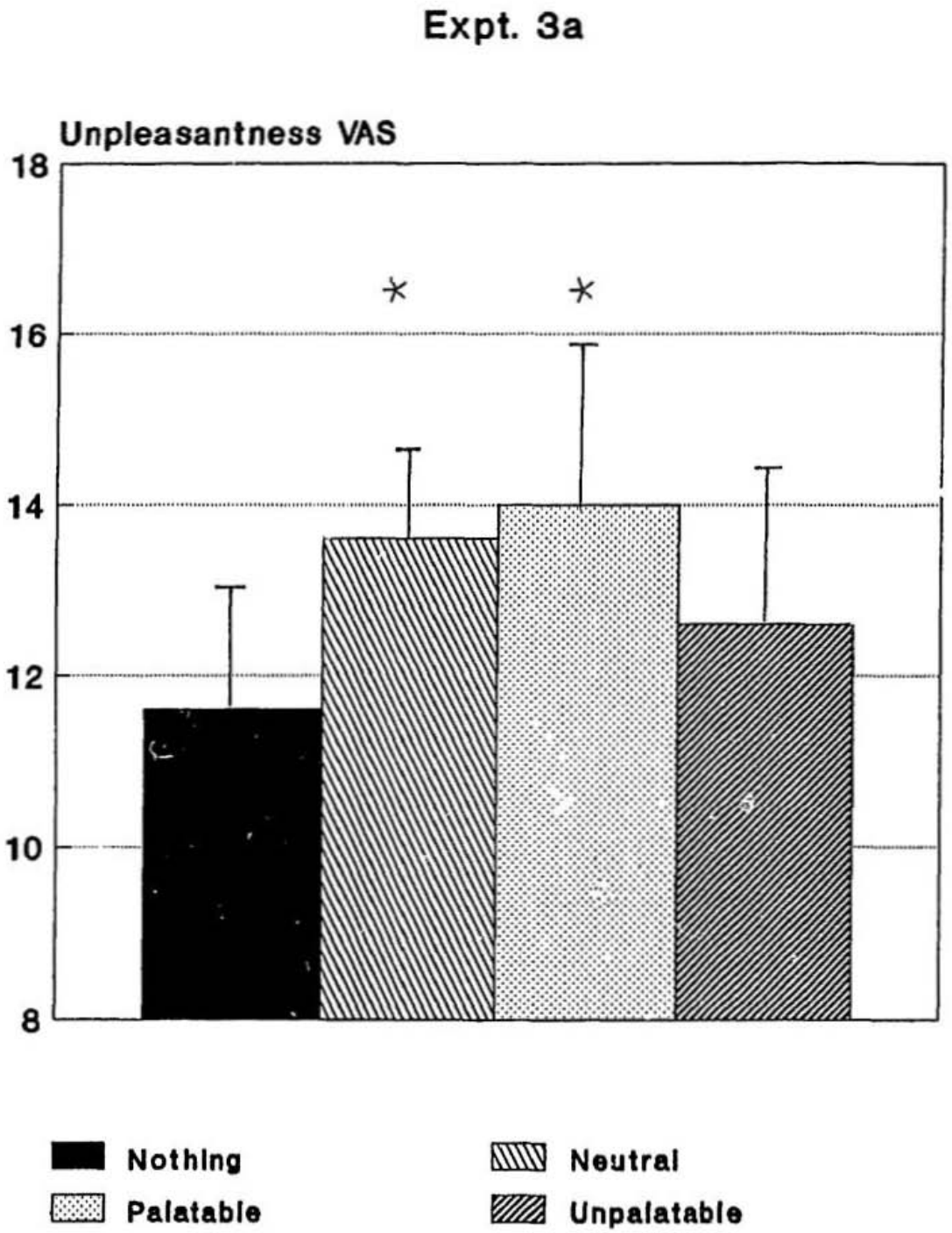

Figure 4.1.4. Post-treatment mean pain unpleasantness ratings to contact heat for **females** (n=40) in each treatment group. * indicates the groups that differ from the nothing (control) group at post-treatment.

the palatable and neutral groups differed significantly from the nothing group [Newman-Keuls, $p < 0.05$]. No significant differences between groups were found for the other two pain measures (both $ps > 0.05$) [see ANCOVA post-treatment means, Table 4.1.1].

In summary, analyses of the tolerance data suggested that, relative to the unpalatable food, the sweet palatable food produced increased analgesia (i.e., a hyperanalgesia) to the contact heat. Or alternatively, relative to the sweet palatable food, the unpalatable food produced decreased analgesia (i.e., a hypoanalgesia; see Figure 4.1.2). Analyses of the unpleasantness data indicated that compared to no treatment (nothing), the sweet palatable food and the neutral food produced increased ratings of unpleasantness.

Trial Effects.

To analyze for stress-induced analgesia, two different analyses were performed. First, the familiarization and pre-treatment means, collapsed across groups, were compared with repeated measures ANOVAs. Significant trial effects were found for measures of pain tolerance [$F(1,35) = 6.04$, $p = 0.019$] and intensity [$F(1,36) = 11.69$, $p = .002$]. However, mean tolerance decreased from familiarization ($M = 45.7^0$ C) to pre-treatment ($M = 45.5^0$ C) and mean intensity VAS

ratings increased from familiarization (M = 10.5) to pre-treatment (M = 11.8), results contrary to that expected for an influence of stress-induced analgesia.

Second, the familiarization, pre-, and post-treatment means for subjects in the control (nothing) group (n=10) were compared with correlated t-tests. No significant differences were found between familiarization and pre-treatment means, nor between pre-treatment and post-treatment means for any of the four pain measures (all ps > 0.05). Therefore, stress-induced analgesia was not evident.

Only 1 of the 41 (2.4%) female subjects kept her forearm on the hot-plate for the maximum temperature of 48° C, and therefore was eliminated from the analyses.

Food Palatability and Hunger.

Following consumption, the mean VAS ratings for each of the treatment foods were 8.70 (S.E.M. = 0.36, range = 7-10) for the cookies, 5.80 (S.E.M. = 1.80, range = 2-8) for the rice cakes, and 1.10 (S.E.M. = 0.10, range = 1-2) for the black olives. A one-way ANOVA performed on the palatability ratings showed a significant Group effect [$F(2,27) = 97.83$, $p < .0001$], with each treatment group differing from all other groups (Newman-Keuls. $p < .05$).

Pearson product-moment correlations revealed significant positive correlations between palatability

ratings and changes in pain threshold (Pearson's r = 0.36, p < 0.05) and pain tolerance (Pearson's r = 0.47, p < 0.01) from pre- to post-treatment. There was no evidence for deprivation-induced analgesia as hunger ratings were poorly correlated with changes in the pain measures from pre- to post-treatment (all ps > 0.05). Pearson product-moment correlations were also used to determine whether the hunger ratings taken at the beginning of the experiment were correlated with the palatability ratings taken after the foods were consumed. Hunger and palatability VAS ratings were not significantly correlated when each group was analyzed separately, nor when all groups were combined (all ps > 0.05).

Treatment and Trial Effects for Tactile Sensitivity.

The means of the tactile thresholds for each group are shown in columns nine and ten of Table 2.6.2. Analyses of tactile thresholds revealed no significant differences among trials (repeated measures ANOVA, $F(1,36) = 1.79$, $p = .189$), nor among groups (ANCOVA, $F(3,35) = 0.59$, $p = .623$).

Correlations Between Subject Variables and Pain Measures.

To determine whether there were any relationships between the VAS pain measures, between the latency pain measures, or between the four pain measures and each of the

subject variables (e.g., body weight, amount of exercise, amount of sleep), Pearson product-moment correlations were conducted. Intensity and unpleasantness measures were highly correlated at pre-treatment (r = 0.40, p < 0.05) as were measures of threshold and tolerance (r = 0.75, p < 0.05). There were no significant correlations between the pain measures and any of the subject variables (all ps > 0.05).

Discussion

The results of the present experiment lend some support for the hypothesis that sweet intake modifies the perception of pain induced by contact heat. Treatment-group comparisons showed that there were significant differences between the palatable and unpalatable groups for post-treatment pain tolerance. Relative to consuming an unpalatable food, consuming a palatable sweet food produced increased pain tolerance (or vice-versa). Although the pain tolerance of the palatable (and unpalatable) group(s) did not differ from the comparison (neutral and nothing) groups, the respective rank order of the pain tolerance scores was as anticipated (i.e., highest for the palatable group, lowest for the unpalatable group, with both the neutral and nothing groups falling in between). This finding confirms the hypothesis that the palatability of the ingested food is important for modifying pain perception. Further support

for the role of palatability is provided by: 1) significant positive correlations between palatability ratings and changes in pain tolerance and (less so) pain threshold following treatment; and 2) the repeated (Expts. 2a & 3a) finding of group differences among post-treatment unpleasantness ratings. Relative to the nothing group, the sweet palatable group and the neutral group showed increased unpleasantness ratings following treatment. Explanations for this result were offered in the discussion of Expt 2a.

The results of the present study also suggest that contact heat may be a better method of pain induction for evaluating analgesia in humans than either pressure algometry or cold-water pressor. First, during pre-treatment, only 1 of the 41 (2.4%) females tested left her arm on the hot-plate until it reached the maximum temperature. In contrast, about 35% of subjects left their fingers in the pressure algometer until it reached the maximum pressure. Thus, using contact heat appears to reduce the potential for ceiling effects. Second, contact heat, in comparison with pressure or cold water, revealed more clearly the role of palatability in analgesia. Finally, repeated exposure to contact heat, like pressure, does not produce stress-induced analgesia, suggesting that the contact-heat method is suitable for evaluating sweet-induced analgesia in humans.

CHAPTER 4.2: EXPERIMENT 3B

Thus far, Expt. 3a has provided the most convincing evidence that food palatability modifies humans' perception of pain, at least in females. Therefore, in an attempt to replicate and extend the findings of Expt. 3a, the present experiment again used the contact-heat method to assess the effects of sweet intake and palatability on analgesia, but this time both males and females were tested.

Method

Subjects. Eighty (40 female and 40 male) university students served as subjects. An additional 2 subjects were tested but not included in the final sample; 1 because it was later discovered that she did not meet the experiment's criteria (i.e., she was not appropriately food-deprived), and 1 because she kept her forearm on the hot-plate at pre-treatment for the maximum temperature of 48° C (i.e., she showed maximum tolerance).

Apparatus. The apparatus (the hot-plate and the von Frey fibers) was the same as described in Experiment 3a.

Procedure. This study used the same procedure as that of Experiment 3a with the following three exceptions. First, males as well as females were tested. Second, before receiving a treatment food, the groups were matched

according to their pre-treatment pain tolerance score. This was achieved by calculating for pre-treatment tolerance, a running group mean which included the subject who was currently being tested. Tolerance was chosen as the matching variable because tolerance was the most sensitive measure in the preceding experiments. Third, rather than presenting the experimental subjects with only one serving of the treatment food, the subjects were offered either four chocolate-chip cookies, four halves of rice cakes, or four black olives and were instructed to eat at least one serving and as much of the food as they wanted. This was to ensure that subjects in the palatable sweet group consumed the number of cookies needed to produce a rewarding effect.

Results

Baseline Comparisons.

Treatment Group Differences. Tables 4.2.1 (females) and 4.2.2 (males) contain the pre-treatment means for each pain measure and for each group. One-way ANOVAs revealed no significant differences among the four groups at pre-treatment for pain threshold, pain tolerance, or intensity and unpleasantness VAS ratings (all ps > 0.05).

Insert Tables 4.2.1 and 4.2.2 about here

Table 4.2.1

Experiment 3b: Pre-treatment and ANCOVA Adjusted Post-treatment Means (and Standard Errors) for **Females** (n=40) in each Treatment Group.

Group	Pre-treatment Measures				Post-treatment Measures			
	Thr (deg.C)	Tol (deg.C)	Int	Unp	Thr (deg.C)	Tol (deg.C)	Int	Unp[1]
Nothing	44.0 (0.3)	45.5 (0.3)	11.8 (1.2)	10.5 (1.6)	44.4 (0.3)	45.1 (0.3)	12.3 (1.4)	12.3 (1.7)
Unpalat	44.0 (0.4)	45.0 (0.4)	11.0 (1.0)	12.0 (1.2)	43.6* (0.4)	44.8 (0.4)	14.0 (1.4)	11.8 (1.4)
Neutral	44.1 (0.2)	45.1 (0.2)	11.7 (1.4)	10.0 (1.8)	44.1 (0.2)	44.9 (0.3)	12.2 (1.4)	12.5 (1.7)
Palatab	44.0 (0.4)	45.3 (0.3)	12.1 (1.2)	10.9 (1.7)	44.4 (0.3)	**45.5** (0.2)	13.1 (1.2)	12.2 (1.6)
Grand Mean	44.0 (0.2)	45.2 (0.2)	11.6 (0.6)	10.8 (0.8)	44.1 (0.2)	45.1 (0.2)	12.9 (0.6)	12.2 (0.8)

Bold-faced #s = Group which differs from the other groups in that column ($p < .05$).

* #s = Group in that column which differs from the palatable and nothing groups ($p < .05$).

[1] Thr = Threshold, Tol = Tolerance, Int = Intensity, Unp = Unpleasantness

Table 4.2.2

Experiment 3b: Pre-treatment and ANCOVA Adjusted Post-treatment Means (and Standard Errors) for **Males** (n=40) in each Treatment Group.

Group	Pre-treatment Measures				Post-treatment Measures			
	Thr (deg.C)	Tol (deg.C)	Int	Unp	Thr (deg.C)	Tol (deg.C)	Int	Unp[1]
Nothing	44.5 (0.3)	46.0 (0.4)	12.5 (1.1)	14.0 (1.2)	44.6 (0.3)	46.0 (0.3)	14.4 (1.0)	13.0 (1.1)
Unpalat	44.8 (0.2)	46.0 (0.2)	14.7 (1.3)	13.7 (1.1)	44.6 (0.2)	46.0 (0.2)	14.4 (1.1)	14.3 (1.4)
Neutral	44.4 (0.3)	45.9 (0.2)	14.3 (0.9)	13.3 (1.2)	44.6 (0.3)	45.9 (0.2)	15.3 (1.0)	14.0 (1.4)
Palatab	44.0 (0.3)	45.8 (0.5)	12.3 (1.5)	10.5 (1.6)	44.6 (0.4)	46.2 (0.4)	14.5 (1.6)	13.4 (1.7)
Grand Mean	44.4 (0.1)	45.9 (0.2)	13.4 (0.6)	12.9 (0.7)	44.6 (0.2)	46.0 (0.2)	14.6 (0.6)	13.7 (0.7)

[1] Thr = Threshold, Tol = Tolerance, Int = Intensity, Unp = Unpleasantness

Gender Differences. To determine whether males and females differed in their sensitivity to pain and touch, one-way ANOVAs were performed on the pre-treatment data for each pain measure (for the female and male pre-treatment means, see Tables 4.2.1 and 4.2.2, respectively) and for tactile thresholds. Significant Gender differences were found for pre-treatment tolerance [$F(1,78) = 12.07$, $p = .0008$], intensity [$F(1,78) = 4.48$, $p = .0375$], and unpleasantness [$F(1,78) = 3.94$, $p = .051$] measures. Compared to males, females reported lower thresholds and lower tolerances but rated their pain as less intense and less unpleasant. Males and females did not differ significantly on either pain thresholds or on tactile thresholds (ANCVAs, both $ps > 0.05$),

Treatment Effects on Pain Perception.

Figures 4.2.1 to 4.2.4 display for each gender, the adjusted post-treatment means for each pain measure.

Insert Figures 4.2.1 to 4.2.4 about here

Analyses of these post-treatment means revealed that only females displayed sweet-induced analgesia. One-way ANCOVAs performed on the female data revealed group effects for pain threshold [$F(3,34) = 4.36$, $p = .0106$] and pain tolerance

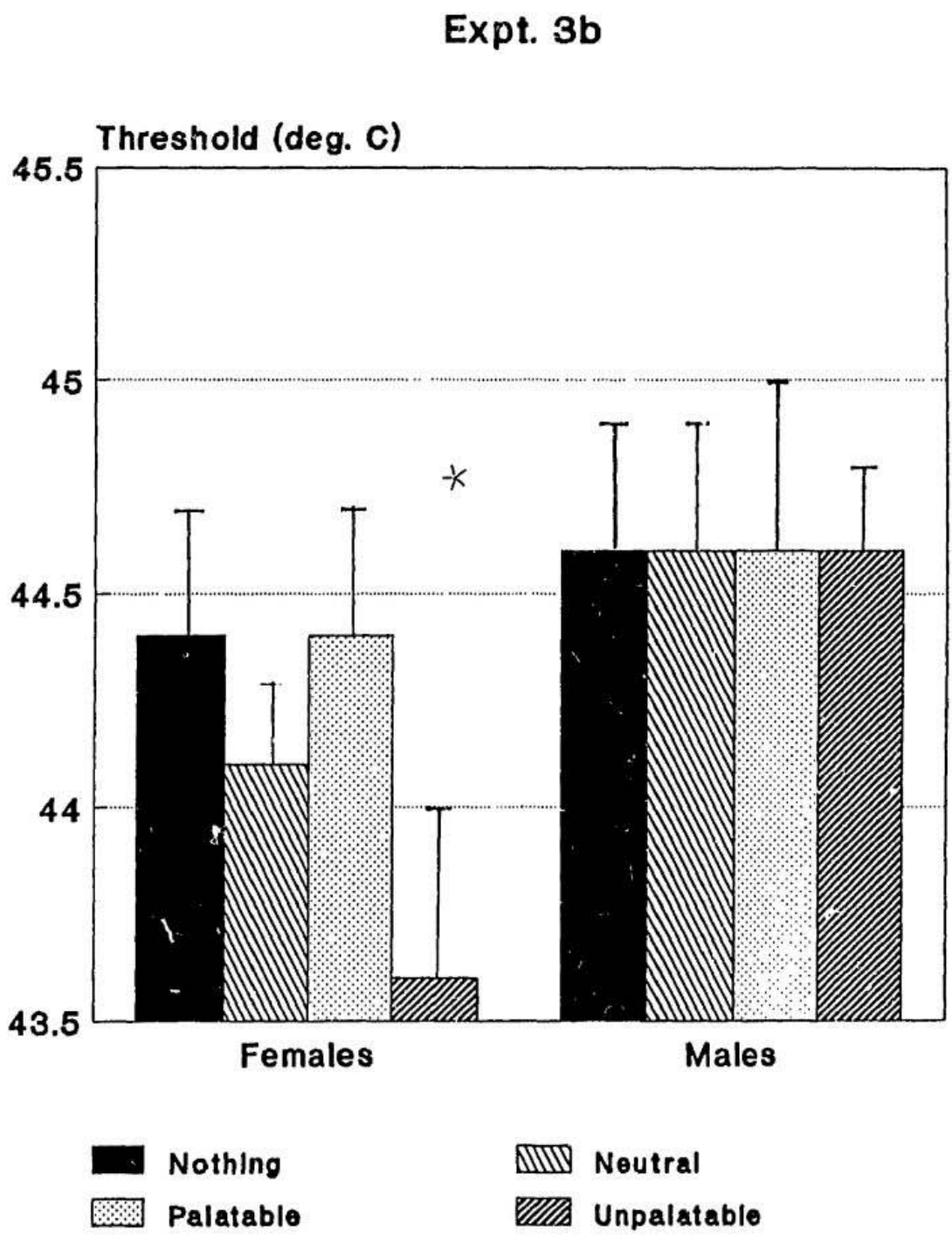

Figure 4.2.1. Post-treatment mean pain thresholds (deg. C) to contact heat for females (n=40) and males (n=40) in each treatment group. * indicates the group that differs from the palatable and nothing groups at post-treatment.

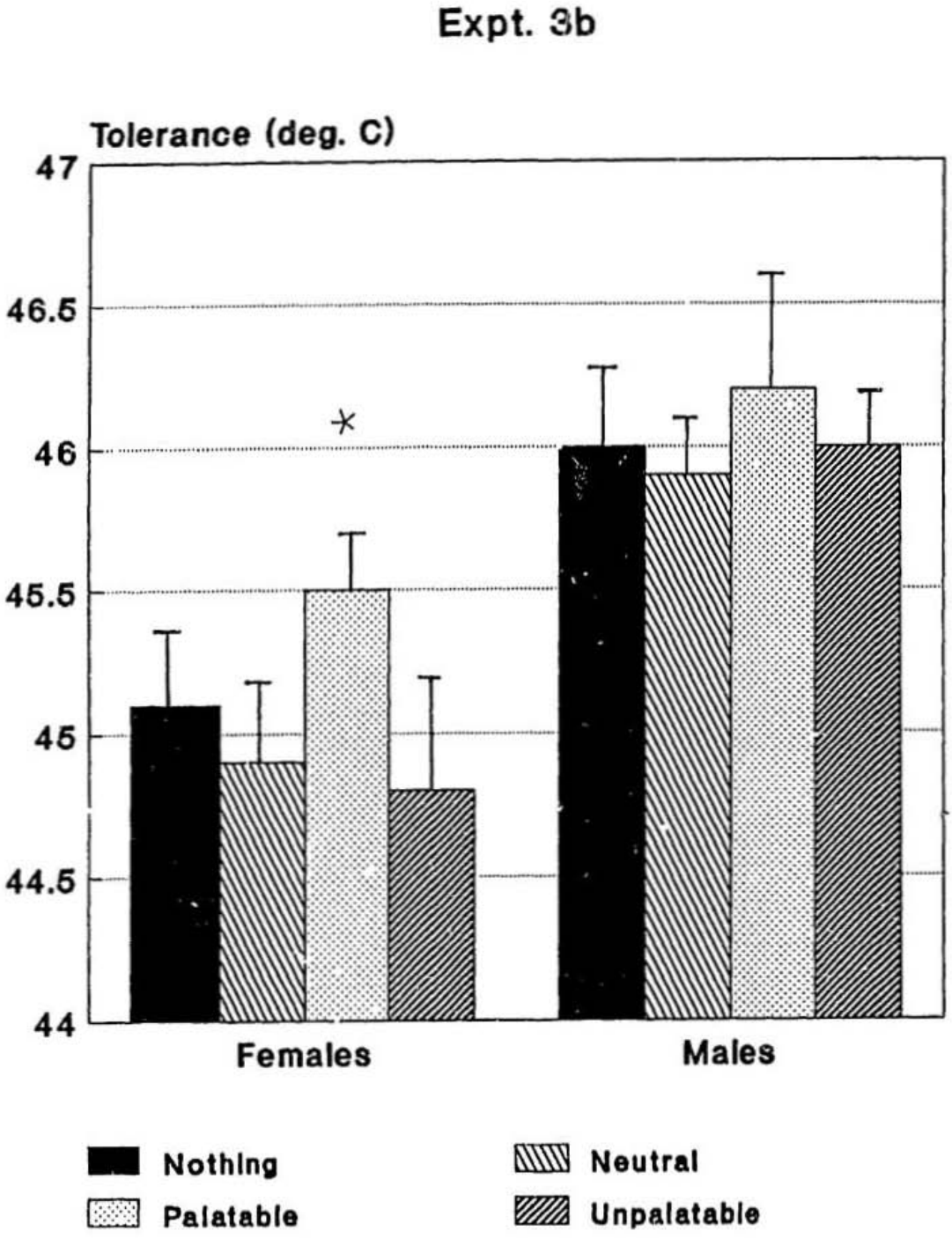

Figure 4.2.2. Post-treatment mean pain tolerances (deg. C) to contact heat for females (n=40) and males (n=40) in each treatment group. * indicates the group which differs from the others at post-treatment.

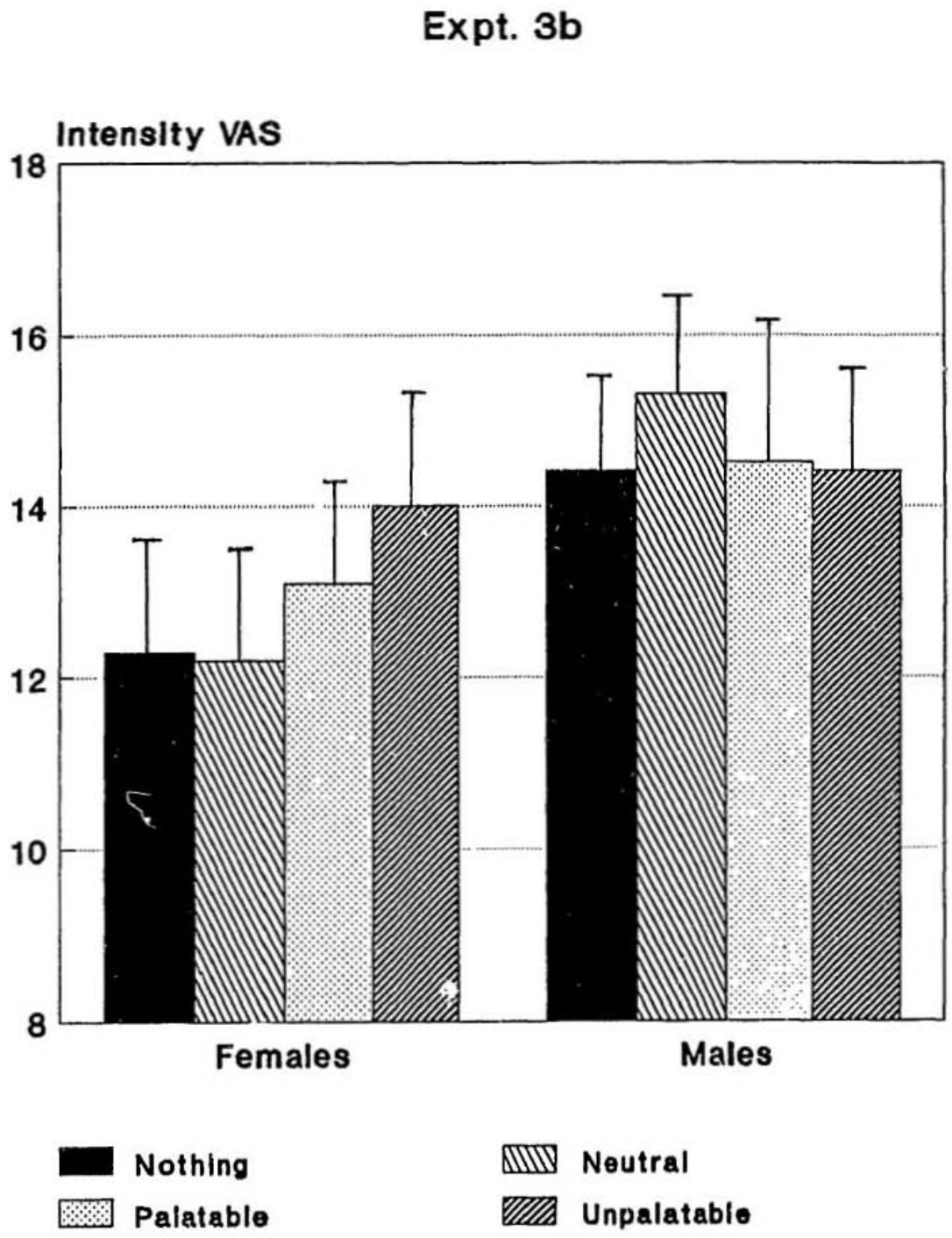

Figure 4.2.3. Post-treatment mean pain intensity ratings to contact heat for females (n=40) and males (n=40) in each treatment group.

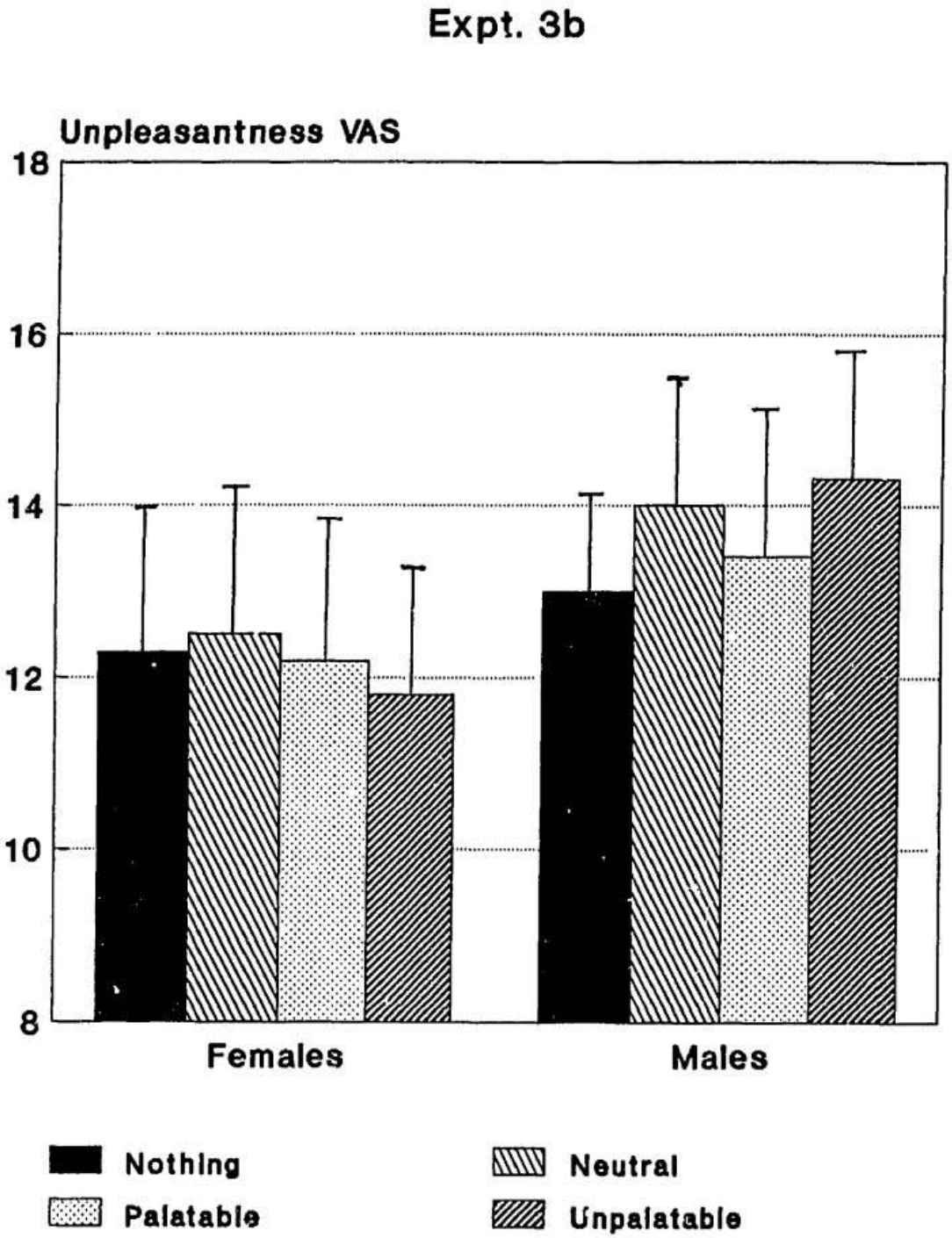

Figure 4.2.4. Post-treatment mean pain unpleasantness ratings to contact heat for females (n=40) and males (n=40) in each treatment group.

[$F(3,35) = 5.20$, $p = .0045$]. Post-hoc comparisons showed that post-treatment mean tolerance of the palatable group was significantly higher than that of all other groups (Newman-Keuls, $p < 0.05$). Moreover, the post-treatment mean threshold of the unpalatable group was significantly lower than that of the palatable and nothing groups (Newman-Keuls, $p < 0.05$). ANCOVA analyses performed on the post-treatment pain measures of males revealed no differences between groups (all ps > 0.05). [For female and male ANCOVA post-treatment means, see Tables 4.2.1 and 4.2.2, respectively].

Trial Effects.

To analyze for stress-induced analgesia, two different analyses were performed. First, the familiarization and pre-treatment means, collapsed across groups, were compared with two-way ANOVAs [2 (Trial) x 2 (Gender)]. Significant trial effects were found for measures of pain tolerance [$F(1,76) = 4.29$, $p = 0.042$], intensity [$F(1,77) = 9.84$, $p = .002$], and unpleasantness [$F(1,77) = 12.28$, $p = .001$]. However, overall mean tolerances decreased from familiarization ($M = 45.69°$ C) to pre-treatment ($M = 45.57°$ C) and both mean intensity and unpleasantness VAS ratings increased from familiarization ($M_{int} = 11.6$; $M_{unp} = 10.8$) to pre-treatment ($M_{int} = 12.5$; $M_{unp} = 11.8$) suggesting that stress-induced analgesia was minimal. Trial x Gender

interactions were found for intensity [$F(1,77) = 9.04$, $p = .003$] and unpleasantness ratings [$F(1,38) = 5.04$, $p = .028$] with males displaying increased ratings of intensity ($M_{fam} = 11.8$, $M_{pre} = 13.5$) and unpleasantness ($M_{fam} = 11.3$, $M_{pre} = 12.9$) between trials, and females showing little change between trials in their ratings of intensity ($M_{fam} = 11.5$, $M_{pre} = 11.5$) and unpleasantness ($M_{fam} = 10.4$, $M_{pre} = 10.7$). This finding suggests that for males, but not females, experience with the heat pain at familiarization may have changed males' responsivity to the heat pain at pre-treatment.

Second, the familiarization, pre-, and post-treatment means for subjects in the control (nothing) group only (n=10) were compared with correlated t-tests. No significant differences were found between familiarization and pre-treatment, nor between pre-treatment and post-treatment for any of the pain measures (all $ps > 0.05$) except intensity ($t(19) = -3.00$, $p = .007$), which increased between trials ($M_{fam} = 10.4$; $M_{pre} = 12.2$; $M_{post} = 12.9$). Therefore, stress-induced analgesia was not evident.

Only 1 of the 81 (1.2%) subjects kept their forearm on the hot-plate for the maximum temperature of 48° C, and therefore was eliminated from the analyses.

Food Palatability and Hunger.

The mean palatability ratings for each treatment food

and each gender are displayed in Table 4.2.3. A two-way ANOVA [4 (Treatment Group) x 2 (Gender)] performed on the palatability ratings showed a significant main effect for Treatment Group [$F(2,54) = 168.94$, $p < .0001$] with each group differing from all other groups (Newman-Keuls. $p < .05$). Males and females did not differ on overall food palatability ratings [$F(1,54) = 0.51$, $p = .48$], nor on individual food ratings [all $ps > 0.05$].

Insert Table 4.2.3 about here

Pearson product-moment correlations revealed significant positive correlations between palatability ratings and changes (from pre- to post-treatment) in measures of pain threshold (Pearson's $r = 0.50$, $p < 0.01$) and pain tolerance (Pearson's $r = 0.41$, $p < 0.05$) for female subjects only. There was no evidence for deprivation-induced analgesia as hunger ratings were poorly correlated with changes in the pain measures from pre- to post-treatment (all $ps > 0.05$). Pearson product-moment correlations were also used to determine whether the hunger ratings taken at the beginning of the experiment were correlated with the palatability ratings taken after the foods were consumed. Hunger and palatability VAS ratings were not significantly correlated when each group was

Table 4.2.3

Experiment **3b**: Mean Palatability Ratings (and Standard Errors) for each Treatment Food and Gender (n=60).

Gender / Food	**Females** Mean	Range	**Males** Mean	Range	Total Mean	Range
Chocolate-chip cookies	8.8 (0.3)	7-10	8.6 (0.5)	6-10	8.7 (0.4)	6-10
Rice cakes	5.8 (0.4)	3-8	4.8 (0.6)	3-7	5.3 (0.5)	3-8
Black olives	1.1 (0.1)	1-2	1.6 (0.3)	1-4	1.4 (0.2)	1-4
Total	5.2 (0.6)	1-10	5.0 (0.6)	1-10	5.1	1-10

analyzed separately, nor when all groups were combined (all ps > 0.05).

Treatment and Trial Effects on Tactile Sensitivity.

Mean tactile thresholds for each group are reported in the last two columns of Table 2.6.2. Analyses of tactile thresholds revealed no significant differences between trials (ANOVA, $F(1,76) = 0.51$, $p = .476$), nor among groups (ANCOVA, $F(3,75) = 1.91$, $p = .136$).

Correlations Between Subject Variables and Pain Measures.

To determine whether there was any relationship between the VAS pain measures, between the latency pain measures, or between the four pain measures and each of the subject variables (e.g., body weight, amount of exercise, amount of sleep), Pearson product-moment correlations were conducted. Intensity and unpleasantness measures were highly correlated at pre-treatment ($r = 0.67$, $p < 0.05$) as were measures of threshold and tolerance ($r = 0.67$, $p < 0.05$). There were no significant correlations between the pain measures and any of the subject variables (all ps > 0.05).

Discussion

As in the preceding experiments, the results from this study suggest that the ingestion of a sweet palatable food

produced increased analgesia in females, but not in males. Relative to females who consumed either unpalatable food, neutral food, or nothing, females who consumed palatable sweet food displayed increased pain tolerance. As in the previous experiments (Expts. 2b and 3a), the post-treatment mean tolerance scores of the palatable and unpalatable groups differed the most (see Figure 4.2.2). Moreover, the post-treatment mean threshold of the unpalatable group was lower than that of the palatable and nothing groups. These findings suggest that the ingestion of an unpalatable food produces an effect on pain responsivity different from that of palatable foods. Possible explanations for the relative hypoanalgesic effect of unpalatable foods are offered in the General Discussion.

The present experiment, like those preceding it, found gender differences for certain pain measures. Compared to males, females endured less heat (showed lower tolerances) but rated the pain as less intense and unpleasant. This may be explained by the fact that the females left their arms on the hot-plate for shorter durations (tolerance) than did males, and thus, they perceived the pain as less intense and less unpleasant than did males.

As found in Expt. 2c and previous studies of heat pain (e.g., Feine et al., 1991), the present study found that males, but not females showed trial differences for some of

the pain measures. This suggests that males' pain responsivity may be influenced by their experience with the experimental pain. This gender difference combined with gender differences in pain sensitivity and palatability ratings (Expt. 2b) warrant the statistical separation of males and females when evaluating sweet-induced analgesia.

CHAPTER 5: GENERAL DISCUSSION

The main finding of this thesis is that sweet-induced analgesia can be demonstrated in human adults. However, sweet-induced analgesia in humans may not be a robust phenomenon as it appears to be limited by a number of experimental parameters, most notably the palatability of the sweets, the type of experimental pain (i.e., the method of pain induction), the type of pain measure, and possibly, the gender of the subjects. The results of the present experiments suggest that the most potent analgesic effects occurred under conditions in which, females (versus males) served as subjects, contact heat (versus cold water or pressure) was used as the method of pain induction, and chocolate-chip cookies (versus sucrose or pop) served as the sweet food. Moreover, tolerance (versus threshold or VAS ratings) appeared to be the pain measure most sensitive to sweet's analgesic effects. The first section of this discussion will address how each of these experimental parameters may influence sweet-induced analgesia.

5.1: FACTORS WHICH MAY INFLUENCE SWEET-INDUCED ANALGESIA.

5.1.1: Method of Pain Induction

In the present experiments, the effects of sweets on analgesia were most apparent when contact heat was used to

induce pain, less so when pressure was used, and not at all when cold water was used. There are several plausible explanations for the different results obtained with the three pain induction techniques.

First, the effects of sweets on the perception of pain may depend on whether the method of pain induction activates opioid or nonopioid pathways. As mentioned in the introduction of this thesis, there are both opioid and nonopioid pain-modulatory systems present in the vertebrate CNS (for reviews, see Mayer & Watkins, 1984; Terman et al., 1984; Watkins & Mayer, 1982). Research with rats has shown that a number of experimental parameters related to the pattern of pain induction (e.g., intensity, duration, temporal pattern, inescapability) can influence which analgesic system is activated (e.g., Maier, Sherman, Lewis, et al., 1983; Tierney, Carmody, & Jamieson, 1991; Terman, Morgan, & Liebeskind, 1986). For example, Liebeskind and his associates have found that "low-severity pain" (i.e., pain which is intermittent, of brief duration, and of lower intensity) activates opioid pathways whereas "high-severity pain" (i.e., pain which is continuous, of longer duration, and of higher intensity) activates nonopioid pathways (Cannon, Terman, Lewis, & Liebeskind, 1984; Lewis, Cannon, & Liebeskind, 1980; Terman et al., 1986; Terman, Shavit, Lewis et al., 1984; but see Tierney et al., 1991). The cold-water

pressor used in Expt. 1 may be classified as high-severity pain because of the very low water temperature used (about 1° C), because subjects reported that the pain was immediate and continuous, and because the pain could last up to five minutes. Both the contact heat and pressure used in subsequent experiments could be classified as low severity pain because they both started gradually (at initial contact, subjects experienced only minimal heat or pressure and no pain), because they were of relatively short duration (up to 30 sec. for pressure and approximately 75 sec. for heat), and because they were of relatively low intensity (0-1250 grams of pressure, and 43 to 48° C heat).

Thus, the pressure and contact heat may have activated opioid pathways whereas the cold water may have activated nonopioid pathways. This explanation is supported by the finding that severe cold-water swims activate a nonopioid-hormonal pain system in rats (Mayer & Watkins, 1984; Terman et al., 1986). Although similar types of studies have yet to be conducted with heat pain or pressure pain, the experiments (e.g., Blass et al., 1987; Holder, 1988) which have demonstrated naloxone-reversible, sweet-induced analgesia in rats have used contact heat to induce pain, which suggests that heat pain activates opioid systems. Therefore, if sweets produce an analgesic effect by releasing EOPs into the CNS (e.g., Dum et al., 1983), then

sweets should not affect nonopioid-modulated cold-water pain but should affect opioid-modulated contact-heat pain. In order to test this explanation in humans, future experiments are needed that assess the analgesic effects of sweets under conditions in which the severity of each type of experimental pain is varied. In particular, experiments are needed that measure the effects of sweets on pain induced by less severe water temperatures, more severe contact heat temperatures, and more severe mechanical pressures.

Alternatively, there may be two or more opioid pain-modulatory systems, each activated by a different method of pain induction, and each differentially sensitive to opioid modulation (including sweet-induced opioid modulation). In other words, heat pain may have shown greater sensitivity to sweet-induced analgesia than either pressure or cold-water pain because contact heat activates a different opioid pathway, specifically one that is sensitive to sweets' analgesic effects. For example, heat pain may activate an opioid analgesia pathway that originates in the PAG, an area rich in mu receptors (Al-Rodhan & Yaksh, 1987, cited in Yaksh & Aimone, 1989). Conversely, pressure or cold-water pain may activate an opioid analgesia pathway that originates in the medulla, an area containing mostly delta receptors (Jensen & Yaksh, 1986, cited in Yaksh & Aimone, 1989). Given that the PAG contains a much greater number of

mu receptors than does the medulla, it is likely that the PAG pathway would show the greatest sensitivity to sweet/opioid modulation. This suggestion is supported by two converging lines of evidence. First, mu agonists, but not delta or kappa agonists, produce analgesia at supraspinal levels (Fang, Moreau, & Fields, 1987, cited in Fields & Basbaum, 1989). Second, sweet ingestion appears to produce analgesia by increasing the activity of beta-endorphin (a mu-selective ligand) in rat hypothalamus (Dum et al., 1983). Because the hypothalamus sends projections to the PAG, this implies that the PAG pathway mediates sweet-induced analgesia. Therefore, in the present experiments, the contact heat pain may have showed greater sensitivity to sweet-induced analgesia than either the cold-water or pressure pain because the heat activated a pathway (likely the PAG-dorsal horn pathway) that is more sensitive to sweet/opioid modulation.

This explanation is supported by the findings of studies which have compared the effectiveness of different opioid agonists on different types of pain. For example, in humans, mu agonists were shown to have their strongest analgesic effects on heat pain whereas kappa agonists had a higher analgesic potency for mechanical pain (Upton, Sewell, & Spencer, 1982; cited in Fields and Basbaum, 1989). Moreover, studies investigating the effects of opioid

antagonists on humans' pain perception have shown that some, but not all, types of pain are altered by opioid antagonists. For example, naloxone, an opioid antagonist which is most effective at mu receptors, modifies humans' sensitivity to thermally- (radiant heat) induced pain (Stacher, Abatzi, Schulte et al., 1988)), but not to pain induced electrically (Stacher et al., 1988; El-Sobky, Dostrovsky, & Wall, 1976), mechanically (e.g, by ischemia in the submaximum tourniquet test), or by cold water (Grevart & Goldstein, 1978). In future studies with humans, it would be interesting to compare the effects of naloxone on pain induced by contact heat, pressure algometry, and cold water.

In summary, contact-heat pain may activate an opioid pain-modulatory pathway that is different from that activated by cold-water or pressure pain, and this heat-activated pathway may be more sensitive to sweet modulation. This explanation of multiple opioid pain-modulatory systems might account for the present finding that sweet-induced analgesia is greatest for pain induced by heat, compared to pain induced by either pressure or cold water.

Another possible explanation for the lack of effect of sweets on cold-pressor pain may be related to the nature of cold-water pain - it stimulates both nociceptive and non-nociceptive afferent nerves, it is cyclical, and it produces

adaptation (Johnson, 1974; Miller et al., 1994; Wolf & Hardy, 1941). Because of this adaptation or "numbing" effect, cold-water pain decreases after the arm is immersed for more than one minute. Therefore, if subjects manage to keep their arm immersed for the first minute, they often are able to keep it immersed indefinitely, resulting in very high tolerance scores (e.g., Miller et al., 1994). These inflated tolerance scores at pre-treatment would make it very difficult to demonstrate sweets' analgesic effects.

Related to this fact is another plausible explanation for the lack of results in Expt. 1. Only male subjects were used in the cold-pressor study. Based on the results of Expts. 2a, 2c and 3b which used either pressure or contact heat and both genders, males appear less likely to demonstrate sweet-induced analgesia than females. Therefore, the lack of results in the cold-pressor study, as well as the weak results found in Expts. 2a and 2c, may be accounted for, in part, by the male subjects. An obvious experiment to address this issue would be to test sweet-induced analgesia in female subjects exposed to the cold-water pressor.

5.1.2: Gender Differences

There are several possible explanations for the presence of sweet-induced analgesia in females and not

males. First, consistent with the findings of other studies which have used a variety of pain inducers (e.g., Arendt-Nielsen & Bjerring, 1988; Buchanan & Midgley, 1987; Buchsbaum et al., 1981; Dubreuil & Kohn, 1986; Feine et al., 1991; Rollman & Harris, 1984; Otto & Dougher, 1985; Woodrow et al., 1972, but see Lautenbacher & Rollman, 1993; Zeltzer et al., 1981), males reported higher pain thresholds and tolerances and lower ratings of intensity and unpleasantness than did females. This gender difference was found in both the pressure and contact heat experiments but could not be assessed in the cold-water pressor experiment because females were not tested. However, males displayed very high tolerances to the cold-water pressor also. Therefore, the analgesic effects of sweet consumption may have been obscured by ceiling effects for males.

One possible explanation for this gender difference in pain sensitivity is that there are reporting biases based on gender differences in attitude, or emotional response. Studies have shown that numerous non-sensory factors can easily influence threshold and tolerance measures (e.g., Al Absi & Rokke, 1991; Clark & Mehl, 1971). A non-sensory variable whose effect was not assessed in the present experiments, but which might account for the gender differences, was the gender of the experimenter. If gender-related differences in pain perception are even partially

related to cultural/sociological factors, the mere presence of an experimenter of a given gender could alter the subjects' willingness to report pain. Results from a few studies suggest that because of cultural demands and expectations, males are less likely than females to report pain, especially in the presence of an attractive female experimenter (Levine & De Dimone, 1991; Takala, 1990). However, in both of these studies, the proper controls were not employed, and the experimenter's attractiveness and masculinity/femininity were maximized. In the present study, the experimenter was always female, but precautions were taken to minimize her attractiveness/femininity (e.g., a standard laboratory coat was worn), and to minimize the amount of interaction between the experimenter and subject. Moreover, results from better, more controlled studies (Feine et al., 1991; Otto & Dougher, 1985) suggest that females show greater sensitivity to pain than do males, independent of experimenter gender.

A second, perhaps more plausible, explanation for gender differences in pain sensitivity is that there are differences in the sensory and/or physiological pain mechanisms of males and females. First, gender differences in pain responsivity may reflect a difference in sensory pain transmission (e.g., see Feine et al., 1991). Alternatively, males and females may possess slightly

different pain-modulatory systems. A recent study (Mogil, Sternberg, Kest, Marek, & Liebeskind, 1993) with mice examined the effects of naloxone and dizocilpine (a N-methyl-D-aspartate (NMDA) receptor antagonist) on both nonopioid and opioid swim stress-induced analgesia (SSIA). It was shown that female mice possessed a gender-specific analgesic mechanism that was estrogen-dependent. This female-specific, estrogen-dependent analgesic mechanism may also be present in human females and may be activated by sweet ingestion. This would account for the presence of sweet-induced analgesia in females but not in males.

A third explanation for the presence of sweet-induced analgesia in females and not males may be that there are gender differences in taste preferences, taste sensitivity, or eating patterns in general. If males are less sensitive to the taste of sweets or show lower preferences for sweets than females, then the sweets may not taste as palatable to males, causing an attenuation of sweets' analgesic effects. Female rats display a stronger preference for sweets (e.g., glucose, saccharin) than male rats (e.g. Valenstein, Kakolewski, & Cox, 1967). Human females show higher gustatory sensitivity, lower thresholds to chemical and electrical stimulation of the tongue, and higher consistency in identification and classification of substances than do males (Doty, 1978, cited in Velle, 1987). Research on human

food cravings (i.e., intense desires to eat specific foods) have demonstrated a number of gender differences. For example, Weingarten & Elston (1991) found that more females than males reported experiencing food cravings (97% of women versus 68% of men), and more men than women reported a positive response to eating a craved food (82% of men vs 57% of women). Also, males and females differed on the particular foods that they crave (e.g., 39% of women vs 14% of men crave chocolate), and finally, the attributions of the origins of cravings differed for men and women (e.g., hunger-elicited for men vs cue-elicited for women). In addition, there are significant differences in the CNS regions that mediate taste in rats. The brainstem which is thought to be important for taste preferences contains a relay area called the parabrachial nucleus of the pons (PbN). Compared to males, the PbN units of female rats, including those that were pregnant, showed larger responses to sweet stimuli, and a greater proportion of the PbN units of females were classified as sweet-sensitive (Di-Lorenzo & Monroe, 1989).

Thus, males may show attenuated sweet-induced analgesia because they have a reduced sensitivity to sweets, resulting in a reduced preference for sweets. In fact, in the present study, females rated the sweets slightly higher in palatability than did males. Therefore, if sweets produce

analgesia because they taste palatable, then the sweets' potential analgesic effect may have been diminished for males. In future studies of sweet-induced analgesia, one should ascertain which sweet foods taste highly palatable to most males, and then establish whether it is the sweets' palatability, its composition, its caloric content, or its post-ingestive factors, which produces the analgesic effect.

5.1.3: Type of Pain Measure

The present results suggest that the efficacy of sweet-induced analgesia depends not only on the method of pain induction but also on the type of pain measure. Compared to measures of pain threshold, pain intensity, and pain unpleasantness, pain tolerance most consistently revealed the analgesic effects of sweets. This is consistent with previous studies which have compared these pain measures and have found that pain tolerance is the most sensitive measure, as well as the least susceptible to experimental confounds (for a review, see Chapman, Casey, Dubner, Foley, Gracely, & Reeding, 1985). For example, relative to pain tolerance, VAS ratings of intensity and unpleasantness are more susceptible to ceiling effects (Feine et al., 1988, 1991), while pain thresholds are more susceptible to the effects of expectancy, instructional set and other psychological variables (Chapman et al., 1985). Despite the

relative superiority of tolerance as a measure of pain, one limitation is the relatively large individual differences that this measure yields (see Chapman et al., 1985). Large intersubject differences may account for the failure of even the pain tolerance measure to reveal sweet-induced analgesia across all experiments. Although attempts were made to compensate for individual differences (e.g., all subjects were right-handed, non-smokers, pain-free, and mildly food-deprived), perhaps additional procedures could have been employed. For example, larger sample sizes and a more detailed questionnaire documenting subjects' sweet intake could have been used.

The observed differences in sensitivity to the analgesic effects of sweets among the different pain measures may also be explained by the multidimensionality of pain perception. Pain perception involves both sensory and affective dimensions (Melzack, 1973). Each of the four pain measures used here may represent a different dimension of the pain experience. For example, unpleasantness and tolerance may represent an affective-reactive dimension of pain, whereas intensity and threshold may represent a sensory-discriminative dimension (e.g., Zelman, Howland, Nichols, & Cleeland, 1989). In other words, threshold and intensity measures represent the sensory transmission of pain whereas tolerance and unpleasantness primarily reflect

the emotional, cognitive, and motivational aspects of pain (supraspinal functions). This distinction is perhaps best elucidated by Jaffe and Martin (1975, cited in Franklin, 1989) who describe two types of analgesia: antinociceptive and dissociative. Antinociceptive analgesics reduce the sensory intensity or threshold of pain whereas dissociative analgesics reduce the "suffering" or the emotional/affective reaction to pain. Franklin (1989) suggests that dissociative analgesia is mediated by the rewarding effects of opioids, or the ability of opioids to induce a positive mood, which may be associated with the activation of the ventral tegmental area-nucleus accumbens (VTA-NAS) reward system (see Wise, 1989). Because sweets presumably increase opioid activity in brain areas associated with reward (e.g., ventral tegmentum, nucleus accumbens, lateral hypothalamus; see Franklin, 1989; Mucha & Iversen, 1986; and Wise, 1989), it is likely that sweets produce analgesia primarily by modulating the affective component of pain. Therefore, the present finding that sweet intake influenced pain tolerance (and, less so, unpleasantness) more than either pain threshold or pain intensity is consistent with Franklin's notion. In fact, behavioral evidence suggests that mood, or cognitive/emotional factors influence pain tolerance more than other pain measures such as pain threshold or pain intensity ratings (Houle, McGrath, Moran, & Garrett, 1988;

Zelman et al., 1989).

Further evidence for this explanation is provided by studies which have compared the effects of various analgesic interventions on the different pain measures. Several investigations have shown that tolerance is more sensitive than threshold to the effects of analgesics (e.g., Chapman et al., 1985; Petrie, 1967, cited in Woodrow & Eltherington, 1988). For example, one study with humans showed that morphine and alcohol increased tolerance, but not threshold, to pain induced by mechanical pressure (Woodrow & Eltherington, 1988). Work from another laboratory revealed that naloxone decreased the latency of mice to jump from a hot-plate but did not affect the shorter latency response of paw-licking (Grevart & Goldstein, 1977). These findings suggest that endogenous opioids may modulate the emotional response to pain (i.e., pain tolerance) rather than the awareness of pain (i.e., pain threshold).

Also consistent with this notion are results from experiments indicating that narcotics produce analgesia by changing the unpleasantness or "pain reaction" rather than by changing the intensity or "pain sensation" (Beecher, 1968, cited in Woodrow & Eltherington, 1988; Price et al., 1985). For example, morphine administered to neurogenic patients reduced pain unpleasantness, but not pain intensity (Kupers, Konings, Adriaensen, & Gybels, 1991; but see

Gracely, Dubner, & McGrath, 1979).

In summary, opiates appear to affect pain tolerance more than pain threshold, and to affect unpleasantness ratings more than intensity ratings. In the present study, ingesting palatable sweet foods also produced this pattern of results. Tolerance and unpleasantness measures, which likely represent affective (emotional and/or cognitive) components of pain, showed greater sensitivity to sweets' analgesic effects than did threshold or intensity measures, which likely represent sensory dimensions of pain. Thus, the present findings are consistent with the argument that endogenous opioids mediate the analgesic effects of sweets, and that opioids primarily modify the affective component of pain.

5.1.4: Food Palatability

To date, researchers have focused mainly on the effects of sweet ingestion on analgesia, and have since coined this phenomenon "sweet-induced analgesia". However, the present findings suggest that a more accurate label may be "palatability-induced analagesia". Food palatability refers to the pleasantness, hedonic value, or rewarding properties of food (Le Magnen, 1992). The present results suggest that the palatability of a sweet food may be the critical factor in producing analgesia. In Experiment 1, subjects did not

show evidence of analgesia following the consumption of an 8% sucrose solution, a beverage which they described as being "too sweet" or "sickeningly sweet". Previous research has shown that a U-shaped relationship exists between sucrose/glucose concentration and pleasantness ratings, with maximal pleasantness (or peak palatability) occurring at moderate concentrations (Le Magnen, 1992). Therefore, in Expt. 1, the sucrose solution may not have produced analgesia because it may have been too concentrated to have tasted palatable. In Expt. 2a, the effects of sweets on analgesia were also weak, perhaps because the soft drinks did not taste very palatable (as evidenced by the finding that the soft drinks were rated relatively low by the subjects). In Expts. 2b-3b, the effects of sweet intake on analgesia were much stronger. Note that in these studies, the sweets that were consumed were chocolate-chip cookies which the subjects rated as highly palatable. These findings along with the positive correlations found between palatability ratings and the changes in some of the pain measures following treatment, suggest that the analgesic effects of a sweet food may depend on its palatability. This explanation supports the findings of Smith et al. (1990) who demonstrated that sweets' analgesic effect on human infants is dependent on its taste properties rather than on post-ingestive factors.

However, the cookies may have produced more analgesia than either the sucrose solution or the soft drinks for different reasons. In addition to sugar, the cookies contained fat and some caffeinated chocolate, whereas the sucrose solution and soft drinks did not. A recent study (Drewnowski et al., 1992) found that naloxone decreased the total caloric intake of several palatable foods, but the reduction was most pronounced for foods that were rich in sugar and fat (e.g., cookies and chocolate). Similarly, recent work with rats (Frye, Cuevas, & Kanarek, 1993) suggested that acute exposure to fat (in the form of corn oil) may be more effective than acute exposure to a 32% sucrose solution for producing analgesia. These findings are consistent with the idea that a food's analgesic effect can be attributed to the food's caloric and/or macronutrient composition, rather than to its palatability.

However, this explanation is unlikely given the findings from both the present study and previous work. First, sweet-induced analgesia was observed in both rats and human infants following the ingestion of solutions that contained only sugar (e.g., sucrose or glucose) and water (e.g., Blass et al., 1989, 1991). Therefore, the presence of fat is not necessary to produce analgesia. Furthermore, in the present study, the post-treatment pain measures of the unpalatable and palatable groups differed, yet the two

foods contained similar amounts of fat (approx. 2 g fat/black olive versus 3 g fat/chocolate-chip cookie). Second, sweet-induced analgesia was observed when rats received either sugar (e.g., in the form of sucrose solutions, waffle candy, or chocolate milk), or saccharin, a non-nutritive sweetener (Bergmann, Cohen, & Lieblich, 1984; Blass et al., 1987; Dum & Herz, 1984). These findings indicate that sugar content (or caloric value) is not the critical factor for producing the effect. Third, studies with rats have demonstrated that following conditioning, analgesia can be produced either by the mere anticipation of a palatable sweet food (Dum & Herz, 1984), or by exposure to an orange odor that was previously paired with morphine (Kehoe & Blass, 1989; Blass Shide, & Weller, 1989).

Collectively, these studies suggest that it is not the macronutrient content (neither the fat nor the sugar content) or the caloric density of a food that is critical for producing sweet-induced analgesia. However, the research is consistent with the idea that the palatability of the food is critical. Nonetheless, because the term "palatability" encompasses an aggregate of factors (including taste, odor, composition, texture, and past associations), a food's composition may play an indirect role in producing analgesia by influencing the palatability of the ingesta.

Although the above evidence argues against the role of macronutrient content directly producing palatability-induced analgesia, it has not eliminated the possible influence of caffeine contained within the cookies' chocolate chips. Perhaps the cookie produced greater analgesia than either the sucrose solution or the caffeine-free soft drinks because of its caffeine content. Pharmacological studies have shown that caffeine can facilitate the turnover of monoamines (especially noradrenaline and dopamine) in several brain regions, and antagonize central adenosine receptors. These are potential mechanisms by which caffeine might modulate the antinociception of pain and possibly, the affective component of pain (for recent reviews, see Sawynok & Yaksh, 1993; and Sawynok & Sweeney, 1989). However, there have been very few behavioral studies that have investigated the antinociceptive effects of caffeine alone on human pain perception. To date, most studies have evaluated the adjuvant actions of caffeine (e.g., Laska, Sunshine, Mueller, et al., 1984). Moreover, the experiments which have evaluated the actions of caffeine on pain have found that single doses of caffeine produce modest or no increases in analgesia. The results from two different studies suggest that 64 mg caffeine is ineffective in producing analgesia to pain arising from either dental extraction

(Forbes, Jones, Kehm, et al., 1990) or non-migrainous headaches (Ward, Whitney, Avery, & Dunner, 1991). Another study evaluating the effects of caffeine on post-operative oral surgery pain found that caffeine doses even as high as 130 mg produced changes in only two of six pain measures (Winter, Appleby, Ciccone, & Pigeon, 1983, cited in Sawynok & Yaksh, 1993). These doses are much higher than those found in the chocolate-chip cookies (approx. 4-5 mg caffeine/cookie) used in the present experiments. Furthermore, animal studies have shown that low doses of caffeine can actually attenuate morphine's antinociceptive action (e.g., Ahlijanian & Takemori, 1985). Only higher doses can enhance morphine analgesia (e.g., Misra, Pontani, & Vadlamani, 1985).

Another possibility is that caffeine can invoke positive mood changes (defined for example in terms of well-being, see File, Bond, & Lister, 1982), and that this positive mood state can change the affective quality of pain. Although the doses of caffeine required to increase euphoria or positive affect are relatively lower (e.g., 64 mg, Lieberman, Wurtman, Emde, et al., 1987; 100 mg, Griffiths, Evans, Heishman, et al., 1990) than those required to produce antinociception, they are still substantially higher than the caffeine doses found in the cookies (approx. 4-5 mg/cookie) used in the present study.

Therefore, it is unlikely that caffeine alone can account for the analgesic effects of the chocolate-chip cookies used in the present thesis. However, one future study which may help to quantify the relative influences of food palatability and/or food composition on palatability-induced analgesia might be to contrast the pain responsivity of groups after they consume diets that vary in fat, sugar, or caffeine content, but that are equal in palatability.

Expts. 3a and 3b were the first to demonstrate that the consumption of an unpalatable food (a black olive) may have an effect on pain sensitivity. Relative to ingesting a palatable sweet food (Expts. 3a and 3b), ingesting an unpalatable food decreased either pain thresholds (Expt. 3b) or pain tolerances (Expt. 3a). To date, no other studies with humans have compared the effects of palatability on pain sensitivity. The only study with rats which has compared the effects of different flavours on analgesia found that chronic (48-hour) exposure to both sweet (glucose/saccharin) flavours and non-sweet (quinine or salt) flavours attenuated the analgesic effects of morphine in rats, as measured by paw-lick latencies on a hot-plate (Holder, 1988). These results suggest that many flavours, independent of palatability or sweetness, activate the opioid-mediated pain system and then produce tolerance to morphine's analgesic effects. However, there is an

alternative explanation for quinine's attenuating effects on morphine analgesia. When quinine was added to the rats' drinking water, consumption was markedly reduced, and water-deprivation causes the release of opioids in rats (see Gambert et al., 1980; Majeed et al., 1986; Przewlocki et al., 1983; Reid et al., 1982; Vaswani & Tejwani, 1986).

In Holder's experiment, the effects of acute quinine (without morphine/saline injections) on rats' pain reactivity was not assessed. Perhaps in non-deprived rats, acute exposure to quinine produces an hypoanalgesic effect, similar to that produced by the unpalatable black olives used in the present experiments. There are at least two possible explanations for why the consumption of black olives produced an hypoanalgesic effect relative to the cookies. First, instead of playing a strictly analgesic role in pain perception, food may play a more modulatory role, with some foods increasing opioid activity and others decreasing its activity. Both unpalatable and palatable foods may modulate opioid activity; unpalatable foods may act by either inhibiting the release of EOPs or by facilitating their re-uptake whereas palatable foods may act by either increasing EOP release or by inhibiting their re-uptake.

Alternatively, unpalatable foods may modulate the activity of another neurotransmitter or neuromodulator

involved in pain modulation, such as the neuropeptide cholecystokinin (CCK). CCK, like the opioid antagonist naloxone, attenuates both morphine analgesia and food ingestion (Faris, Komisaruk, Watkins, & Mayer, 1983; Watkins, Kinscheck, Kaufman et al., 1985). CCK, injected into the ventromedial hypothalamus, causes a decrease in eating (Faris et al., 1983). Moreover, food consumption increases hypothalamic levels of CCK (McLaughlin, Baile, Della-Fera, & Kasser, 1985). The effects of CCK on eating (and analgesia) are thought to be mediated, at least in part, by its influence on opioid systems that potentiate eating (Leibowitz & Stanley, 1986). Therefore, in the present study, the consumption of unpalatable foods may have released CCK into the CNS where it then interacted with opioid mechanisms, blocking opioid action and producing hypoanalgesia. Margules (cited in Reid, 1985) predicted the existence of an endogenous opioid receptor antagonist (or endoloxone) that functions to dampen EOP activity. CCK may be this endoloxone which, when released, results in an attenuated analgesia or an antianalgesia (see below). To test these ideas further, studies are needed in which rats' CNS levels of both CCK and EOPs are measured following exposure to palatable and unpalatable foods.

5.1.5: Pain Escapability and Conditioned Analgesia

Another experimental parameter which may influence palatability-induced analgesia in human adults is the perceived 'escapability' or controllability of the pain or stressor (see Maier, 1986). Previous work with rats has shown that in order for stress/pain (e.g., cold-water swims or electrical shocks) to activate an opioid-mediated, rather than a nonopioid-mediated pain system, the stress/pain must be viewed as inescapable (Jackson, Maier, & Coon, 1979; Maier, Drugan, & Grau, 1980; Maier, Sherman, Lewis et al., 1983; Terman et al., 1984). For ethical reasons, human adult subjects are informed, prior to testing, that they can remove themselves from the pain at anytime. Therefore, for human adults the pain is escapable and hence, it may not activate opioid-mediated pathways whereas with rats and human infants (e.g., undergoing circumcision or heel-lance) the pain is usually inescapable. In addition, because human subjects are told that they may remove the noxious stimulus at anytime, this information may serve as a safety signal which triggers antianalgesia systems. Previous studies suggest that the human CNS may contain circuitry, called antianalgesia systems, that can inhibit pain suppression (e.g., Faris et al., 1983; Watkins et al., 1985). A recent study with rats has shown that environmental signals for safety inhibit stress-induced analgesia and abolishes

morphine's analgesic effects (Wiertelak, Maier, & Watkins, 1992). This antianalgesia is mediated, at least in part, by CCK in the spinal cord. Because palatability-induced analgesia is mediated by EOPs, safety signals existing in the present experiments may have released CCK into the subjects' CNS, thus attenuating any analgesic effects of the palatable sweet ingesta. In other words, because the subjects were aware that the pain was escapable, antianalgesia systems may have suppressed any analgesia induced by the palatable sweets.

5.2: THE EFFECTS OF PALATABLE SWEET INGESTA ON TACTILE SENSITIVITY

In the present studies, tactile thresholds were measured to determine whether palatable sweet intake modulated pain systems exclusively or other systems as well. Palatable sweet consumption did not alter tactile thresholds. Therefore, the primary effect of the palatable sweet ingesta was to produce analgesia (a specific reduction of pain sensation), rather than producing a non-specific anesthesia (a general loss of feeling or sensation). This finding is consistent with that of previous studies which have suggested that activation of endogenous pain-modulatory systems (e.g., by vaginal stimulation) does not affect human adults' sensitivity to touch (Whipple & Komisaruk, 1985,

1988; Whipple, Martinez-Gomez, Oliva-Zarate et al., 1989; Whipple, Ogden, & Komisaruk, 1992). Therefore, a rewarding experience (e.g., palatable sweet consumption, vaginal stimulation) seems to have a direct effect on the pain system, rather than acting as a generalized "distractant", depressant, or anesthetic (see Whipple & Komisaruk, 1988).

5.3: POSSIBLE WEAKNESSES OF THE PRESENT EXPERIMENTS

5.3.1: The Use of Multiple Trials

One possible problem with the present studies is the use of a design which incorporates repeated measures (or multiple trials). On a theoretical level, it is problematic to use multiple trials for two reasons. First, because the subjects receive pain on repeated trials, the pain experienced during the first trial may cause opioid release, and thus analgesia to the pain received during the second trial (a phenomenon that has been termed stress-induced analgesia; e.g., see Hayes et al., 1978). Second, following the exposure to pain on the first trial, environmental cues paired with the pain (e.g., the sight of the hot-plate, pressure algometer, or cold-water pressor) may serve as a conditioned stimulus to elicit analgesia on subsequent trial(s). The mere expectation of pain has been shown to produce a naloxone-sensitive analgesia in rats (termed conditioned analgesia or anticipatory analgesia; see

Fanselow & Bolles, 1979; Hayes et al., 1978; Watkins, Cobelli, & Mayer, 1982; Watkins & Mayer, 1982).

If conditioned or stress-induced analgesia had occurred for the subjects in the present experiments, then the pain experienced at baseline trials would have decreased pain sensitivity (e.g., subjects would have shown increased pain tolerance) on subsequent trials, thus obscuring any analgesic effects induced by the palatable sweets. However, analyses showed that conditioned or stress-induced analgesia did not occur in the present study. For example, for subjects in the control groups, mean intensity and unpleasantness ratings increased between trials, while mean thresholds and tolerances decreased between trials. These results indicate that "sensitization" (enhanced pain sensitivity), rather than stress-induced analgesia (decreased pain sensitivity), occurred following repeated exposure to the noxious stimuli. Although it cannot be determined from the present study whether sensitization occurred at peripheral (e.g., nociceptor) or at central levels (e.g., dorsal horn neuron), the non-injurious nature of the noxious stimuli (i.e., they did not produce tissue damage or any other injury) would suggest central sensitization (Woolf, 1989, 1994).

The alternative to multiple-trial experiments are single-trial experiments which may solve the potential

problem of both stress-induced analgesia and sensitization. However, even in a single-trial study, conditioned analgesia may still occur because subjects must be informed, prior to testing, that they will receive pain. Therefore, future studies, whether employing single or multiple trials, should continue to evaluate whether the mere expectation of pain can produce analgesia. Moreover, it should also be determined whether the mere expectation of something positive (e.g., palatable sweet foods) can elicit analgesia in humans as it can in rats. Kehoe & Blass (1989) found that after pairing an orange scent with a morphine injection, presenting the orange scent alone increased pain thresholds in ten-day old rats, suggesting that the orange scent caused a release of endogenous opioids. Similarly, Dum & Herz (1984) found that rats who were expecting to receive candy while sitting on a hot plate displayed a naloxone-reversible increase in paw-lick latencies.

One interesting finding in the present experiments was that trial effects were found more often for males than for females. For example, in Expts. 2c and 3b, only male subjects showed significant changes in their ratings of intensity and unpleasantness between familiarization and pre-treatment trials. This finding, along with that of previous studies (e.g., Feine et al. 1991), suggest that male subjects are more influenced by experience with

experimental pain than are female subjects, adding to the list of reasons why human females may serve as better subjects than males in preliminary studies of palatability-induced analgesia.

5.3.2: Non-Randomized Experiments

In several of the present experiments (Expts. 2b, 2c, 3a, and 3b), subjects were not randomly assigned to treatment groups, but instead were pre-assigned based on their pre-test food ratings. This was to ensure that each group (e.g., the unpalatable group) consisted of subjects with a specific food preference (e.g., a strong dislike for black olives). Without pre-assignment (or subject selection), the data from many subjects would have had to be discarded because of mismatches between food preferences and treatment groups. However, randomization would have produced the same result; many subjects would still have had to be discarded because of mismatched food ratings, but in this case, only after the data were collected. Pre-tests showed that it is very difficult to select a treatment food that is rated differently (i.e., as either palatable, unpalatable, or neutral) by a large sample of subjects. For example, very few people rate chocolate chip cookies low in palatability, or black olives high in palatability. Therefore, subject selection would still be necessary,

whether subjects were randomly assigned or pre-assigned to treatment groups.

Nonetheless, a lingering problem with subject selection is that groups may have differed at baseline. For example, subjects who were assigned to the unpalatable group based on their low black olive ratings may have been inherently different (e.g., in terms of opioid levels, or pain sensitivity) from subjects who were assigned to the palatable sweet group based on their high chocolate-chip cookie ratings. However, to address the problem of baseline group differences (i.e., of subject selection), a number of precautions were taken. Firstly, ANCOVA was selected for the evaluation of treatment effects. ANCOVA is the analysis of choice when subjects cannot be randomly assigned to groups because it adjusts the group means to what they would be if all subjects scored identically on the covariate (in this case, the pre-treatment measure). In other words, individual differences at baseline are removed from the analyses so that, presumably, the only differences remaining are the effects of the treatment. Secondly, a between-groups analysis of the pre-treatment pain measures was performed to ensure that there were no differences in pain sensitivity among the groups before treatment. Thirdly, for each pain measure, the pre-treatment group means were ranked in ascending order to determine whether there were

consistent differences in pain sensitivity among groups (e.g., relative to the other groups, did the unpalatable group always have the lowest pain tolerance?). Inspection of these pre-treatment means showed no apparent differences between groups on any of the pain measures. This suggests that groups did not differ in their pain sensitivity and perhaps not in their opioid levels. Fourthly, at the end of each experiment, each subject was administered a questionnaire which included questions concerning their current eating habits (e.g., amount of sweets/day; last time they ate/drank). Subjects did not appear to differ in the amount of sweets they consumed, nor did their pain sensitivity correlate with their eating habits. And finally, in the last (and most critical) experiment (Expt. 3b), subjects were pre-assigned to groups according to their pre-treatment tolerance score. This was to ensure that for each sex, all four groups had the same average tolerance at pre-treatment so that any treatment effects were not obscured by baseline group differences. Therefore, based on these analyses and precautions, it appears unlikely that there were inherent differences among the treatment groups that could account for any of the effects observed in the present study.

5.3.3: Correlations Between Subject Variables and Pain Perception: Small Sample Size and Subject Homogeneity

Although previous research with humans has shown that pain responsivity can be modulated by a number of subject variables (e.g., smoking, recent alcohol consumption, medication, exercise, phase of menstrual cycle; see Hapidou & De Catanzaro, 1988; Pomerlau et al., 1984), the present experiments failed to find any significant correlations between subject variables and measures of pain sensitivity. These low correlations may be due, at least in part, to the somewhat small sample sizes, and to the relative homogeneity of subject characteristics (e.g., age, handedness, university students). Nonetheless, it is recommended that these correlations continue to be measured in future experiments.

5.4: CONCLUSIONS AND FUTURE STUDIES

In summary, the present study showed that under certain conditions, the consumption of palatable sweet foods can produce analgesia to experimental pain, at least in adult females. This study was the first to demonstrate that palatability-induced analgesia in humans can persist after infancy (e.g., Blass et al., 1987) and childhood (Miller et al, 1994). However, this phenomenon does not appear to be as pronounced in late childhood (Miller et al., 1994) or

adulthood (present study) as it does in infancy. One possible explanation may be that because adults and children have a much wider variety of foods available to them, and perhaps have a history of palatable sweet ingestion, they may find the sweet foods to be less palatable or rewarding than do infants. Alternatively, it may be that this phenomenon diminishes with age because it no longer serves any biological advantage (e.g., mother-infant attachment, energy conservation, see Kehoe & Blass, 1986; Blass, 1992).

In animals, palatability-induced analgesia has been shown to be opioid-mediated (e.g., Bergmann et al., 1985; Blass et al., 1987). Further studies with human adults are needed to ascertain whether the palatability-induced analgesia displayed in this thesis, was also mediated by EOPs. One method used with rats to determine whether palatability-induced analgesia is opioid-mediated is to first produce palatability-induced analgesia, and then administer an opioid antagonist to observe whether the palatability-induced analgesia is reversed (e.g., Blass et al., 1987). Because naltrexone (Trexan), a pure opioid antagonist, can be orally administered, is considered safe, and has a long duration, it would probably be the most suitable antagonist to use in experiments attempting to show that palatability-induced analgesia is opioid-mediated in humans. Also, as previously demonstrated with rats, a

second method used to determine whether palatability-induced analgesia is opioid-mediated is to test for cross-tolerance between morphine analgesia and palatability-induced analgesia (e.g., Bergmann et al., 1985). Because morphine produces tolerance and dependence, this experiment may not be recommended with human subjects. However, with humans, it may be possible to test for cross tolerance between a milder narcotic analgesic (e.g., codeine) and palatability-induced analgesia.

Nevertheless, even without these additional studies, given the previous evidence with rats that palatable sweet ingesta operate through an endogenous opioid system (e.g., Blass et al., 1987), it is likely that the palatability-induced analgesia demonstrated with human adults in this thesis was also opioid-mediated. If future studies ascertain that consuming palatable sweet foods produces an opioid-mediated analgesia, this will help us to better understand human intrinsic pain-modulatory systems. Improved knowledge of our pain systems has the potential to provide new and more effective approaches to the therapeutic treatment of pain.

Footnotes

1. Within the controlled clinical setting, opiate abuse (defined in terms of addiction, or psychological dependence) is extremely rare (e.g., Melzack, 1990; Miller & Jick, 1978; Porter & Jick, 1982; Tywcross, 1978). Even patients who are allowed to self-administer opioids for brief periods discontinue the drug when their pain is relieved (Jaffe, 1990; Melzack, 1990).

2. Although there is strong evidence for a link between the EOPs and the rewarding effects of sweet ingestion, there may be other systems involved in the control of sweet intake. For example, morphine may increase sweet consumption because centrally-administerd morphine increases glucose metabolism and impairs insulin secretion (Giugliano, 1984; Kornetsky, Huston-Lyons, & Porrino, 1991). Therefore, the opioid reward system may be interlinked with a number of other systems involved in sweet ingestion.

3. Naltrexone and naloxone can antagonize analgesia produced by a variety of nonopioid manipulations (e.g., the administration of acetylcholine, or nitrous oxide) (Hayes, Price, & Dubner, 1977). Opioid antagonists can also produce nonspecific actions, such as motor impairment (Katz, 1979) and illness (Frenk & Rogers, 1979), actions which may

influence pain responsivity. However, these nonopioid antianalgesic and "side" effects are produced by only large doses of opioid antagonists, doses much higher than those needed to reverse the analgesia produced by either opiates or sweets. Moreover, opioid antagonists in low concentrations bind preferentially to opiate rather than nonspecific sites (Snyder, 1975). Therefore, given the relatively low, non-discriminable, doses of opioid antagonists (e.g., 0.5 mg/kg b.wt. naltrexone; Blass et al., 1987) needed to reverse sweets' analgesic effects, it is likely that sweet-induced analgesia is mediated primarily by opioid, rather than by nonopioid, systems.

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APPENDIX A

Standardized Instructions: Forearm Immersion

Thank you for volunteering as a subject for our study on subjective discomfort. While speaking with you on the phone, I told you that your left forearm would be immersed in cold water. Therefore, at various times throughout the experiment, I will ask you to rate your level of physical discomfort using these two scales. (HAND OUT VASs) There are two aspects of pain that we are interested in measuring: the intensity or how strong the pain feels, and the unpleasantness or how disturbing the pain is to you. The distinction between these two aspects of pain might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds or how unpleasant it is to hear it. The intensity of pain is like loudness; the unpleasantness of pain depends not only on intensity but also on other factors which may affect you such as whether you like or dislike the music being played.

These are two scales for measuring each of these two aspects of pain. Note that the bottom of the intensity scale corresponds to "no sensation" and the top to "the most intense that one can imagine". Similarly, the bottom of the unpleasantness scale refers to "not bad at all" and the top to "the most unpleasant that one can imagine". Although some pain sensations may be equally intense and unpleasant, I would like you to judge the two aspects independently. Do you understand the difference between the intensity and unpleasantness of pain?

(1) Now, please mark on the scales where you would currently rate your level of physical discomfort in terms of intensity and unpleasantness. Please turn to the next page where there are unmarked scales.

FOREARM IMMERSION: Pre-treatment Trial

Please roll up the sleeve on your left arm. In a minute, I will ask you to place your forearm in the water in front of you. I want you to place your lower arm flat on the bottom of the tub (DEMONSTRATE WITH OWN ARM IN EMPTY CONTAINER). Now, please listen carefully to these instructions. When the cold water first feels painful, that is, when you perceive any pain at all, I want you to say "PAIN" and I will record the time. If, at any time, you feel that the pain is too uncomfortable to continue any longer, you can remove your arm from the water. After you remove your arm, I will ask you to rate the intensity and the unpleasantness of your physical discomfort on the two scales.

Are you ready? Please place your left arm in the water. (START STOPWATCH) Make sure that you say "PAIN" when you first experience any pain (RECORD TIME WHEN S SAYS "PAIN". ALSO, IF

THE S REMOVES HIS HAND BEFORE 4 MINS HAS ELAPSED, RECORD THAT TIME).

(AFTER 4 MINS). Please remove your arm from the water. Dry off your arm with the towel provided and leave it wrapped in the towel. Please, do not touch your arm.

(2) Now on the scales provided, mark your current level of physical discomfort in terms of intensity and unpleasantness. Please turn to the next page where there are unmarked scales.

MONOFILAMENTS: Pre-treatment Trial

Next, I will measure your sensitivity to touch. I will do this by applying these hair-like nylon fibers to the back of your right hand (DEMONSTRATE ON OWN HAND - APPLY FIBER TO DORSAL AREA BETWEEN INDEX FINGER AND THUMB). I want you to tell me when you first feel the tip of the fiber touch your hand. So that you do not see when I apply the fibers, I want you to place your right hand behind this curtain.

Let's begin. Please report to me each time that you first feel a fibre tip being applied to the back of your hand by saying "NOW". (START AT FIBER # 2.44. In an ascending/descending order apply each fiber 3 times and record the # of the fiber that the S reports feeling the fiber 3/3 times.)

TREATMENT (Experiment 1):

NONSOLUTION GROUP

In about 15 minutes, we will repeat this procedure. Until then, I would like for you to read something from this psychology text. (GIVE S PSYCHOLOGY TEXT).

SOLUTION GROUPS

Note that there are 5 small cups of solution in front of you. The solutions consist of plain water and may contain sugar. I want you to put the contents of the first cup in your mouth but do not swallow it. Swish the contents around. I will tell you when 20 seconds is up and then you can swallow it. If the amount of solution is too great for you to swish comfortably, you may swallow a little, but continue to swish the remainder. (AFTER 20 SEC). Please swallow the solution. (AFTER 2 MINUTES). Put the contents of the second cup in your mouth but do not swallow it. Swish the contents around and I will tell you when 20 sec. is up and then you can swallow it. (AFTER 20 SEC). Please swallow the solution. (AFTER 2 MINUTES). Put the contents of the third (fourth and fifth) cup in your mouth but do not swallow it. Swish the contents around. I will tell you when 20 sec. is up and then you can swallow it (AFTER 20 SEC). Please swallow the solution. (REPEAT FOR FOURTH AND FIFTH CUP.)

(3) Would you now rate on your unmarked scales your current levels of physical discomfort, in terms of intensity and

unpleasantness. Please turn to the next page where there are more unmarked scales.

FOREARM IMMERSION: Post-treatment Trial
Next, I will again ask you to put your left forearm in the water. Remember to say "NOW" when you first feel pain. And if, at any time, the pain becomes too uncomfortable to continue any longer, remove your hand from the water. Then you will rate your level of pain of the two scales.

Are you ready? Please place your left arm in the water. (START STOPWATCH) Make sure that you say "NOW" when you first experience any pain (RECORD TIME WHEN S SAYS "NOW". ALSO, IF THE S REMOVES HIS HAND BEFORE 4 MINS, RECORD THAT TIME). (AFTER S REMOVES HAND OR AFTER 4 MINS) Please remove your hand from the water. Dry off your hand with the towel provided and leave it wrapped in the towel.

(4) Now on the blank scales, please mark your current level of physical discomfort in terms of intensity and unpleasantness. You can now remove the towel and roll down your sleeve.

MONOFILAMENTS: Post-treatment Trial
Now, again I will measure your touch sensitivity. Please place your right hand behind the curtain and tell me when you first feel the fiber tip touch your hand by saying "NOW". (START WITH FIBER # 2.44. In an ascending/descending order, apply each fiber 3 times and record the # of the fiber which the S detects 3/3 times).

Next, I would like to take a measure of your height and weight. Please remove your shoes. (RECORD MEASURES).

QUESTIONNAIRE
Next I would like you to fill out a personal data form that I will hand to you in a few minutes. First I will give you a few instructions. I want you to answer the questions as accurately and as honestly as you can. I assure you that all your answers, as well as your data and discomfort ratings, will be confidential. You will notice that your name is not asked for anywhere on any of the papers. Also, at the end of the session I will ask you to put your personal questionnaire, your data sheet, and your discomfort scales together in a brown envelope which will be placed with the envelopes from the other 120 subjects. The data will be coded anonymously on the computer. Therefore, you have no reason to fear that we will identify your responses with who your are. You will remain anonymous.

When you complete the questionnaire, please put it in the brown envelope along with your discomfort ratings and data and place it on the table on your way out (GIVE S THE DAT SHEET AND

RATINGS). On this table, there is a sheet of paper with my phone # and office room # on it. Take one with you and if you have any questions about the study you can call me. However, I can not tell you what the study is about until all subjects have been tested. But, when all the data has been collected I will post the purpose and the results of the study on my door. Please do not discuss any aspect of this procedure with anyone until all the data has been collected.
(HAND OUT QUESTIONNAIRE) Now, please complete all the questions on the personal data form. Please answer the questions accurately and honestly. And thank you for participating in the study.

APPENDIX B

Standardized Instructions: Finger Pressure

Thank you for volunteering as a subject for our study on subjective discomfort. While speaking with you on the phone, I told you that I would be applying pressure to your fingers. Therefore, at various times throughout the experiment, I will ask you to rate your current level of physical discomfort on these two scales (HAND OUT VASs). There are two aspects of pain that we are interested in measuring: the intensity or how strong the pain feels, and the unpleasantness or how disturbing the pain is to you. The distinction between these two aspects of pain might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds or how unpleasant it is to hear it. The intensity of pain is like loudness; the unpleasantness of pain depends not only on intensity but also on other factors which may affect you such as whether you like or dislike the music being played.

These are two scales for measuring each of these two aspects of pain. Note that the bottom of the intensity scale corresponds to "no sensation" and the top to "the most intense that one can imagine". Similarly, the bottom of the unpleasantness scale refers to "not bad at all" and the top to "the most unpleasant that one can imagine". Although some pain sensations may be equally intense and unpleasant, I would like you to judge the two aspects independently. Do you understand the difference between the intensity and unpleasantness of pain?

(1) Now please mark on the scales where you would currently rate your level of physical discomfort in terms of intensity and unpleasantness. Please turn to the next page where there are unmarked scales.

FINGER PRESSURE: Pre-treatment Trial

You may be curious as to what I will use to apply pressure to your fingers. (LIFT CURTAIN AND SHOW METER). I will apply pressure to each of your four fingers on your left hand starting with your index finger. In a minute, I will ask you to place your left index finger on the 1 mm diameter point of the meter and I will gradually apply pressure to your finger by pushing this foot pedal. (DEMONSTRATE USING YOUR OWN FINGER). Now, please listen carefully to these instructions. When the finger pressure first becomes painful, that is, when you feel any pain at all, I want you to say "PAIN". When the finger pressure becomes too uncomfortable to continue any longer, I want you to say "STOP", and I will stop it. However, just before you think you will say "STOP", I want you to rate the intensity and unpleasantness of your discomfort or pain on the scales provided. (For EXP 1,

Ratings apply for only the pinky or fourth finger). Are the instructions clear? Good. I will pull this curtain so that you can not monitor the level of pressure that is being applied (PULL CURTAIN).

Are you ready? Please slide your left arm under the curtain and place your left index finger in the meter. (ADJUST THE FINGER). Remember to say "PAIN" when the finger pressure first becomes painful and say "STOP" when the finger pressure becomes too uncomfortable to continue. And don't forget to rate you level of pain just prior to saying "STOP" (START PRESSURE AND TIMER, RECORD THE #S AND TIMES AT WHICH THE S SAYS "PAIN" AND "STOP" AND REMOVE FINGER). (REPEAT FOR OTHER THREE FINGERS WITH A 5 SEC INTERVAL BETWEEN EACH).

(IF S FAILS TO SAY STOP BEFORE 30 SECONDS HAS ELAPSED):

(2) Now please mark on the scales where you would currently rate your level of physical discomfort in terms of intensity and unpleasantness. Please turn to the next page where there are more unmarked scales.

MONOFILAMENTS: Pre-treatment Trial

Next, I will measure your sensitivity to touch. I will do that by applying these hair-like nylon fibers to the back of your right hand (DEMONSTRATE ON OWN HAND - APPLY FIBER TO DORSAL AREA BETWEEN THE INDEX FINGER AND THUMB). What I want you to do is to tell me when you first feel the tip of the fiber touch your hand. Say "NOW" whenever you feel it. So that you do not see when the fibers are being applied, I want you to place your right hand behind the curtain.

Let's begin. Please report each time that you first feel a fibre tip being applied to the back of your hand by saying "NOW". (START AT FIBER 2.44. In an ascending/descending order. apply each fiber 3 times and record the # of the fiber which the S reports feeling 3/3 times).

TREATMENT (Experiment 2a)

NONSOLUTION GROUPS

In about 5 minutes, we will repeat this procedure. Until then, I would like you to read something from this psychology text. (HAND OUT PSYCHOLOGY TEXTBOOK)

SOLUTION GROUPS

a)WATER GROUP - During the next 5 minutes, I want you to sit here and drink some water. I want you to drink as much as you would like. (POUR A GLASS OF WATER AND PLACE THE GLASS AND THE JUG OF WATER IN FRONT OF THE SUBJECT).

b)POP GROUP - During the next 5 minutes, I want you to sit here and drink some pop. Which do you prefer: Coke or Sprite/7-UP?

(POUR THE PREFERRED POP IN A GLASS AND PLACE THE GLASS AND THE POP CAN IN FRONT OF THE SUBJECT). I want you to drink as much as you would like.

(3) Would you rate on your unmarked scales your current levels of physical discomfort, in terms of intensity and unpleasantness. Please turn to the next page where there are more unmarked scales.

FINGER PRESSURE: Post-treatment Trial
Now we will repeat the finger pressure again. Please place your left index finger in the meter. Remember to say "PAIN" when the finger pressure first becomes painful and say "STOP" when the finger pain becomes too uncomfortable to continue. And remember to rate your level of pain just prior to saying "STOP". (ADJUST FINGER, PULL CURTAIN, START PRESSURE & TIMER. RECORD THE METER READINGS AT "PAIN" AND "STOP". REPEAT FOR THE OTHER THREE FINGERS WITH A 5 SEC INTERVAL BETWEEN EACH).

(IF S FAILS TO SAY "STOP" BEFORE 30 SECONDS HAS ELAPSED:)
(4) Now on the blank scales, mark your current level of physical discomfort in terms of unpleasantness and intensity.

MONOFILAMENTS: Post-treatment Trial
Now, I will again measure your touch sensitivity. Please place your right hand behind the curtain and tell me when you first feel each fiber tip touch the back of your hand by saying "NOW". (START WITH FIBER # 2.44. In an ascending/descending order, apply each fiber 3 times & record the # of the fiber which the S reports feeling 3/3 times).

Next, I want to measure your height and weight. Please remove your shoes. (RECORD MEASURES).

POP GROUP ONLY.
Next, I would like you to rate how much you like the pop that you drank earlier on this 10 point scale.

QUESTIONNAIRE
Next I would like you to fill out a personal data form that I will hand to you in a few minutes. First I will give you a few instructions. I want you to answer the questions as accurately and as honestly as you can. I assure you that all your answers, as well as your data and ratings, will be confidential. You will notice that your name is not asked for anywhere on any of the papers. Also, at the end of the session I will ask you to put your personal questionnaire, your data sheet and all your ratings in this brown unmarked envelop, and place it somewhere in the

pile of envelopes from the other subjects. The data will be coded anonymously on the computer. Therefore, you have no reason to fear that we will identify your responses with who your are. You will remain anonymous.

When you complete the questionnaire, please put it in the brown envelope along with your discomfort ratings & data and place it on the table on your way out (GIVE THE SUBJECT THE DATA SHEET AND RATINGS). On this table, there is a sheet of paper with my phone # and office room # on it. Take one with you and if you have any questions about the study you can call me. However, I can not tell you what the study is about until all subjects have been tested. But, when all the data has been collected, I will post the purpose and the results of the study on my door. Please do not discuss any aspect of this procedure with anyone until all the data has been collected.

(HAND OUT THE QUESTIONNAIRE) Now, please complete all the questions on the personal data form. Please answer the questions accurately and honestly. And thank you for participating in the study.

APPENDIX C

Standardized Instructions: Forearm Heat

Hello. Thank you for volunteering as a subject for our study on subjective discomfort. Before we get started, I would like for you to rate your current level of hunger on this scale (GIVE S A HUNGER SCALE). The 1 corresponds to "not hungry at all" and the 10 corresponds to "extremely hungry". Now please rate your current level of hunger.

While speaking with you on the phone, I told you that I would be applying heat to your forearm. Therefore, at various times throughout the experiment, I will ask you to rate your current level of physical discomfort using these two scales (HAND OUT 6 VASs). There are two aspects of pain that we are interested in measuring: the intensity or how strong the pain feels, and the unpleasantness or how disturbing the pain is to you. The distinction between these two aspects of pain might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds or how unpleasant it is to hear it. The intensity of pain is like loudness; the unpleasantness of pain depends not only on intensity but also on other factors which may affect you such as whether you like or dislike the music being played.

These are two scales for measuring each of these two aspects of pain. Note that the bottom of the intensity scale corresponds to "no sensation" and the top to "the most intense that one can imagine". Similarly, the bottom of the unpleasantness scale refers to "not bad at all" and the top to "the most unpleasant that one can imagine". Although some pain sensations may be equally intense and unpleasant, I would like you to judge the two aspects independently. Do you understand the difference between the intensity and unpleasantness of pain?

(1) Now please rate your current level of physical discomfort in terms of intensity and unpleasantness on the scales provided.

FOREARM HEAT: Familiarization trial

You may be curious as to what I will use to apply heat to your forearm. (LIFT CURTAIN AND SHOW HOT-PLATE). In a minute, we will run a practice trial in which I will ask you to place your left forearm flat on this metal plate. I will gradually apply heat to your arm. Make sure that only your forearm rests on the plate and that it presses firmly against the plate (DEMONSTRATE USING YOUR OWN ARM). Now, please listen carefully to these instructions. When the heat first becomes painful, that is, when you feel any pain at all, I want you to say "PAIN". When the heat becomes too uncomfortable to continue any longer, I want you to say "STOP", and remove your arm immediately. However, as soon

as you say "STOP", I want you to rate the intensity and unpleasantness of your discomfort or pain using the two scales again. Are these instructions clear? Good.

Are you ready? Please place your left forearm firmly on the plate. (ADJUST THE ARM). Remember to say "PAIN" when the heat first becomes painful and say "STOP" when the finger heat becomes too uncomfortable to continue. And don't forget to rate you level of pain as you remembered it the moment that you said "STOP" (START heat at 43^0 C and reset timer to 0 sec., RECORD the temperature, latencies, intensity and unpleasantness ratings at which the Ss say "STOP").
(IF S FAILS TO SAY "STOP" BEFORE THE TEMP. HAS REACHED 48^0 C, TELL SUBJECT TO REMOVE ARM AND):

(2) Now please rate your current level of physical discomfort in terms of intensity and unpleasantness.

MONOFILAMENTS: Familiarization trial
Next, I will measure your sensitivity to touch. I will do that by applying these hair-like nylon fibers to the back of your left hand (DEMONSTRATE ON OWN HAND - APPLY FIBER TO DORSAL AREA BETWEEN THE INDEX FINGER AND THUMB). What I want you to do is to tell me when you first feel the tip of the fiber touch your hand. Say "NOW" whenever you feel it. So that you do not see when the fibers are being applied, I want you to place your right hand behind the curtain.

Let's begin. Please report each time that you first feel a fibre tip being applied to the back of your hand by saying "NOW". (START AT FIBER 3.22. In an ascending/descending order. apply each fiber 3 times and record the # of the fiber which the S reports feeling 3/3 times).

READING:

In about 5 minutes, we will repeat this procedure. Until then, I would like you to sit here and read something from this psychology text (GIVE S THE TEXTBOOK AND POINT OUT THE PASSAGE TO BE READ). Don't worry, you will not be tested on what you read.

(AFTER 5 MINS HAS ELAPSED:)
(3) Now please rate your current level of physical discomfort in terms of intensity and unpleasantness.

FOREARM HEAT: Pre-treatment Trial
Now we will repeat the forearm heat again using your left arm. Please place your left forearm firmly on the metal plate. Remember to say "PAIN" when the heat first becomes painful and say "STOP" when the heat pain becomes too uncomfortable to continue. And remember to rate your level of pain as soon as you say "STOP". (ADJUST ARM, PULL CURTAIN, START PLATE at 44^0 C and timer at 0 sec. RECORD THE TEMP AND TIME READINGS AND THE RATINGS

AT "STOP").
(IF S FAILS TO SAY "STOP" BEFORE 48^0 C, remove arm and say)
(4) Now please rate your current level of physical discomfort in terms of intensity and unpleasantness.

MONOFILAMENTS: Pre-treatment Trial
Now, I will again measure your touch sensitivity but this time we will use your right hand. Please place your right hand behind the curtain and tell me when you first feel each fiber tip touch the back of your hand by saying "NOW". (START WITH FIBER # 3.22. In an ascending/descending order, apply each fiber 3 times & record the # of the fiber which the S reports feeling 3/3 times).

TREATMENT (Experiments 3a):
"NOTHING" GROUP:
In about 5 minutes, we will repeat this procedure. Until then, I would like you to read something from this psychology text. (GIVE S THE PSYCHOLOGY TEXTBOOK)

FOOD GROUPS:
a)"DISLIKE" GROUP - During the next 5 minutes, I just want you to sit here and while you do that, I want you to eat a black olive. (GIVE S A BLACK OLIVE ON A TOOTHPICK)

b)"NEUTRAL" GROUP - During the next 5 minutes, I just want you to sit here and while you do that, I want you to eat a rice cake. (GIVE S 1/2 OF A RICE CAKE WRAPPED IN A NAPKIN)

c)"LIKE" GROUP - During the next 5 minutes, I just want to sit here and while you do that, I want you to eat a chocolate chip cookie (GIVE S A COOKIE WRAPPED IN A NAPKIN)

(5) Now please rate your current level of physical discomfort in term~ of intensity and unpleasantness.

FOREARM HEAT: Post-treatment Trial
Now we will repeat the forearm heat again using your left arm. Please place your left forearm firmly on the metal plate. Remember to say "PAIN" when the heat first becomes painful and say "STOP" when the heat pain becomes too uncomfortable to continue. And remember to rate your level of pain as soon as you say "STOP". (ADJUST ARM, PULL CURTAIN, START HOT-PLATE at 44^0 C and timer at 0 sec. RECORD THE TEMP AND LATENCY READINGS AND THE RATINGS AT "STOP").

(IF S FAILS TO SAY "STOP" BEFORE 48^0 C, remove arm and say)
(6) Now please give me ratings of your current level of physical discomfort in terms of intensity and unpleasantness.

MONOFILAMENTS: Post-treatment Trial
Now, I will again measure your touch sensitivity. Please place your right hand behind the curtain and tell me when you first feel each fiber tip touch the back of your hand by saying "NOW". (START WITH FIBER # 3.22. In an ascending/descending order, apply each fiber 3 times & record the # of the fiber which the S reports feeling 3/3 times).

FOOD GROUPS ONLY.
Next, I would like you to rate how much you like the food (NAME APPROPRIATE FOOD) that you ate earlier on this 10 point scale. (GIVE SUBJECT A FOOD SCALE)

HEIGHT AND WEIGHT
Next, I want to measure your height and weight. Please remove your shoes. (RECORD MEASURES).

QUESTIONNAIRE
The last thing I want you to do is to fill out a questionnaire that I will hand to you in a few minutes. First I will give you a few instructions. I want you to answer the questions as accurately and as honestly as you can. I assure you that all your answers, as well as your data and ratings, will be confidential. You will notice that your name is not asked for anywhere on any of the papers. Also, at the end of the session I will ask you to put your personal questionnaire, your data sheet and all your ratings in this brown unmarked envelop, and place it somewhere in the pile of envelopes from the other subjects. The data will be coded anonymously on the computer. Therefore, there is no way that we could ever identify your responses with who your are. You will remain anonymous.
When you complete the questionnaire, please put it in the brown envelope along with your discomfort ratings & data and place it on the table on your way out (GIVE THE SUBJECT THE DATA SHEET AND RATINGS). On this table, there is a sheet of paper with the experimenter's phone # and office room # on it. Take one with you and if you have any questions about the study you can call her. However, I can not tell you what the study is about until all subjects have been tested. But, when all the data have been collected, I will post the purpose and the results of the study on my door. Please do not discuss any aspect of this procedure with anyone until all the data have been collected.

(HAND OUT THE QUESTIONNAIRE) Now, please complete all the questions on the questionnaire. Please answer the questions accurately and honestly. And thank you for participating in the study.

APPENDIX D

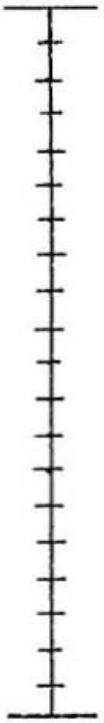
INTENSITY

Most intense that one could imagine

No sensation

UNPLEASANTNESS

Most unpleasant that one could imagine



Not bad at all

APPENDIX E

Personal Questionnaire

1. Subject's Birthdate (day/month/year):

2a. On average, how many hours do you sleep a night?
 b. How many hours did you sleep last night?
 c. Rate how well rested you feel today.

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      I-----|-----|-----|-----|-----|-----I
   Most                                  Least
Rested Ever                          Rested Ever
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3a. How many times do you exercise per week?
 b. When did you last exercise?
 c. What did you do for this exercise?
 d. How long did you do this exercise for?

4a. How long has it been since you ate something?
 b. What did you eat last?

5a. Are you taking any non-prescribed drugs/medications?
 b. If yes, which drug(s)?
 c. And when did you last take the drug(s)?

6a. Are you taking any prescribed drugs/medications?
 b. If yes, which drug(s)?
 c. And why was(were) the drug(s) prescribed?

7. Describe, in the space below, any (a)current or (b)previous medical problems which you've had in the past 6 months:
 (a)

 (b)

8a. Before the experiment, when did you last drink a non-alcoholic beverage?
 b. What was this drink?

9a. When did you last drink an alcoholic beverage?
 b. What was this drink?
 c. On average, how much alcohol do you drink per week?

10. When was the last time that you engaged in any type of sexual activity?

11a. Do you smoke?
  b. If yes, approximately how many cigarettes do you smoke
     (i) per day?
     (ii) per week?

12a. On average, how much sweets (chocolates, candy, desserts, pop, etc.) do you consume per day?
  b. What sweet(s), in particular, do you consume the most of?

For Females Subjects Only:
13a. When did you last menstruate?
  b. What is the length of your menstrual cycle?
  c. Are your periods regular?

14a. Do you sometimes experience menstrual pain?
  b. If so, rate the pain.

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                    |-----|-----|-----|-----|-----|-----|
Not Bad                                                 Extremely
                                                         Painful
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15. At present, are you using birth control (or contraceptive) pills?