CANNABIDIOLIC ACID METHYL ESTER (HU-580) TREATMENT IN TWO PRECLINICAL MODELS OF SCHIZOPHRENIA: THE ROLE OF CB1 AND 5-HT1A RECEPTORS

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Abstract

Schizophrenia is a heterogeneous psychiatric disorder that is difficult to treat, and current treatment options are limited in their efficacy due to unpleasant side effects. It is paramount that new treatments are discovered that are better tolerated and have a high degree of symptom relief. Schizophrenia pathology is extremely complex and involves down-regulated cannabinoid receptor 1 (CB1R) and up-regulated 5-hydroxytryptamine 1A receptor (5-HT1AR) in the prefrontal cortex (PFC). HU-580 is a newly synthesized cannabinoid compound that is an agonist to 5-HT1AR and an antagonist to CB1R with the potential to reverse schizophrenia pathology. We examined the potential of cannabidiolic acid methyl ester (HU-580) treatment in two preclinical models of schizophrenia using C57BL/6 mice. The models used were the N-methyl-D-aspartate receptor (NMDAR) antagonism using dizocilpine (MK-801) and the maternal immune activation (MIA) with a dual hit component. We investigated if these models would induce schizophrenia-like behaviors, receptor sensitization, and neurophysiology, and if these effects were reversed/blocked by HU-580. This study found that MK-801 induced hyperlocomotion, immobility, social withdrawal, novel object preference deficits, down-regulation of CB1R and 5-HT1AR, deficits in difference response on mismatch negativity. The MIA model induced social deficits, increased latency to enter a lit box compartment, novel object preference deficits, increased escape behavior, down-regulated CB1R, and up regulated 5-HT1AR. HU-580 blocked the effects of MK-801 in hyperlocomotion, immobility, and cognitive deficits, and CB1R/5-HT1AR down-regulation. HU-580 also prevented MIA induced anxiety-like behavior, cognitive deficits and 5-HT1AR up-regulation. This study supports the involvement of CB1R and 5-HT1AR in the PFC in schizophrenia mouse models and provides evidence for the efficacy of HU-580 treatment.

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List of Abbreviations

2-AG	2-Arachidonoylglycerol
5-HT	5-hydroxytryptamine
5-HT1AR	5-hydroxytryptamine receptor 1A
5-HT2AR	5-hydroxytryptamine receptor 2A
AEA	Anandamide
ANOVA	Analysis of Variance
BORIS	Behavioral Observation Research Interactive Software
CB1R	Cannabinoid receptor type 1
CB2R	Cannabinoid receptor type 2
CBD	Cannabidiol
CBDA	Cannabidiolic Acid
CSF	Cerebral Spinal Fluid
D1	Dopamine Receptor D1
D2	Dopamine Receptor D2
D3	Dopamine Receptor D2
eCB	Endocannabinoid
EEG	Electroencephalogram
ELISA	enzyme-linked immunosorbent assay
FST	Forced swim test
GABA	γ-Aminobutyric acid
HPA	Hypothalamic-Pituitary-Adrenal Axis
HU-580	Cannabidiolic Acid Methyl Ester
LPS	Lipopolysaccharide
MIA	Maternal Immune Activation
MK-801	Dizocilpine
MMN	Mismatch Negativity
mRNA	Messenger Ribonucleic Acid
NMDAR	N-methyl-D-aspartate receptor
NORT	Novel Object Recognition Test
OFT	Open Field Test
PFC	Prefrontal Cortex
PND	Post Natal Day
PV	Parvalbumin
SIT	Social Interaction Test
VTA	Ventral Tegmental Area

Chapter 1: Introduction

Schizophrenia is a heterogenous psychotic disorder that remains incurable. There are roughly over 21 million people living with schizophrenia, a prevalence that has been increasing over the last two decades (Charlson et al., 2018). The economic burden of schizophrenia has been rapidly increasing (e.g., approximately 343.2 billion dollars in the United States) over the last decade, highlighting its difficulty of treatment and its increased prevalence (Kadakia et al., 2022).

Schizophrenia comes with multiple symptom presentations that typically emerge in late adolescence and early adulthood (Gogtay et al., 2011). Symptoms occur in varying degrees and are categorized as positive, negative, and cognitive symptoms (Marder & Galderisi, 2017; Marzouk et al., 2020; Bowie & Harvey, 2006). While the exact diagnostic specification of symptoms has been debated since the classification of schizophrenia, there is agreement that there are five main negative symptoms of interest: blunted affect (e.g., decreased ability to express emotions), alogia (e.g., poverty of speech), anhedonia (e.g., reduced experience of pleasure), asociality, and avolition (e.g., lack of motivation; Marder & Galderisi, 2017). Positive symptoms include auditory and visual hallucinations, delusional perception, and paranoia; more nuanced symptoms can also occur such as feelings and impulses attributed to the will of others (Frith & Fletcher, 2009). Individuals with schizophrenia can also suffer several cognitive symptoms in which typical cognitive functioning is diminished. These symptoms include deficits in attention, working memory, verbal learning and memory, and executive functions (Bowie & Harvey, 2006). While positive and negative symptoms disrupt interpersonal function and everyday activities, negative symptoms are more strongly correlated to poorer baseline functioning (Rabinowitz et al., 2012; Leifker, Bowie, & Harvey, 2009). Indeed, negative

symptoms predict individuals' functional outcomes, however, neurocognition deficits across a myriad of domains (e.g., working memory, verbal learning, and attention) appear to mediate this outcome (Ventura et al., 2009).

Antipsychotic pharmacological options typically include first- and second-generation antipsychotics. While acute treatments show moderate efficacy (Haddad & Correll, 2018), they are known to come with unpleasant extrapyramidal side effects and may not provide long term relief (Lally & MacCabe, 2015). With decreased baseline functioning, negative symptoms appear to be more resistant against current antipsychotic treatment (Correll & Schooler, 2020). This makes it even more difficult to treat individuals with enduring negative symptoms. Thus, it is paramount to search and identify new alternative treatments that are better tolerated and continue to provide high levels of efficacy in symptom relief.

The main barrier in schizophrenia research is predicated on its heterogeneous manifestation and its complex pathophysiology. There is converging evidence suggesting that schizophrenia is a neurodevelopmental disorder of which prodromal symptoms may be seen at an early age (Owen et al., 2011). However, it is likely that manifestations of schizophrenia differ in an idiosyncratic manner making it difficult to find consistent pathologies. Thus, it is crucial that researchers continue to unravel the mechanisms involved in schizophrenia and potential pharmacological manipulations that could counteract its pathology.

1.1. Schizophrenia Pathology Hypotheses

Schizophrenia pathology is known to be complex and is now understood to include a myriad of dysfunctions in neural systems. Historically, symptoms have been linked to the dysfunctions of dopamine. Literature now incorporates the involvement of several other neural systems (i.e., dopamine, glutamate, neurodevelopment, dual hit), and is changing the way we

look at schizophrenia. While dopamine dysfunction remains to be one of the primary and consistent pathologies measured, alternative hypotheses provide early potential explanations to the upstream mechanisms of dopamine dysfunction. Moreover, specific regions of the brain, such as the PFC, are more affected by circuitry and system abnormalities in schizophrenia (Selemon & Zecevic, 2015; Wible et al., 2001; Limongi et al., 2021). Areas of the PFC (e.g., the medial prefrontal cortex; mPFC) are responsible for stress-response. Gomes and Grace (2017) showed that mPFC connections to the ventral tegmental area (VTA) were vulnerable to stress-induced dopamine-dysregulation when animals were exposed to stress during adolescence and caused schizophrenia-like behaviors. Therefore, while dopamine dysfunction remains an integral part of symptom explanation, it isn't the only mechanism involved and research continues to investigate schizophrenia pathology.

1.1.1. The Dopamine Hypothesis

For decades schizophrenia has been historically linked to the dopamine system. This began with the use of antipsychotics that were found to reduce psychotic symptoms and were later discovered to block dopamine receptor D2 (Cunningham & Johnstone, 2018). Thus, it was believed that increased dopamine was the culprit of psychotic symptoms. The dopamine hypothesis has since evolved to incorporate new findings. Originally thought to have been caused by hyperdopaminergia (i.e., increased dopamine activity), schizophrenia is now better understood as the sum of complex activities of the dopamine system with regional differences of hyper- and hypodopaminergia (i.e., decreased dopamine activity; Howes & Kapur, 2009). The dopamine hypothesis states that negative and cognitive symptoms are linked to decreased dopamine activity in the mesocortical pathway and positive symptoms are linked to increased dopamine activity in the mesolimbic pathway (Brisch et al., 2014). More recently, the VTA of

the midbrain has been shown to project through these pathways via dopaminergic signaling and influence interneuron behavior (Sonnenschein, Gomes & Grace, 2020). Schizophrenia is associated with dopamine dysfunction and dysregulation in the aforementioned midbrain pathways (Sonnenschein, Gomes & Grace, 2020). Hyperdopaminergia in the prefrontal cortex (PFC) is associated with cognitive and negative symptoms, whereas positive symptoms are associated with increased dopamine activity in the striatum (Howes & Kapur, 2009; Goldman-Rakic et al., 2004; Tamminga, 2006). Indeed, studies revealed heightened presynaptic dopaminergic availability (Hietala et al., 1995; Hietala et al., 1999; Howes et al., 2009, Lindström et al., 1999), increased dopamine release (Abi-Dargham et al., 1998, Breier et al., 1997; Kestler, Walker, & Vega, 2001; Laruelle et al., 1996), and increased baseline dopamine (Abi-Dargham et al., 2000) in the striatum of acute psychotic patients. More recent studies have been able to replicate such findings (Howes et al., 2013; Mizrahi et al., 2013; Pogarell et al., 2012; Kegeles et al., 2010; Abi-Dargham et al., 2009). Some of the differences across symptomatology may also lie in the differential receptor densities seen within the dopamine system. It appears that dopamine receptor D1 density-decrease in the PFC is more associated with negative and cognitive symptoms, whereas increased subtype D2 and D3 density in striatum are associated with positive symptoms (Howes & Kapur, 2009; Goldman-Rakic et al., 2004; Tamminga, 2006).

Unfortunately, simply targeting this pathology using medications isn't the best solution. Treatment targeted at this system results in low efficacy and unpleasant side effects (Lally & MacCabe, 2015). This is because the dopamine system is vulnerable to disruption and is responsible for many functions across the brain (Iversen & Iversen, 2007; Grace & Gomes, 2019). Patients using medications designed to target the dopamine system, specifically D2

blockade, experience extrapyramidal side effects that may be serious (Sykes et al., 2017). New discoveries of other pathologies, and their relative functional relations, have provided some additional explanation of dopamine dysfunction in schizophrenia. Moreover, new literature provides alternative targets for pharmacological treatments that may influence a normalization of dopamine dysfunction downstream.

1.1.2. The Excitatory/Inhibitory Imbalance

There is a recent focus on the hypothesized imbalance between excitatory and inhibitory neurotransmission in the brain in schizophrenia. Most notably, the excitatory glutamate receptor N-methyl-D-aspartate (NMDAR) and inhibitory parvalbumin-containing (PV) γ-aminobutyric acid (GABA) interneurons (Liu et al., 2021). The excitatory/inhibitory (E/I) imbalance hypothesis proposes that there is an excess of excitatory activity or a deficit in inhibitory activity in certain brain regions of individuals with schizophrenia.

1.1.2.1. NDMA Receptors

Schizophrenia symptoms have been linked to hypofunction of NMDA receptors (NMDAR; Nakazawa & Sapkota, 2020). This began with the observation that NMDAR antagonists could evoke a wide array of symptoms resembling schizophrenic phenotypes in healthy human subjects (Krystal et al., 1994; Javitt & Zukin, 1991; Anis et al., 1983; Javitt, 1987). Moreover, similar behaviors induced by NMDAR hypofunction in animals are seen in humans (Seillier & Giuffrida, 2009; Bubeníková-Valešová et al., 2008). NMDAR blockade worsens symptoms by increasing dopaminergic signaling (Schmidt & Fadayel, 1996). Indeed, glutamate dysfunction can affect dopamine activity (McCutcheon, Krystal, & Howes, 2020). Reports show that first-episode psychosis in encephalitis is associated with increases in antibodies that are anti-NMDAR and disrupt the normal function of the NMDAR system

(Lennox et al., 2017; Moscato et al., 2014). In animal models, NMDAR antagonists are used to induce schizophrenia-like behaviors (Jones, Watson, & Fone, 2011). Sustained exposure to NMDAR antagonists decreases the expression of PV interneurons in rodents and monkeys (Cochran et al. 2003; Rujescu et al. 2006; Xi et al., 2009).

Glutamate is believed to play a key factor in the development of schizophrenia through the NMDAR system. Evidence for this hypothesis comes from stimulants such as amphetamines causing psychotic symptoms akin to acute schizophrenia (Snyder et al., 1974; Bramness & Rogmli, 2016). Moreover, NMDAR inhibitors are frequently used as validated models of schizophrenia in animal research, and symptoms induced in humans are indistinguishable from clinical schizophrenia (Krystal et al., 1994; Javitt & Zukin, 1991; Anis, et al., 1983; Javitt, 1987). Consistent with the dopamine hypothesis, however, is that amphetamine induced psychosis is likely still linked to dopamine activity, as they increase dopamine availability, but also modulate glutamatergic activity in dopamine neurons (Uno & Coyle, 2019; Underhill et al., 2014).

1.1.2.2. Parvalbumin Interneurons

PV interneurons mediate the balance between GABA and glutamate signaling (Nahar, Delacroix, & Nam, 2021). PV GABAergic interneuron stimulation in the VTA silences PFC pyramidal neurons (See *Supplemental Figure 1* for schizophrenia circuitry; Gorelova, Seamans, & Yang, 2002; Tseng et al., 2006). Irregularities of PV interneurons are believed to be a primary pathology of schizophrenia by disrupting glutamate, GABA, and dopamine activity (Boley, Perez, Lodge, 2014; Nahar, Delacroix, & Nam, 2021). When PV GABAergic interneurons in the VTA is stimulated, the projected signaling to PFC results in silencing of pyramidal neurons (Gorelova, Seamans, & Yang, 2002; Tseng et al., 2006). PV interneurons have reduced density in schizophrenia pathology and may be a cause of glutamate and dopamine dysfunction (Kaar et

al., 2019). With fewer PV GABAergic interneurons silencing pyramidal neurons, the PFC becomes disinhibited and hyperactivates the VTA, leading to increased activity of dopaminergic neurons (Yan, Wang, & Zhou, 2019; Zhong Qin, & Yan, 2020; Nahar, Delacroix, & Nam, 2021). Fitzgerald et al. (2012) were able to show that knocking out cannabinoid receptor type 1 (CB1R) in the medial PFC of mice resulted in decreased PV interneurons and dopamine receptor distribution.

1.1.3. The Neurodevelopmental and Dual Hit Hypothesis

Our discussion so far has only been on the causes of symptoms and not the causes of the disorder. The neurodevelopmental hypothesis, including dual hit variations, attempts to explain the development of schizophrenia. It was first proposed in the 1980s by Weinberger (1986 & 2017) as well as Murray and Lewis (1987). However, it has been acknowledged as far back as 1896 that there were prodromal-like signs in children's behavior that foreshadowed the development of schizophrenia (Klosterkötter, Schultze-Lutter, & Ruhrmann, 2008; Weinberger, 2017; Murray & Lewis, 1987). This theory has been accepted as the likely course of development of schizophrenia and is now used scientifically to investigate schizophrenia (Lim, Taylor, & Malone, 2012). Weinberger (2017) proposes that schizophrenia may result from early developmental obstruction (e.g., lesions) that later leads to differential structural brain development. Weinberger (2017) also proposes that it is more appropriate to think of schizophrenia similarly to other developmental disorders such as autism or intellectual disabilities, rather than a psychiatric disease. Recent analysis of genetic risk factors for autism and schizophrenia supports this perspective (Velthorst et al., 2018). This perspective can aid in more appropriate treatment choices that teach individuals with schizophrenia cognitive and coping strategies earlier on.

Evidence for the neurodevelopmental theory of schizophrenia comes from studies that indicate early signs of neural structure and epidemiological differences (Weinberger, 2017). Murray and Lewis (1987) point to key findings that show cerebral ventricles are enlarged in individuals with schizophrenia, and recent findings confirm this to be a prevalent occurrence in schizophrenia (Eom et al., 2020). Additionally, complications of pregnancy are more common in those with schizophrenia, and ventricular enlargement is frequent in pregnancy complications (Suvisaari et al., 2013; Gilmore et al., 2008; Murray & Lewis, 1987). Neuroinflammation is linked to detrimental effects, neural damage, and is believed to be a mechanistic cause of psychiatric disorders (Fourrier, Singhal, & Baune, 2019). Moreover, maternal infection during pregnancy results in neuroinflammation and neurodevelopmental deficits that have been linked to an increased risk of developing schizophrenia (Khandaker et al., 2013). Additionally, early brain pathway alterations are prodromal biomarkers for the later development of psychosis and may be caused by early insult (Howes et al., 2011; Khandaker et al., 2013).

The dual hit theory acknowledges the prerequisite of early events impacting the development of schizophrenia but suggests that its development is exacerbated by additional stressors (Feigenson, Kusnecov, & Silverstein, 2014). Indeed, literature shows there is a strong genetic component to schizophrenia (Modai & Shomron, 2016; Guerrin et al., 2021) associated with multiple factors composed of life-stressors integral to its development (Bayer, Falkai, & Maier 1999; Stilo & Murray, 2019; Zwicker, Denovan-Wright, & Uher, 2018). There are several aspects of the environment that are involved in interplay with genomic vulnerability. During pregnancy and birth pre-natal complications, fetal growth disruption, and improper womb environment and nutrition contribute to the likelihood of developing schizophrenia (Cannon et al., 2002; al-Haddad et al., 2019; Cattane et al., 2020; King et al., 2010; Tochigi et al., 2004).

Indeed, these risk factors are also associated with disrupted GABAergic and glutamatergic receptors (e.g., NDMAR) due to inflammation and oxidative stress (Cattane et al., 2020). From an early age into adulthood, life-events such as childhood trauma stemming from multiple sources (e.g., sexual, physical, and psychological; Varese et al., 2012), experiencing bullying, social discrimination/trauma (Varese et al., 2012; Stowkowy and Addington, 2012), early-onset cannabis use (Di Forti et al., 2014; Marconi et al., 2016), and socioeconomic factors (Allardyce and Boydell, 2006; Byrne et al., 2004) all constitute multi-hit components contributing to the development of schizophrenia. Indeed, there are many complex experiences one can have that contribute to developing psychiatric illness. It is proposed that this occurs through inflammatory mechanisms activated by stress and negative experience (Guerrin et al., 2021). In schizophrenia, there are many inflammatory mechanisms involved that have been shown to disrupt the GABAergic and glutamatergic systems (de Bartolomeis et al., 2022; Guerrin et al., 2021; Meyer & Feldon 2009).

The aforementioned hypotheses depict an extremely complex and heterogeneous development of schizophrenia that is also likely idiosyncratic in nature. Thus, identifying targets for treatment is difficult. Moreover, while these hypotheses are subdivided here for readability, they are not separate from each other and are heavily linked. Each provides an alternative perspective into the same manifestation of schizophrenia in an attempt to complement explanatory power and give more options for treatment targets. Furthermore, over the decades researchers have found new modulatory biomechanisms in schizophrenia pathology that are easier to target and provide sufferers with more reliable relief and potentially fewer side effects (Stępnicki, Kondej, & Kaczor, 2018).

1.2. Neuroregulatory Systems as Treatment Targets

Current treatment options for schizophrenia tend to target late pathology, for example with D2 blockade, however, we know this has its downfalls. There are other neural systems that can be targeted that regulate these same mechanisms, but do not result in these unpleasant side effects. The endocannabinoid system (eCB) is newly understood to be involved in schizophrenia development and symptom severity, and pharmacological antagonist targets of CB1R show promise in providing relief (Roser, Vollenweider, & Kawohl, 2010). Moreover, the 5-hydroxytryptamine receptor 1A (5-HT1AR) of the serotonin system is involved in schizophrenia pathology and symptom relief (Newman-Tancredi, 2010).

1.2.1. The Endocannabinoid System

The use of cannabis worsens symptoms and can contribute to earlier onset of schizophrenia (Patel, Khan, & Hamid, 2020). This led researchers to further investigate the role of the eCB system in psychotic illness. The eCB system consists of cannabinoid receptors and their respective lipid ligands that function to modulate the release of neurotransmitters (Pertwee and Ross, 2002). One way it does this is by providing negative feedback via retrograde neurotransmission (Pertwee, 2005; Katona & Freund, 2008; Kano, 2014). CB1Rs are found in the central and peripheral nervous system and are typically located on glial cells and neurons (Pertwee and Ross, 2002). Their primary function is to regulate neurotransmission by way of retrograde presynaptic inhibition (Pertwee and Ross, 2002; Pertwee et al., 2010).

Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the most known eCBs and are endogenous ligands for the CB1R (Mackie, 2005; Lu & Mackie, 2016). Increased AEA levels in serum, plasma, and in whole blood have been seen in schizophrenia in both treated and untreated patients as compared to healthy controls (De Marchi et al., 2003; Koethe et al., 2019;

Potvin et al., 2008; Wang et al., 2018). Some studies have shown that increased AEA is not seen in patients with first episode psychosis who are naive to antipsychotic medication (Giuffrida et al., 2004; Reuter et al., 2017) while other findings suggest a negative association between AEA levels and psychotic symptoms (Leweke et al., 2007). Giuffrida et al. (2004) found that AEA levels were up to eight times higher in drug naïve acute schizophrenic individuals, and AEA levels were negatively correlated with psychotic symptoms in schizophrenia patients.

It is proposed that cannabis use contributes to the onset of schizophrenia, especially when used in adolescents (Hall & Degenhardt, 2008). One reason may be that it disrupts the balance of the eCB system by introducing exogenously influence activation, however, it is unclear how using cannabis causes the onset of schizophrenia. The results of Leweke et al. (2007) showed a negative association between AEA levels and psychotic symptoms in those who did not use cannabis, Morgan et al. (2013) found negative associations between AEA levels of the cerebral spinal fluid (CSF) and persistent psychotic symptoms in healthy cannabis users when drug-free. Indeed, in first-episode antipsychotic-naive schizophrenic patients, and in those at risk, history of cannabis use is not likely a cause of AEA levels (Reuter et al., 2017; Koethe et al., 2009; Giuffrida et al., 2004). Normalized AEA levels after antipsychotic treatment are associated with symptom remission (De Marchi et al., 2003; Wang et al., 2018). In addition, at-risk or prodromal individuals were shown to have increased levels of AEA (Appiah-Kusi et al., 2019; Koethe et al., 2009; Koethe et al., 2019).

Recently, investigations have begun to unravel regionally different eCB pathology of CB1R in schizophrenia. The reason for this emerging interest is that CB1Rs are known to be associated with cognitive symptoms, severity, and impairment in schizophrenia (Chase et al., 2016; Ferretjans et al., 2014), and greater CB1R messenger ribonucleic acid (mRNA) presence

is associated with greater positive and negative symptoms and severity (Chase et al., 2016). Indeed, individuals with schizophrenia (treated and untreated) show elevated CB1R mRNA in peripheral blood (D'Addario et al., 2017; Moretti et al., 2018; Chase et al., 2016). Some studies show increased CB1R presence with a link to worsened symptoms (Ceccarini et al., 2013). However, there are regional differences such as decreased CB1R levels in the PFC (Volk & Lewis, 2016).

It appears that in schizophrenia, endogenous agonists of the CB1Rs are in higher concentration and are therefore continuously agonizing CB1R (Eggan et al., 2010). This likely leads to down regulation and may be linked to worsened psychotic symptoms (Jacobson et al., 2019; Eggan et al., 2010). Therefore, CB1 sensitivity is low and unstable, requiring more agonist activity for proper regulatory functioning. Given that the function of CB1 is retrograde feedback and inhibition, it can be assumed that this would lead to the disinhibition we see in schizophrenia pathology. CB1R are present in the PFC and are generally located on axons of medium spiny neurons and are often co-localized with D2 receptors (Fitzgerald, Shobin, & Pickel, 2012). Moreover, Fitzgerald et al. (2011) found that when CB1R were knocked out of mice, there was a significant decrease in PV interneurons in the PFC. By targeting this receptor with an antagonist, sensitization should normalize resulting in symptom relief. Indeed, animal studies show that CB1 antagonism, but not agonism, provides symptom relief (Kruk-Slomka et al., 2016).

1.2.2. The Serotonin System

The neuromodulatory serotonergic system has been implicated in psychotic illness and has been shown to be an effective target for schizophrenia systems (Lobo et al., 2022). Serotonin was first implicated in schizophrenia when atypical antipsychotics, which mechanistically had greater affinity for serotonin receptors, provided efficaciousness in treating negative side effects

with significantly less extrapyramidal side effects compared to typical antipsychotics (Haro & Salvador-Carulla, 2006; Lobo et al., 2022). It is also understood that serotonin is one of the primary regulators of dopamine (Kim, 2021). Specifically, the 5-HT1AR is consistently found to have increased density in the cortices of those with schizophrenia (Hashimoto et al., 1991; Ohno, 2011). Kim (2021) believes it is primarily an imbalance between 5-HT1AR and 5-hydroxytryptamine receptor 2A (5-HT2AR) that is implicated in the pathology of the development of schizophrenia. Brain imaging studies have shown that 5-HT1AR density is increased in the dorsolateral PFC while 5-HT2AR density is decreased (Ngan et al., 2000; Tauscher et al., 2002). This pathology is akin to what is seen in depression and likely partially explains the presence of negative symptoms in schizophrenia (Wang et al., 2016; Szewczyk et al., 2009). Targeting this receptor with a 5-HT1AR agonist mechanistically reverses the known pathophysiology of schizophrenic GABAergic interneuron dysfunction, leading to negative and cognitive symptom relief (Lladó-Pelfort et al., 2012). Significant morphological differences, such as cortical thickness and functional connectivity, were shown to be linked to 5-HT2A gene polymorphism rs6313 (Kang et al., 2020). Reduced hippocampal volume in first-episode psychosis participants has been linked to 5-HT1AR gene expression, and researchers suggest a closer consideration of 5-HT1AR manipulation as a possible treatment for decreased hippocampus volume in first-episode psychosis (Park et al., 2021). Additionally, decreased 5-HT2AR density has been shown in prodromal patients (Hurlemann et al., 2008). Kim (2021) believes that increased 5-HT1AR density in schizophrenic patients may be sensitized due to overstimulating the 5-HT2ARs. There also appears to be decreased 5-HT1AR binding in the amygdala of schizophrenic patients that is inversely related to negative symptoms specifically (Yasuno et al., 2004).

The 5-HT1ARs occur in both pre- and postsynaptic neurons (Palacios et al., 1990; Hamon et al., 1990). The presynaptic 5-HT1ARs restrain the firing rate of 5-hydroxytryptimaine (5-HT) neurons and the synthesis of 5-HT (Baumgarten & Grozdanovic, 1995). The postsynaptic 5-HT1AR is located in limbic and cortical areas and is responsible for anxiolytic, anti-impulsive, and antidepressant effects; it also attenuates the glutamate activation of noradrenergic neuron action potentials (Baumgarten & Grozdanovic, 1995). Activity of the 5-HT2ARs is inhibited by 5-HT1AR stimulation (Baumgarten & Grozdanovic, 1995), and chronic treatment with 5-HT1AR agonists can down-regulate 5-HT2ARs (Eison & Mullins, 1996). The main function of the 5-HT1AR is to behave as a regulator for the 5-HT system (Albert, Vahid-Ansari, & Luckhart, 2014). Activating 5-HT1ARs results in decreased 5-HT release from the raphe nuclei, leading to decreased 5-HT availability (Blier et al., 1998; Yohn, Gergues, & Samuels, 2017; Celada, Bortolozzi, & Artigas, 2013). Moreover, 5-HT1AR agonists increase pyramidal cell activity in the PFC, and could potentially restore some schizophrenia pathology by reversing hypofrontality via PV interneuron activation and desensitizing 5-HT2A (Lladó-Pelfort et al., 2012; Eison & Mullins, 1996; Baumgarten & Grozdanovic, 1995).

Dopaminergic and serotonergic neurons can communicate with the eCB in order to regulate excitability within the brain via glutamate and GABA (Peters, Cheer, & Tonini, 2021). This implies that impacting any system involved in some way will likely affect the other systems.

1.3. Cannabidiolic Acid Methyl Ester as a Treatment for Schizophrenia

Cannabidiolic acid (CBDA) methyl ester (HU-580) is a more stable CBDA analogue that has been shown to be a strong agonist of 5-HT1AR, and an antagonist of CB1R (Pertwee et al., 2018; Navarro et al., 2020). Research on HU-580 or CBDA is quite limited. However, HU-580

has been shown to provide anxiolytic and antidepressant effects in animal studies (Hen-Shoval et al., 2018; Pertwee et al., 2018; Alegre-Zurano, Martín-Sánchez, & Valverde, 2020; Assareh et al., 2020**;** Rock et al., 2017). Therefore, additional theoretical guidance comes from what is known about cannabidiol (CBD), since CBDA is its precursor and has a similar mechanism of action.

CBD and derivatives have been demonstrated to possess a good safety profile (Szaflarski et al., 2018), and are therefore potential candidates for the development of antipsychotic treatments. CBD is proposed as a potential adaptogen that is somewhat effective in relieving psychotic symptoms. Early rationale was that CBD has been shown to reduce symptoms brought on by psychotomimetic drugs (Moreira & Guinaraes, 2005). Recently, peripubertal studies show that early administration in animal models of schizophrenia can rescue the subject from negative symptoms; decreased sociability and recognition memory deficit (Stark et al., 2019). However, there are several studies that show CBD's effectiveness in positive, negative, and cognitive symptom reduction is mixed and might depend on dose and treatment regimen (Schoeversa, Leweke, & Leweke, 2020). McGuire et al. (2018) conducted a randomized control trial for the treatment of schizophrenia comparing CBD and placebo. Results indicated that those treated with CBD were better off at the end of treatment and had greater reduction of positive symptoms but not negative symptoms, as compared to placebo (McGuire et al., 2018). Additional results just shy of significance showed that the CBD group had better cognitive improvements; motor speed and executive functions (McGuire et al., 2018).

Recently, CBD was shown to decrease the firing rate of 5-HT receptors in the raphe nuclei (De Gregorio et al., 2019). Decreased firing rate was prevented by a 5HT1A antagonist, but not prevented by a CB1 antagonist (De Gregorio et al., 2019). This directly links specific

pharmacological functioning of CBD on 5HT1A receptors that are independent of CB1 activity. Moreover, this effect was moderated by increasing doses of CBD and repeated treatment of CBD increased 5-HT firing through desensitization of 5-HT1AR's (De Gregorio et al., 2019). This study focused on neuropathic pain procedures which caused decreased 5-HT firing, allodynia, and anxiety-like behaviors across several behavioral tests. One week of CBD treatment significantly reduced allodynia, anxiety-like behavior, and 5-HT activity normalized (De Gregorio et al., 2019). Indeed, CBD has been shown to have an anxiolytic effect that is attenuated by 5HT1AR antagonists (Campos, Ferreira, & Guimarães, 2012).

CBD as a compound is unstable and its bioavailability is dependent on dose, state, and route of administration, and as such may prove to be quite variable in its efficacy (Millar et al., 2018). CBDA (and its methyl ester form) was synthesized to combat the issue of stability. Compared to CBD, CBDA has been recorded as being more effective in reducing anxiety and nausea at lower doses (Rock & Parker, 2013; Rock et al., 2017). Indeed, in clinical trials of CBD as an antipsychotic, efficacy seems to be linked to dose dependence (Leweke et al., 2012; Boggs et al., 2018). Further, HU-580 has been reported to be more effective at enhancing 5-HT1AR activation (Pertwee et al., 2018). The more potent treatment option (i.e., CBDA/HU-580) may be more consistent in its efficacy.

1.4. Sex Differences and Important Considerations

It is important to note that there are several aspects of schizophrenia and its pathology that differ between sexes. While men and women do not generally differ in prevalence, men are at risk for an earlier age of onset (e.g., between 21 and 25 years old), but onset for women generally occurs either between 25 and 30 years old or above the age of 45 (Li et al., 2016). However, females are at risk of earlier onset if cannabis use occurs (Calakos et al., 2017).

Symptom phenotypes differ as well. Men are more likely to experience negative symptoms and to be more severe and/or intense than women (Li et al., 2016). One such reason for sex-different experiences is the involvement of the gene Val158Met (RS4680) that is responsible for the production of the catechol-O-methyltransferase (COMT) enzyme. COMT is an enzyme responsible for the degradation and regulation of dopamine in the PFC. De Castro-Catala et al. (2015) showed that the Val158Met polymorphism was sex dependent and men with such variation scored higher in negative traits and symptoms of schizophrenia (de Castro-Catala et al., 2015).

There are also important differences between neurotransmitter systems. Bristow et al., (2015) were able to show that in men, GABA activity and gene expression was decreased in those with schizophrenia. However, females' expression was much higher in those with schizophrenia (Bristow et al., 2015). Locklear et al. (2016) investigated sex differences in the effects of NMDA antagonists in rats and found that NMDA antagonism increased prefrontal dopamine in male rats but decreased it in female rats. While not in the context of psychotic illness, men tend to have lower availability of CB1Rs in the frontal cortex and PFC, suggesting a vulnerability for dysfunction (Laurikainen et al., 2019; Borgan et al., 2021). Liu et al. (2020) found key sex differences in CB1R distribution and mRNA expression in C57BL/6 mice. Among structures, male mice had significantly more CB1R in the striatum and ventral hippocampus CA1, but female mice showed differences in expression of CB1R mRNA in the amygdala.

1.4. Current Study

This study investigated the pathophysiology of CB1R and 5-HT1ARs in two preclinical models of schizophrenia, as well as the therapeutic and preventative effects of HU-580 as a treatment. First, a study was conducted using an NMDA antagonist. We assessed behavioral,

neurophysiological, and receptor changes of dizocilpine (MK-801) in mice and tested to see if HU-580 provided therapeutic relief. This pilot study provided important information about the therapeutic potential of HU-580 and opened the way for further investigation. Next, we assessed behavioral and receptor changes of the maternal immune activation (MIA) model and tested to see if HU-580 provided preventative effects. This approach allowed us to incorporate the neurodevelopmental hypothesis and the dual-hit hypothesis of schizophrenia.

By agonizing 5-HT1AR and antagonizing CB1R, HU-580 should provide opposing mechanistic effects of schizophrenia pathology, and all behavioral deficits should be rescued. Pathologically, MK-801 and MIA exposures should result in increased levels of 5HT1AR in the PFC that is normalized through HU-580 treatment. Conversely, MK-801 and MIA exposure should result in decreased levels of CB1R in the PFC that is also normalized through HU-580 treatment. We proposed that both models would induce schizophrenia-like behavioral deficits and receptor expression changes consistent with schizophrenia pathology that would be reverse/blocked by HU-580 treatment.

Chapter 2: Materials and Method

2.1. MK-801 Experiment

2.1.1. Animals

This experiment utilized adult C57BL/6 mice (Charles-River Saint-Constant, PQ, Canada) single housed weighing 25 – 35g. Experiments were conducted between 8:00 and 20:00. All procedures were in accordance with the ethical guidelines by Memorial University's institutional animal care and use committee and the Canadian Institutes of Health Research. Mice were pseudo-randomized into two factors, exposure (control or MK-801, n = 30 per factor, 15 male and 15 female) and treatment (HU-580 - 0.01ug/kg, HU-580 - 0.05ug/kg, or vehicle; n = 20

per level, 10 male and 10 female), creating six groups: Ctrl, Ctrl+0.01, Ctrl+0.05, MK, MK+0.01, and MK+0.05 (n = 10 per group, 5 male and 5 female).

Additionally, an oddball paradigm (see explanation below) was conducted separately using additional mice (n = 7-8 per group, 3-4 male and 3-4 female) in an identical paradigm and were randomized between the same factors and subjected to identical treatment protocols seen below.

2.1.2. *Drugs*

The vehicle consisted of 5% Tween 80, 5% polyethylene Glycol, and 90% saline (0.9%). The HU-580 was dissolved in the vehicle and administered at 0.01ug/kg (low-dose) and 0.05ug/kg (high-dose). MK-801 was dissolved in 0.9% saline and administered at 0.3mg/kg. All injections were calculated around a mean average animal weight of 30 grams. Drugs were purchased from Sigma-Aldrich. All drugs were administered intraperitoneally (i.p.).

2.1.3. MK-801 model of schizophrenia

MK-801 is an NMDA antagonist that is often used to create an acute model of schizophrenia in animal research (Olszewski et al., 2008). MK-801 is a widely used approach that has been shown to induce a number of behaviors in rodents that are indicative of schizophrenia (Rung et al., 2005; Bubeníková-Valešová et al., 2008). These behaviors include increased locomotor activity, changes in locomotor activity in response to stress, pre-pulse inhibition deficits, impaired spatial memory, and social withdrawal (Bubeníková-Valešová et al., 2008). Indeed, NMDA hypofunction is greatly implicated as a valid method to model schizophrenia in animals, and similar behaviors are seen in humans (Seillier & Giuffrida, 2009; Bubeníková-Valešová et al., 2008). Additionally, this model is especially fitting for the current project as CBD has been shown to reverse some of the behaviors induced by MK-801 that are aligned with schizophrenia

(Gururajan, Taylor, & Malone, 2011). This model exposed mice to MK-801 (0.3mg/kg) or saline via an injection once daily for seventeen days.

2.1.4. HU-580 Treatment

We also tested the effects of HU-580 in relieving induced symptom-like behaviors of MK-801. On day 7, mice received treatment or saline and were subject to behavioral tests. Following, mice continued co-treatment of MK-801 or saline and HU-580 or vehicle for an additional ten days and were subjected to follow up behavioral tests.

2.1.5. Behavioral assay

Using open field test (OFT), social interaction test (SIT), novel object recognition test (NORT), and forced swim test (FST) we assessed if MK-801 induced positive, negative, and cognitive deficits consistent with schizophrenic-like behaviors. Behavioral data was acquired automatically through a video tracking software EthoVision and manually via Behavioral Observation Research Interactive Software (BORIS; Friard & Gamba, 2016). In the case of manual data acquisition, raters were blinded to subject identification and group. Three identical testing chambers (24 x 54.5 x 40 cm^3) were used and modified to fit each test, excluding FST. Chambers and all objects used in each test were cleaned with 70% ethanol between trials. Measures were categorized as positive-, negative-, and cognitive-like symptom behaviors.

OFT. Locomotive activity (total distance traveled in cm) was assessed using the OFT to identify psychomotor agitation as a positive-like symptom behavior (Powell & Miyakawa, 2006). Mice were placed in the OFT chamber (24 x 24 x 40 cm^3) and were recorded for 10 minutes. The first 5 minutes was designated for habituation and the last 5 minutes was video recorded. Standard lighting was used.

SIT. This test is frequently used to assess sociability in mice and is a validate approach (Kaidanovich-Beilin et al., 2011; Yang, Silverman, & Crawley, 2011). Mice were placed in the center of the testing chamber with two plexiglass dividers at each end of the chamber, isolating smaller chambers at each end. In phase 1, a same-sexed stranger conspecific was placed in a wire cage at one end of the testing chamber, and an empty wire cage was placed at the other end of the testing chamber. Plexiglass walls were lifted, and mouse behavior was recorded for 5 minutes. Mice were then returned to the center area, and a second same-sexed conspecific was placed in the empty cage. Mouse behavior was recorded for an additional 5 minutes. Spontaneous social behavior was measured in phase 1 by dividing time spent with a stranger conspecific with time spent with an empty cage to produce a social behavior index (SI). Social recognition memory index (SMI) was measured in phase 2 by dividing time spent with a stranger conspecific with time spent with a familiar conspecific. Mice were assessed for decreased social interaction and decreased social recognition memory as a negative-like symptom behavior.

NORT. In phase 1, two identical red Christmas bulbs (2.5 x 2.5 cm^3) were mounted at each end of the testing chambers using small sections of Velcro. Mice were placed in the center chamber, dividers were removed, and recording commenced for 5 minutes. In phase 2, one of the red Christmas bulbs was replaced with a gold bell (2.5 x 2.5 cm^3) for acute tests or a small pinecone ornament (2.5 x 2.5 cm^3) for sub-chronic tests. Mice were placed in the center chamber, dividers were removed, and behavior was recorded for 5 minutes. Object recognition was used to identify cognitive-like symptom deficits.

FST. Mice were placed in a glass tube (8.5 x 20 cm) that was filled halfway with water at room temperature (20 – 25 degrees Celsius). They were left to swim for a 2-minute habituation period

before recording mobility behavior for 4 minutes. Immobility time was calculated as a measure of despair or negative-like symptom behavior.

2.1.6. EEG Oddball Paradigm

Electroencephalogram (EEG) recordings were used in the oddball paradigm of mismatch negativity (MMN) to assess auditory processing deficits found in schizophrenia (Umbricht & Krljes, 2005). This measure was used to validate MK-801's effects as relevant to schizophrenia. Mice underwent mild surgical procedures for EEG cap implantation, and days of surgery were timed so that the first day of possible recordings following recovery was the final day of treatment. Thus, recordings are based on sub-chronic timing only of 17 days of treatment.

In preparation of surgeries, mice were acclimated to the surgery room for 1 hour prior. Each mouse was anesthetized with a vaporized isoflurane oxygen mixture in an induction chamber (2.5% isoflurane in oxygen, 1.0 L/min). Before stereotaxic mounting, mice were examined using tail- and foot-pinch reflexes to ensure the mouse was fully anesthetized and then given Meloxicam (4mg/kg, i.p.). Once stereotaxic mounted on a heating pad, mice were given a 1ml saline injection for hydration throughout the surgery and gel was placed on the eyes to prevent drying. An incision was made along the top of the head just in front of the brow line back to the point of lambda; Peroxide was used to clean the skull. The stereotaxic coordinate arm was positioned at the point of bregma and adjusted using the coordinates AP 2.7 and ML 3.5. These coordinates (Aleksandrov et al., 2019; Featherstone et al., 2015), placed the arm over the auditory cortex. From this point, marks were made on the skull to indicate three points to implant recording screws: left and right auditory cortex and a ground. Once screws were implanted, dental cement was used to mount and position the EEG cap and the connecting wires were

soldered. Additional dental cement was used to secure the cap and close the incision. Mice were then placed in recovery on a heating pad and given dietary supplements and hydrogel.

Mice were given five days of recovery and then field potential recordings were collected. Prior to recordings, mice were given a terminal injection of urethane as an anesthetic (1mg/kg). Once fully anesthetized, mice were connected to EEG recording software and placed inside of a soundproofed chamber with speakers; brain activity was recorded using Sirenia Acquisition. During recording, mice were recorded for a 10-minute baseline period, and then recorded while playing a 10-minute audio clip of a 7kHz standard tone played every 500ms with a deviant tone varying from 5kHz to 9kHz increased at 100Hz intervals played every 13 seconds. EEG recordings were exported as EDF files for later analysis. This paradigm is a validated protocol for oddball EEG recordings specifically for schizophrenia in both animal and human studies (Tada et al., 2019). MATLAB EDF reader was used to analyze EEG recordings. Amplitude in response to the deviant auditory stimuli was measured by recording N1 and P1 peak to peak values, taking the difference, and averaging across all ERP's in each recording. See *Supplemental Figure 2* for examples of deviant and standard ERP response waves.

2.2. MIA Experiment

2.2.1. Animals

This experiment utilized adult C57BL/6 mice (Charles-River Saint-Constant, PQ, Canada) group housed (2 – 4 per cage) weighing 25 – 35g. Experiments were conducted between 8:00 and 20:00. All procedures were in accordance with the ethical guidelines by Memorial University's institutional animal care and use committee and the Canadian Institutes of Health Research. Mice were pseudo-randomized into three factors, exposure (control or Lipopolysaccharide[LPS]), dual hit (saline or yohimbine) and treatment (HU-580 - 0.01ug/kg or

vehicle), creating eight groups: Ctrl, CtrlHU, CtrlYo, CtrlYoHU, LPS, LPSHU, LPSYo, and LPSYoHU (n = 9-14 per group, 4-7 male and 5-7 female).

2.2.2. *Drugs*

The vehicle consisted of 5% Tween 80, 5% polyethylene Glycol, and 90% saline (0.9%). The HU-580 was dissolved in the vehicle and administered at 0.01ug/kg. LPS and Yohimbine were dissolved in saline and administered at 0.1mg/kg and 5mg/kg, respectively. All injections were calculated around a mean average animal weight of 30 grams. Drugs were purchased from Sigma-Aldrich. All drugs were administered intraperitoneally (i.p.).

2.2.3. MIA model of schizophrenia

The MIA model of schizophrenia in rodents is an ecologically valid model in response to prenatal exposure to LPS used to emulate the neurodevelopment of schizophrenia. Moreover, it has been shown to recapitulate schizophrenia PV interneuron dysfunction pathology (Vojtechova et al., 2021). During mouse breeding, two female mice and one male mouse were group housed for up to 14 days. Prior to grouping, bedding was swapped into the female's cage(s) for three days to habituate females to the male scent. Females were checked for vaginal plugs twice daily and recorded until both dams were impregnated; the male mice were then removed. On gestational day 14, dams were injected with either LPS (0.1 mg/kg) or saline. MIA is modeled via administration of LPS during early and/or mid-gestation (Carbone et al., 2023). This timing has been shown to induce neuroinflammation, pathophysiological deficits, and schizophrenia-like social and cognitive behaviors (Zager et al., 2015; Carbone et al., 2023; Talukdar et al., 2020). Pups were weaned on post-natal day (PND) 20. From PND 21 – 27, pups were given HU-580 (0.01ug/kg, i.p.) treatment in attempts to prevent vulnerabilities induced by the MIA model. Timing is based on Han et al. (2016) who showed cognitive and BDNF signaling deficits seen

during the juvenile stage of development. Treatment during this stage also prevented these deficits (Han et al., 2016). To complement the validity of this model, we also induced a later life stressor (i.e., a dual hit component mimic) by injecting mice with Yohimbine during development (PND 38). Yohimbine is an anxiogenic compound by way of α2-adrenergic receptor antagonism and activates the hypothalamic-pituitary-adrenal (HPA) stress axis (Myers, Banihashemi, & Rinaman, 2005).

2.2.4. Behavioral assay

Behavioral data was acquired automatically through a video tracking software EthoVision and manually via Behavioral Observation Research Interactive Software (BORIS; Friard & Gamba, 2016). In the case of manual data acquisition, raters were blinded to subject identification and group. On PND 61 – 66, mice were subjected to one behavioral test a day. Early adult age was determined based on previous literature (Brust et al., 2015). All chambers and objects used in each test were cleaned with 70% ethanol between trials. Measures were categorized as positive-, negative-, and cognitive-like symptom behaviors.

SIT. The testing protocol of SIT was nearly identical to that of the MK-801 experiment. Mouse behavior was recorded for 10 minutes per phase, rather than 5 minutes, and all behaviors measured were identical.

NORT. The testing protocol for NORT was adjusted and improved. In phase 1, two identical red Christmas bulbs (2.5 x 2.5 cm^3) were mounted at each end of a Y-maze chamber using small sections of Velcro. Mice were placed in the center chamber, dividers were removed, and recording commenced for 5 minutes. Phase 2 occurred 4 hours after phase 1. During phase 2, one of the red Christmas bulbs (position was counterbalanced) was replaced with a gold bell (2.5 x

2.5 cm^3). Mice were placed in the center chamber, dividers were removed, and behavior was recorded for 5 minutes. Object recognition was used to identify cognitive-like symptom deficits.

OFT. Mice were placed in the OFT chamber (50 x 50 x 50 cm^3) and were recorded for 10 minutes. The first 5 minutes were designated for habituation and the last 5 minutes were video recorded.

FST. The testing protocol was identical to the MK-801 experiment.

Light-dark box. The light-dark box was used as an additional measure of anxiety-like positive symptoms. An opaque box (24 x 18 x 20 cm) with a door (5 x 10 cm) was placed at one end of a Plexiglass chamber (24 x 54.5 x 40 cm^3), taking up 1/3 the space (Bourin & Hascoët, 2003). Lights mounted above the chamber emitted direct light (450 lumens) into the open area of the chamber. Mice were placed inside the dark box and the door was covered. Once recording began, the cover was removed, and mice were recorded for 10 minutes. Time spent in the dark box and latency to enter the light area were used as measures of anxiety-like behavior.

2.3. Enzyme-linked Immunosorbent Assay (ELISA)

ELISA protocol was conducted for both experiments and were identical. On the day of brain extraction, brains were flash frozen on dry ice and stored in a -80 freezer. The PFC was removed using a cryostat machine and scalpels and was kept frozen throughout the entire process. The PFC was identified using a mouse brain atlas and visual landmarks identified as a collection of the prelimbic, infralimbic, and anterior cingulate cortex areas. The tissue removed was within AP 2.93mm and 1.33mm. Tissue was weighed and placed in micro vials for storage. To prepare the samples for ELISA, 1x phosphate-buffered saline (PBS) was micro-pipetted into the vials at a concentration of 10% tissue and 90% PBS as per recommendations in the kits used. Samples were then centrifuged at 1000 x g for 20 minutes and the supernatant was removed and

stored in a -80 freezer. On the day of testing, instructions were followed for each kit thoroughly. Each ELISA kit was purchased from MyBioSource, and this study tested for CB1R (Catalogue: MBS2533482) and 5-HT1AR (Catalogue: MBS287600).

2.4. Data analysis

Data were analyzed using one-way, two-way, and/or three-way analysis of variance (ANOVA) on SigmaPlot 15 to assess group differences, main effects, and interaction effects of exposure, treatment, and sex. The focus of analysis relied on group differences using one-way ANOVA. When and/or if one-way ANOVA was not successful, two-way or three-way ANOVA was used to uncover potential main effects missed. In the event of significant ANOVA, Dunnett's method post hoc analysis was used for follow-up analysis and to control family wise risk of type 1 error. Data are shown as mean +/- standard error of the mean (SEM). Exclusionary criteria included extreme outliers, side preference behavior, and unreasonable immobility or prolonged freezing. To be concise and maintain readability, only significant effects are reported.

Although not the focus, sex differences are an important consideration that was included in the analysis of this study. However, this analysis is exploratory in nature to elucidate important differences that may exist. Despite this, sample sizes are low in sex dependent effects (e.g., 4 - 5 per sex per group). Therefore, any effects found are assumed robust with the understanding that small effects may still be missed.

Chapter 3: Results

3.1. MK-801 Experiment

The effects of MK-801 administration and HU-580 treatment were assessed on behavior, receptor expression, and MMN. Results were analyzed using one-way or two-way ANOVA to assess group differences, main effects, and interaction effects.

3.1.1. Positive Symptom-like Behavioral Measure

OFT: At 7 days, in females results revealed a significant interaction between exposure to MK-801 and treatment of HU-580 on total distance traveled (CM), $F(2,24) = 4.356$, $p = 0.024$. Dunnett's post hoc revealed that MK (M = 762.696, SD = 123.944) was trending towards traveling significantly more than Ctrl (M = 600.930, SD = 160.251), MD = 161.765, $q = 1.683$, $p = 0.105$, and MK+0.01 (M = 498.434, SD = 211.761) was significantly less active than MK (M = 762.696, SD = 123.944), MD = 264.262, $q = 2.749$, $p = 0.021$. At 17 days results showed a significant difference between groups in total distance traveled (CM), $F(5,54) = 7.065$, $p < 0.001$. Dunnett's post hoc revealed that compared to Ctrl (M = 507.541, SD = 171.562), MK-801 (M = 889.621, SD = 312.669), MD = 382.080, $q = 3.755$, $p = 0.002$, and MK+0.05 (M = 992.224, SD = 277.479), MD = 484.683, $q = 4.763$, $p < 0.001$, traveled significantly more. In males, results were significant, $F(5,24) = 7.843$, $p < 0.001$. Dunnett's post hoc revealed that compared to Ctrl (M = 479.282, SD = 198.022), MK+0.05 (M = 1157.157, SD = 300.419) traveled significantly more, MD = 677.874, $q = 5127$, $p < 0.001$. In females, showed a significant difference between groups in total distance traveled (CM), $F(5,24) = 8.487$, $p < 0.001$. Dunnett's post hoc revealed that MK-801 (M = 1132.174, SD = 194.739) traveled significantly more than Ctrl (M = 535.799, SD = 158.165), MD = 596.375, $q = 5.761$, $p < 0.001$, Ctrl+0.01 (M = 668.763, SD = 83.481), MD = 463.411, $q = 4.477$, $p < 0.001$, Ctrl+0.05 (M = 712.275, SD = 96.458), MD 419.899, $q = 4.057$, $p = 0.002$, MK+0.01 (M = 603.433, SD = 257.934), MD = 528.741, $q = 5.108$, $p < 0.001$, and MK+0.05 (M = 827.292, SD = 122.390), MD = 304.882, $q = 2.945$, $p = 0.029$ (See *Figure 3*).

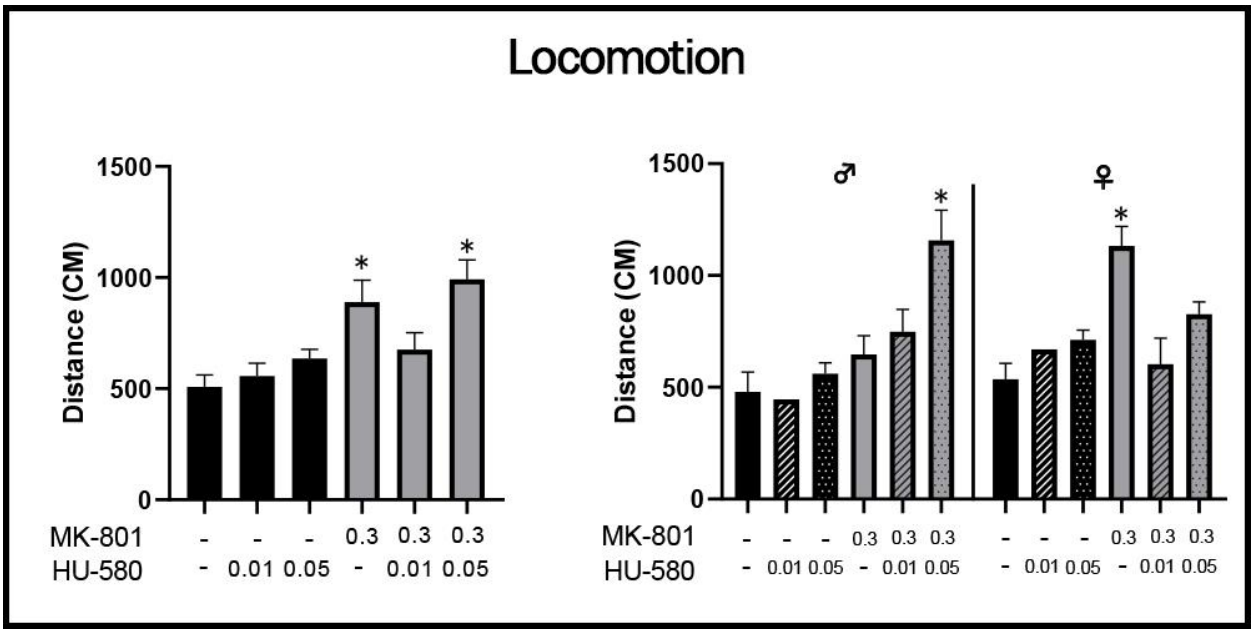

Figure 3. Comparison of the effects of MK-801/HU-580 in the OFT in pooled (left) and sex separated (right) analysis; average (±SEM) distance traveled (CM). Administration of MK-801 (0.3mg/kg, i.p.) daily for 17 days induced hyperlocomotion in sex-dependent manner that was attenuated by low-dose (0.01ug/kg, i.p.) HU-580 treatment. Synergistically, MK-801 and high-dose (0.05ug/kg, i.p.) HU-580 treatment induced hyperlocomotion in male mice.

3.1.2. Negative Symptom-like Behavioral Measures

SIT: At 7 days results revealed a main effect of exposure to MK-801 on SI, $F(1,53) = 6.051$, $p = 0.017$. Dunnett's post hoc revealed that MK mice (M = 1.845, SD = 0.22) had a significantly lower SI than control mice (M = 2.605, SD = 0.216), MD = 0.759, $q = 2.439$, $p = 0.018$. Moreover, MK (M = 1.677 , SD = 0.395) had an SI that was marginally lower than Ctrl (M = 2.764, SD = 0.375), MD = 1.087, $q = 1.997$, $p = 0.051$. In males, results showed a significant main effect of exposure to MK-801 on SI, $F(1,24) = 9.002$, $p = 0.006$. Dunnett's post hoc revealed that MK mice (M = 1.777, SD = 0.777) had a significantly lower SI than control mice (M = 3.115, SD = 1.481), MD = 1.339, $q = 3$, $p = 0.006$. In females, results showed a significant interaction between exposure to MK-801 and treatment of HU-580, $F(2,24) = 3.777$, $p = 0.037$. Dunnett's post hoc revealed that Ctrl (M = 3.046, SD = 1.834) had a significantly

higher SI than MK (M = 1.596, SD = 0.244), MD = 1.45, $q = 2.451$, $p = 0.022$, and Ctrl+0.05 (M = 1.379, SD = 0.481), MD = 1.666, $q = 2.817$, $p = 0.018$ (See *Figure 4*).

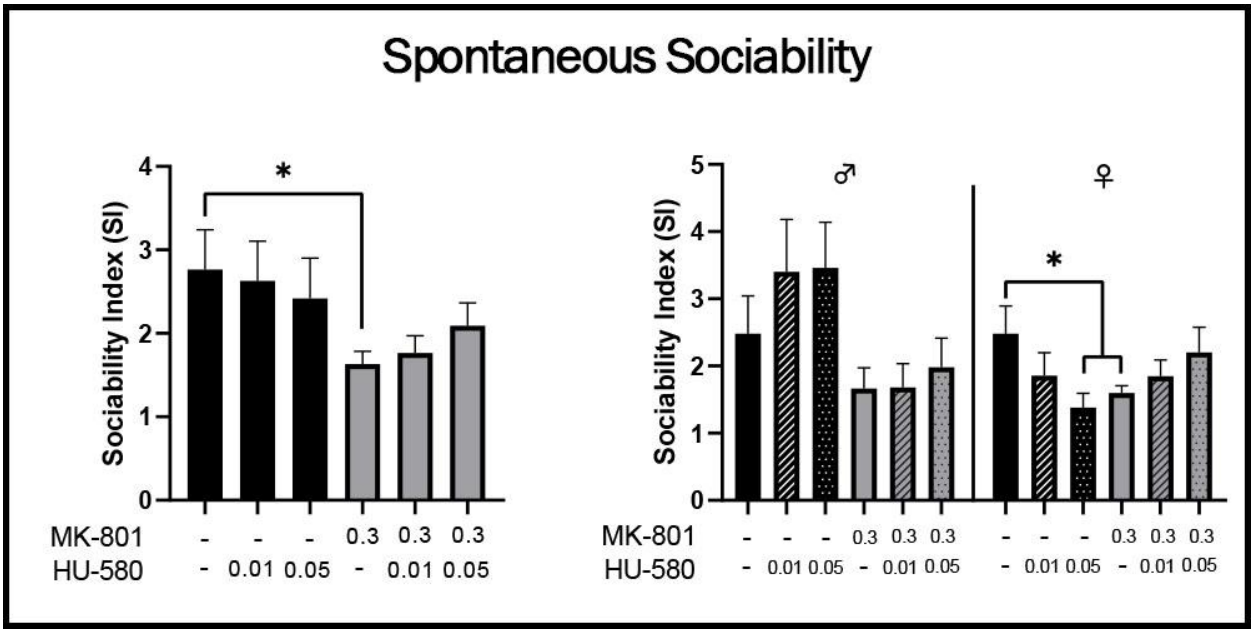

Figure 4. Comparison of the effects of MK-801/HU-580 in the SIT in pooled (left) and sex separated (right) analysis; average (±SEM) sociability index (SI). Administration of MK-801 (0.3mg/kg, i.p.) daily for 7 days induced spontaneous sociability deficits (i.e., social withdrawal). High-dose (0.05ug/kg, i.p.) HU-580 treatment induced social withdrawal in female mice at 7 days, but this effect was lost at 17 days.

FST: At 7 days results revealed a significant interaction between exposure to MK-801 and treatment of HU-580 on time spent being immobile, $F(2,54) = 5.952$, $p = 0.005$. Dunnett's post hoc revealed that MK+0.01 (M = 119.114, SD = 67.534) was significantly less immobile than MK (M = 164.754, SD = 36.058), MD = 45.640, $q = 2.563$, $p = 0.025$, and Ctrl+0.01 (M = 181, 238, SD = 18.418), MD = 62.125, $q = 3.488$, $p < 0.001$. In females, results showed a significant interaction between exposure to MK-801 and treatment of HU-580 on time spent being immobile, $F(2,24) = 7.180$, $p = 0.004$. Dunnett's post hoc revealed MK+0.01 (M = 79.794, SD = 75.388) spent significantly less time being immobile than MK (M = 161.268, SD = 25.60), MD = 81.474, $q = 3.074$, $p = 0.010$. At 17 days results showed a significant difference between groups in time spent being immobile, $F(5,54) = 3.058$, $p = 0.017$. Dunnett's post hoc revealed

that compared to Ctrl (M = 179.729, SD = 34.305), both MK (M = 218.972, SD = 27.616), MD = 39.243, q = 2.984, p = 0.018, and MK+0.05 (M = 223.827, SD = 14.747), MD = 44.098, q = 3.353, p = 0.007, were significantly more immobile. In males, results trended towards a significant main effect of exposure to MK-801 on time spent being immobile, $F(1,24) = 3.403$, p = 0.077. Dunnett's post hoc trended towards MK-801 mice (M = 208.368, SD = 27.631) being more immobile than control mice (M = 186.820, SD = 35.807), MD = 21.548, q = 1.845, p = 0.077. In females, results trended towards a significant main effect of exposure to MK-801 on time spent being immobile, $F(1,24) = 2.976$, p = 0.097. Dunnett's post hoc revealed that MK (M = 236.797, SD = 4.435) were significantly more immobile than Ctrl (M = 196.991, SD = 35.908), MD = 39.806, q = 2.223, p = 0.036, and MK+0.01 (M = 193.755, SD = 40.899), MD = 43.042, q = 2.404, p = 0.045 (See *Figure 5*).

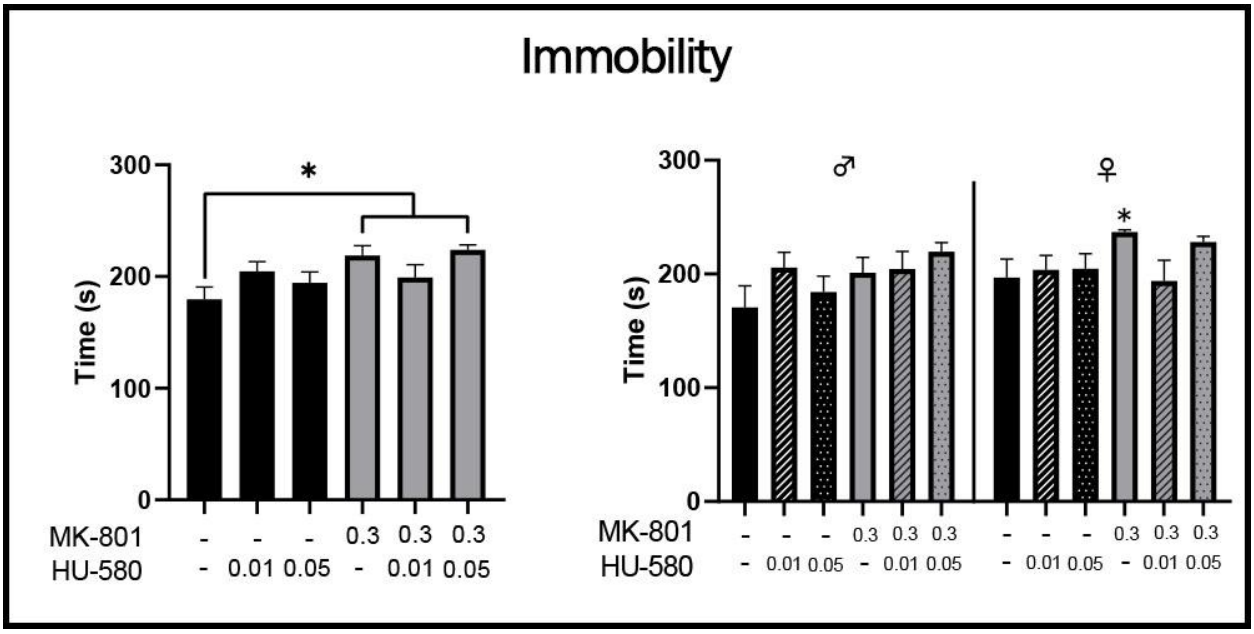

Figure 5. Comparison of the effects of MK-801/HU-580 in the FST in pooled (left) and sex separated (right) analysis; average (±SEM) time of immobility (s). Administration of MK-801 (0.3mg/kg, i.p.) daily for 17 days induced immobility (i.e., despair-like behavior) primarily in female mice. Low-dose (0.01ug/kg, i.p.) HU-580 treatment blocked the effects of MK-801 in female mice.

3.1.3. Cognitive Symptom-like Behavioral Measure

NORT: At 7 days results showed a significant difference between groups in difference time with the novel object, $F(5,52) = 4.148$, $p = 0.003$. Dunnett's post hoc revealed that MK (M = -15.35, SD = 22.633) had a significantly lower difference time with the novel object than Ctrl (M = 15.436, SD = 22.623), MD = 30.786, $q = 2.77$, $p = 0.033$, Ctrl+0.05 (M = 16.712, SD = 21.955), MD = 32.062, $q = 2.885$, $p = 0.024$, MK+0.01 (M = 29.871, SD = 34.836), MD = 45.221, $q = 3.39$, $p = 0.001$, and MK+0.05 (M = 17.847, SD = 24.296), MD = 33.197, $q = 2.907$, $p = 0.023$. In males' results showed a significant difference between groups in difference time with the novel object, $F(5,24) = 3.107$, $p = 0.027$. Dunnett's post hoc revealed that MK (M = -24.120, SD = 24.009) had a significantly lower difference time with the novel object than MK+0.01 (M = 40.368, SD = 43.596), MD = 64.488, $q = 3.518$, $p = 0.008$. In females results showed a significant difference between groups in difference time with the novel object, $F(5,21) = 2.942$, $p = 0.036$. Dunnett's post hoc revealed that MK (M = -6.75, SD = 19.592) had significantly lower difference time with the novel object than Ctrl (M = 32.28, SD = 10.949), MD = 38.86, $q = 2.845$, $p = 0.04$, and Ctrl+0.05 (M = 31.567, SD = 20.43), MD = 38.147, $q = 2.962$, $p = 0.031$. At 17 days, the full analysis was not significant. In females' results showed a significant difference between groups in difference time with the novel object, $F(5,23) = 2.781$, $p = 0.042$. Dunnett's post hoc revealed that MK (M = -15.357, SD = 32.087) had significantly lower difference time with the novel object than MK+0.01 (M = 66.435, SD = 42.025), MD = 81.792, $q = 3.202$, $p = 0.016$ (See *Figure 6*).

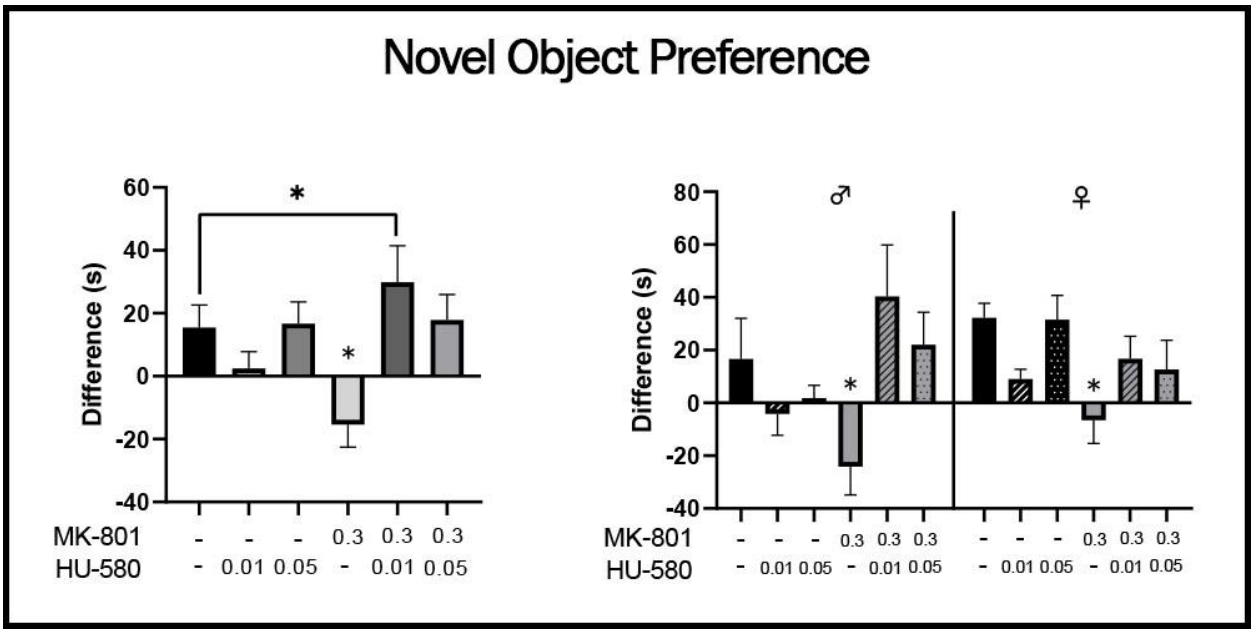

Figure 6. Comparison of the effects of MK-801/HU-580 in the NORT in pooled (left) and sex separated (right) analysis; average (±SEM) difference time (s) with the novel object. Administration of MK-801 (0.3mg/kg, i.p.) daily for 7 days induced novel object preference deficits. Both low-dose (0.01ug/kg, i.p.) and high-dose (0.05ug/kg, i.p.) HU-580 treatment blocked the effects of MK-801.

3.1.4. ELISA.

CB1R: Results showed a significant difference between groups in CB1R concentration, $F(3,36) = 3.405$, $p = 0.028$. Dunnett's post hoc revealed that MK (M = 868.171, SD = 187.744) had significantly lower CB1R concentration than Ctrl (M = 1151.893, SD = 344.877), MD = 283.722, $q = 2.531$, $p = 0.042$, and MK+0.01 (M = 1189.108, SD = 290.687), MD = 320.937, $q = 2.864$, $p = 0.019$. MK CB1R concentration was marginally less than MK+0.05 (M = 1127.731, SD = 111.976), MD = 259.560, $q = 2.316$, $p = 0.068$. In females, results showed a significant difference between groups in CB1R concentration, $F(3,16) = 5.404$, $p = 0.009$. Dunnett's post hoc revealed that MK (M = 755.483, SD = 75.661) had significantly lower CB1R concentration than Ctrl (M = 1188.093, SD = 299.908), MD = 432.610, $q = 3.439$, $p = 0.009$, and MK+0.05 (M = 1197.826, SD = 54.206), MD = 442.343, $q = 3.516$, $p = 0.008$. MK+0.01 (M = 1017.288, SD =

244.288) trended towards a greater CB1R concentration than MK, MD = 261.805, $q = 2.081$, $p = 0.13$ (See *Figure 7*).

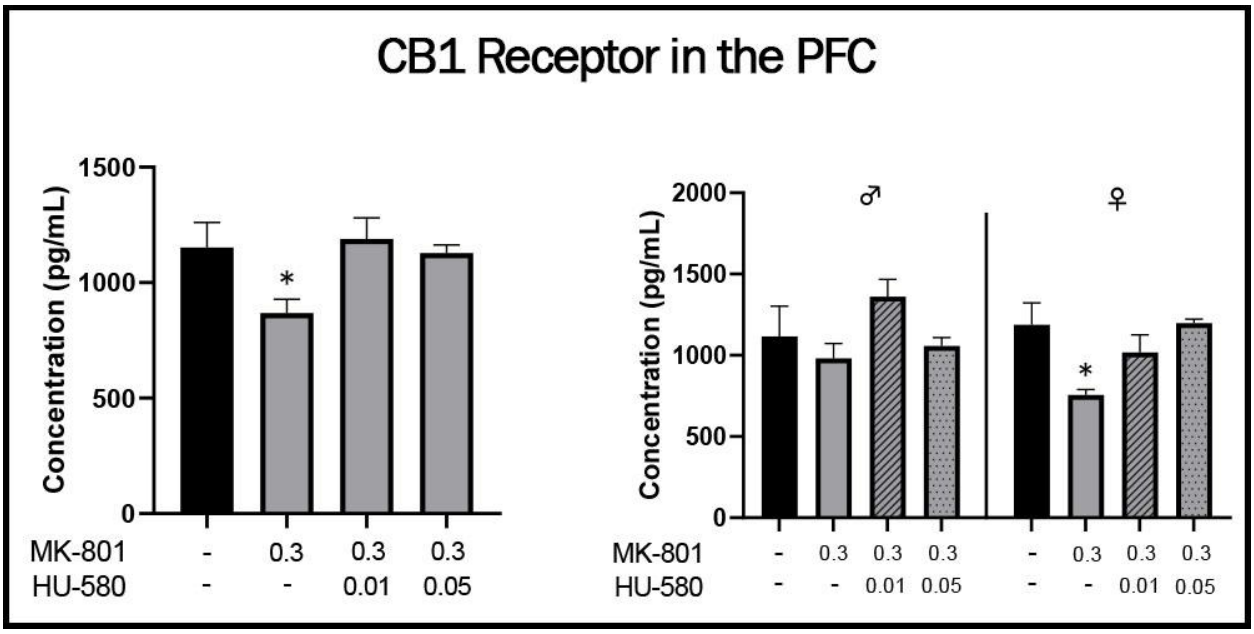

Figure 7. Comparison of the effects of MK-801/HU-580 in the CB1R ELISA in pooled (left) and sex separated (right) analysis; average (±SEM) concentration (pg/ml). Administration of MK-801 (0.3mg/kg, i.p.) daily for 17 days induced down regulation of the CB1Rs in the PFC of female mice. Both low-dose (0.01ug/kg, i.p.) and high-dose (0.05ug/kg, i.p.) HU-580 treatment blocked the down regulation effects of MK-801.

5-HT1AR: Results showed a significant difference between groups in 5-HT1AR concentration, $F(3,36) = 12.893$, $p < 0.001$. Dunnett's post hoc revealed that MK (M = 86.386, SD = 30.55) had significantly lower 5-HT1AR concentration than Ctrl (M = 150.418, SD = 39.378), MD = 64.032, $q = 4.963$, $p < 0.001$, MK+0.01 (M = 142.419, SD = 24.399), MD = 56.033, $q = 4.343$, $p < 0.001$, and MK+0.05 (M = 158.752, SD = 15.809), MD = 72.366, $q = 5.609$, $p < 0.001$. In females' results showed a significant difference between groups in 5-HT1AR concentration, $F(3,16) = 158.263$, $p < 0.001$. Dunnett's post hoc revealed that MK (M = 58.308, SD = 2.539) had significantly lower 5-HT1AR concentration than Ctrl (M = 114.917, SD = 10.129), MD = 56.609, $q = 13.560$, $p < 0.001$, MK+0.01 (M = 120.154, SD = 4.379), MD =

61.846, $q = 14.815$, $p < 0.001$, and MK+0.05 (M = 146.577, SD = 6.785), MD = 88.269, $q = 21.144$, $p < 0.001$. In males' results showed a significant difference between groups in 5-HT1AR concentration, $F(3,16) = 32.858$, $p < 0.001$. Dunnett's post hoc revealed that MK (M = 114.464, SD = 11.073) had significantly lower 5-HT1AR concentration than Ctrl (M = 185.919, SD = 15.347), MD = 71.456, $q = 9.343$, $p < 0.001$, MK+0.01 (M = 164.684, SD = 9.001), MD = 50.220, $q = 6.567$, $p < 0.001$, and MK+0.05 (M = 170.927, SD = 12.072), MD = 56.463, $q = 7.383$, $p < 0.001$ (See *Figure 8*).

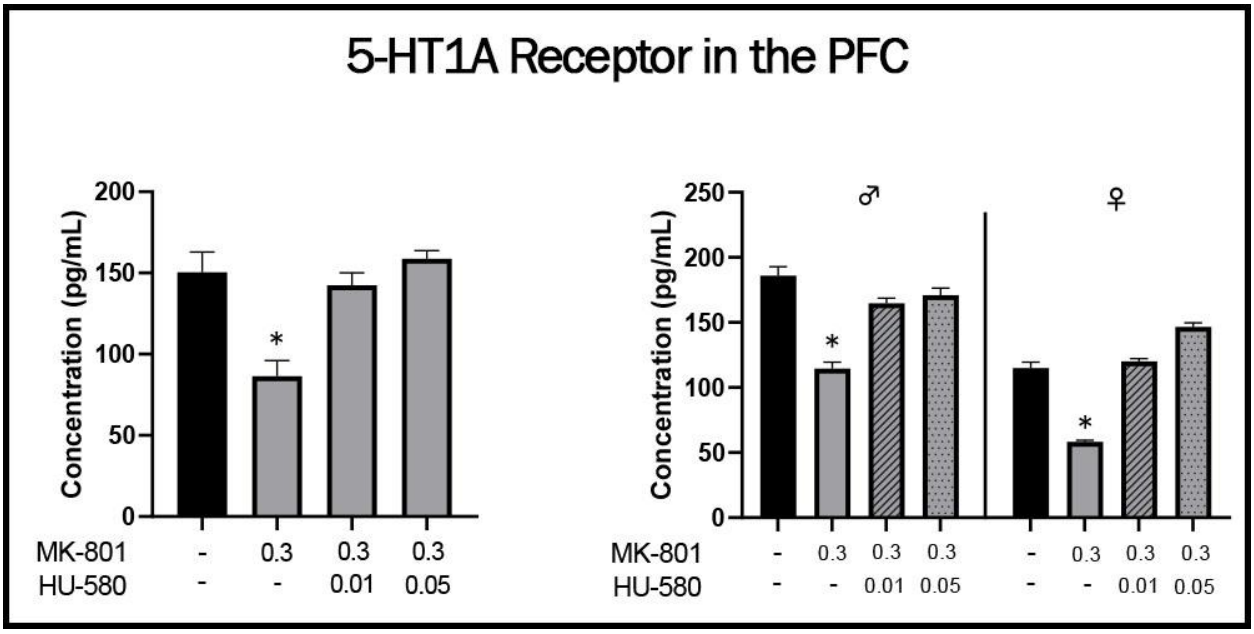

Figure 8. Comparison of the effects of MK-801/HU-580 in the 5-HT1AR ELISA in pooled (left) and sex separated (right) analysis; average (±SEM) concentration (pg/ml). Administration of MK-801 (0.3mg/kg, i.p.) daily for 17 days induced down regulation of the 5-HT1ARs in the PFC. Both low-dose (0.01ug/kg, i.p.) and high-dose (0.05ug/kg, i.p.) HU-580 treatment blocked the down regulation effects of MK-801.

3.1.5. EEG Oddball Paradigm.

Deviant Response Amplitude: Results showed a significant difference between groups in deviant response amplitude, $F(3,26) = 15.758$, $p < 0.001$. Dunnett's post hoc revealed that Ctrl (M = 1042.443, SD = 496.684) had a significantly greater deviant response amplitude than MK (M = 171.301, SD = 43.929), MD = 871.142, $q = 5.955$, $p < 0.001$, MK+0.01 (M = 168.944, SD

= 22.369), MD = 873.499, $q = 5.972$, $p < 0.001$, and MK+0.05 (M = 320.71, SD = 310.851), MD = 721.732, $q = 4.777$, $p < 0.001$. In females, results showed a significant difference between groups in deviant response amplitude, $F(3,12) = 5.113$, $p = 0.017$. Dunnett's post hoc revealed that Ctrl (M = 824.024, SD = 550.307) had a significantly greater deviant response amplitude than MK (M = 193.151, SD = 44.947), MD = 630.873, $q = 3.198$, $p = 0.02$, MK+0.01 (M = 169.399, SD = 29.947), MD = 654.625, $q = 3.318$, $p = 0.016$, and MK+0.05 (M = 221.17, SD = 74.70), MD = 602.854, $q = 3.056$, $p = 0.026$. In males, results showed a significant difference between groups in deviant response amplitude, $F(3,11) = 22.213$, $p < 0.001$. Dunnett's post hoc revealed that Ctrl (M = 1325.138, SD = 205.964) had a significantly greater deviant response amplitude than MK (M = 149.451, SD = 34.775), MD = 1175.687, $q = 7.106$, $p < 0.001$, MK+0.01 (M = 168.488, SD = 16.436), MD = 1156.649, $q = 6.991$, $p < 0.001$, and MK+0.05 (M = 453.431, SD = 485.052), MD = 871.706, $q = 4.878$, $p = 0.001$ (See *Figure 9*).

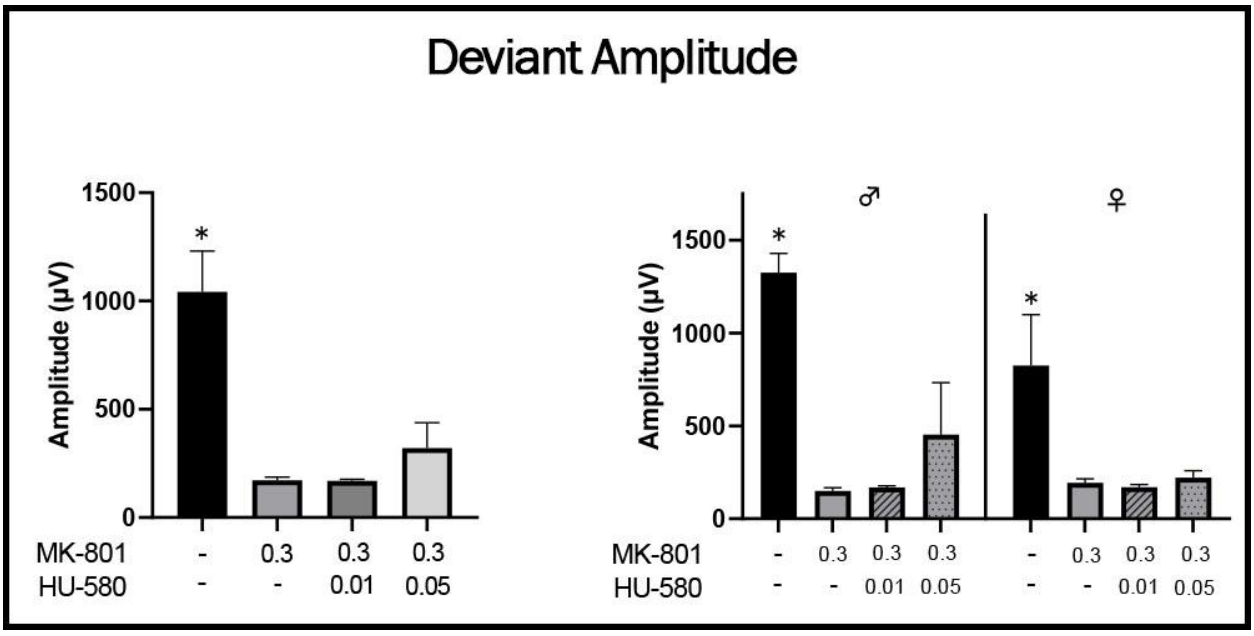

Figure 9. Comparison of the effects of MK-801/HU-580 in deviant response amplitude of the Oddball paradigm in pooled (left) and sex separated (right) analysis; average (±SEM) deviant response amplitude (µV). Administration of MK-801 (0.3mg/kg, i.p.) daily for 17 days induced deficits in deviant response amplitude to the oddball tone.

Standard Response Amplitude: Results showed a significant difference between groups in standard response amplitude, $F(3,26) = 8.924$, $p < 0.001$. Dunnett's post hoc revealed that Ctrl (M = 290.438, SD = 97.636) had a significantly greater standard response amplitude than MK (M = 140.685, SD = 39.822), MD = 149.753, $q = 4.140$, $p < 0.001$, MK+0.01 (M = 117.841, SD = 28.372), MD = 172.597, $q = 4.771$, $p < 0.001$, and MK+0.05 (M = 158.047, SD = 94.066), MD = 132.391, $q = 3.544$, $p = 0.004$. In males, results showed a significant difference between groups in standard response amplitude, $F(3,11) = 6.408$, $p = 0.009$. Dunnett's post hoc revealed that Ctrl (M = 308.255, SD = 37.998) had a significantly greater standard response amplitude than MK (M = 130.337, SD = 44.102), MD = 177.918, $q = 3.647$, $p = 0.01$, and MK+0.01 (M = 116.50, SD = 27.49), MD = 191.755, $q = 3.93$, $p = 0.006$. See *Supplemental Table 1* and *Figure 10* for comparison of standard and deviant amplitudes.

Difference Response Amplitude: Results showed a significant difference between groups in difference response amplitude, $F(3,26) = 15.509$, $p < 0.001$. Dunnett's post hoc revealed that Ctrl (M = 752.004, SD = 428.819) had a significantly greater difference response amplitude than MK (M = 51.102, SD = 19.629), MD = 700.902, $q = 5.828$, $p < 0.001$, MK+0.01 (M = 30.615, SD = 18.442), MD = 721.389, $q = 5.998$, $p < 0.001$, and MK+0.05 (M = 162.664, SD = 221.947), MD = 589.341, $q = 4.745$, $p < 0.001$. In females, results showed a marginally significant difference between groups in difference response amplitude, $F(3,11) = 3.283$, $p = 0.062$. Dunnett's post hoc revealed that Ctrl (M = 398.834, SD = 393.065) had a significantly greater difference response amplitude than MK (M = 42.118, SD = 11.13), MD = 356.717, $q = 2.765$, $p = 0.044$, MK+0.01 (M = 50.216, SD = 18.883), MD = 348.618, $q = 2.702$, $p = 0.049$, and marginally greater difference response amplitude than MK+0.05 (M = 85.356, SD = 33.89), MD = 313.478, $q = 2.43$, $p = 0.078$. In males, results showed a significant difference between groups in difference

response amplitude, $F(3,11) = 25.124$, $p < 0.001$. Dunnett's post hoc revealed that Ctrl (M = 1016.881, SD = 215.627) had a significantly greater difference response amplitude than MK (M = 19.113, SD = 17.802), MD = 997.768, $q = 7.608$, $p < 0.001$, MK+0.01 (M = 51.988, SD = 23.246), MD = 964.893, $q = 7.357$, $p < 0.001$, and MK+0.05 (M = 265.741, SD = 343.756), MD = 751.141, $q = 5.303$, $p < 0.001$ (See *Figure 11* and *Figure 10*).

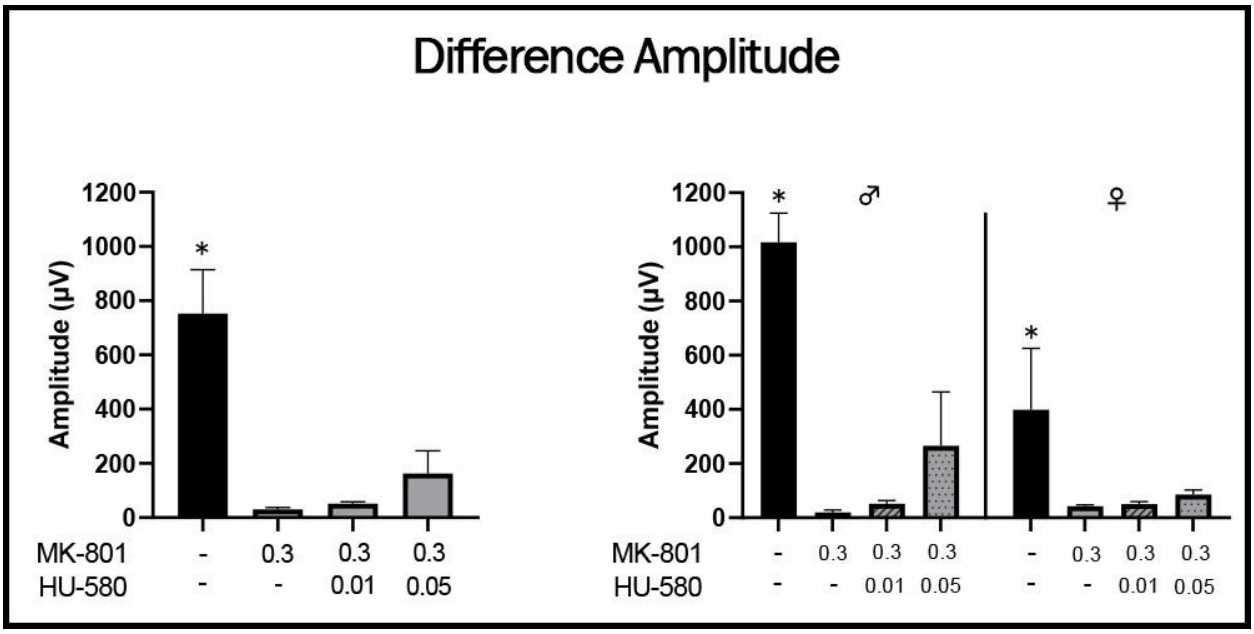

Figure 11. Comparison of the effects of MK-801/HU-580 in difference response amplitude of the Oddball paradigm in pooled (left) and sex separated (right) analysis; average (±SEM) difference response amplitude (µV). Administration of MK-801 (0.3mg/kg, i.p.) daily for 17 days induced deficits in difference response amplitude (i.e., deviant amplitude – standard amplitude).

Overall, MK-801 sex-dependently induced marked hyperlocomotion, immobility, social withdrawal, novel object preference deficits, down-regulation of CB1R and 5-HT1AR, and deficits in deviant and difference response amplitude. HU-580 blocked the effects of MK-801 in hyperlocomotion, immobility, cognitive deficits, down-regulation of CB1R and 5-HT1AR.

3.2. MIA Experiment

The effects of exposure to LPS and yohimbine, and HU-580 treatment were assessed on behavior and receptor expression. Results were analyzed using one-way or three-way ANOVA to assess group differences, main effects, and interaction effects.

3.2.1. Positive Symptom-like Behavioral Measures

OFT. A three-way ANOVA was conducted on exposure to LPS, Yohimbine, and treatment of HU-580 on total distance traveled (CM). Results trended towards a significant main effect of Yohimbine on total distance traveled (CM), $F(1,82) = 3.052$, $p = 0.084$. Dunnett's post hoc showed that mice given Yohimbine (M = 2620.914, SD = 71.207) traveled less than mice given saline (M = 2693.814, SD = 75.084), MD = 177.973, $q = 1.746$, $p = 0.085$.

Light-dark Box Test. A three-way ANOVA was conducted on exposure to LPS, Yohimbine, and treatment of HU-580 in time spent in the dark box. Results showed a significant main effect of treatment on time spent in the dark box, $F(1,82) = 5.416$, $p = 0.022$. Dunnett's post hoc revealed that mice given HU-580 (M = 286.404, SD = 53.207) spent significantly less time in the dark box than mice given saline (M = 313.412, SD = 54.129), MD = 27.008, $q = 2.318$, $p = 0.023$. In females, results revealed that treatment of HU-580 trended towards a significant main effect on time spent in the dark box, $F(1,40) = 3.192$, $p = 0.082$. Dunnett's post hoc showed that mice given HU-580 (290.395, SD = 54.125) trended towards spending less time in the dark box than mice given vehicle (M = 319.735, SD = 57.046), MD = 30.321, $q = 1.768$, $p = 0.085$. In males, results revealed a significant main effect of exposure to LPS on time spent in the dark box, $F(1,34) = 5.456$, $p = 0.026$. Dunnett's post hoc showed that mice given LPS (M = 309.051, SD = 54.088) spent significantly more time in the dark box than mice given saline (M = 273.877, SD = 51.865), MD = 35.174, $q = 2.322$, $p = 0.026$.

A one-way ANOVA was conducted on latency to leave the dark box. Results showed a significant difference between groups on latency to leave the dark box, $F(7,71) = 2.302$, $p = 0.036$. Dunnett's post hoc showed that LPSYo (M = 10.21, SD = 12.887) had a significantly higher latency than Ctrl (M = 3.13, SD = 1.225), MD = 7.08, $q = 2.872$, $p = 0.031$, CtrlHU (M = 2.645, SD = 1.516), MD = 7.566, $q = 2.867$, $p = 0.033$, CtrlYo (M = 2.269, SD = 1.018), MD = 7.941, $q = 2.881$, $p = 0.032$, LPS (M = 3.131, SD = 2.193), MD = 7.08, $q = 3.022$, $p = 0.022$, marginally significantly higher latency than CtrlYoHU (M = 3.253, SD = 1.815), MD = 6.957, $q = 2.636$, $p = 0.06$, and trended towards a higher latency than LPSHU (M = 4.497, SD = 4.491), MD = 5.713, $q = 2.245$, $p = 0.15$, and LPSYoHU (M = 4.474, SD = 2.93), MD = 5.736, $q = 2.391$, $p = 0.108$ (See *Figure 12*).

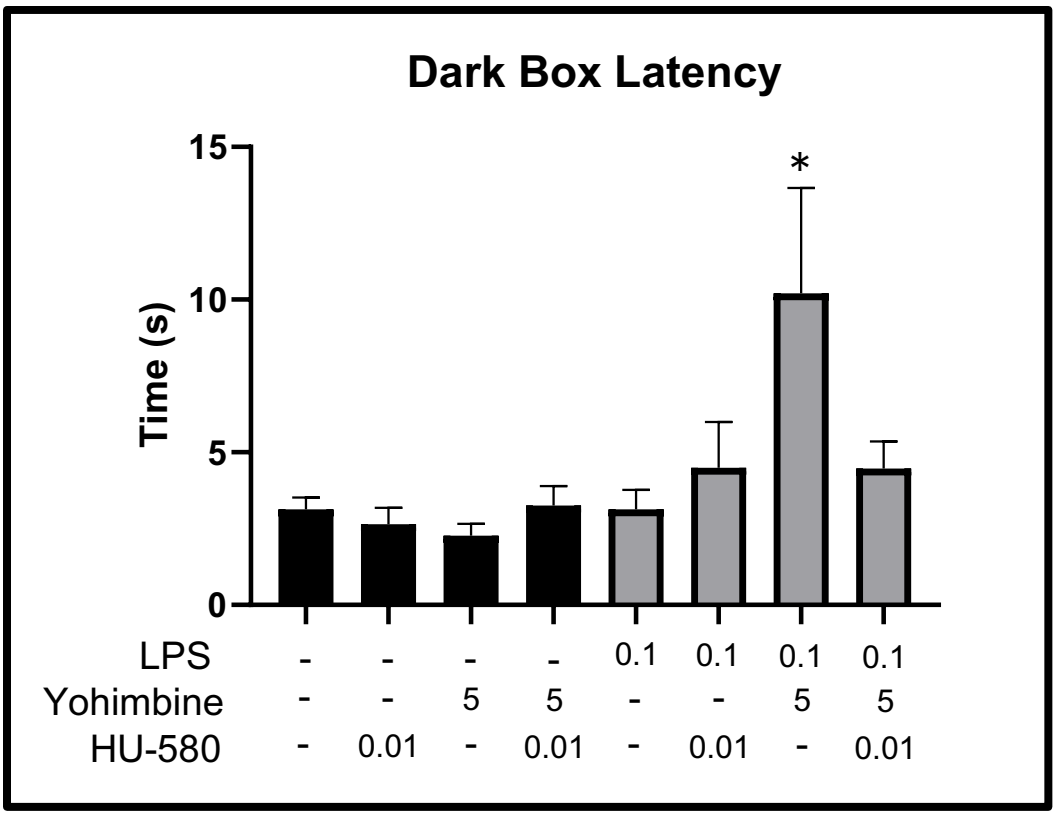

Figure 12. Comparison of the effects of LPS/Yohimbine/HU-580 in the LDBT; average (±SEM) latency in time (s) to leave the dark box. Pre-natal exposure of LPS (0.1mg/kg, i.p.) combined with exposure to Yohimbine (5mg/kg, i.p.) at PND 38 induced increased latency to leave the dark box.

3.2.2. Negative Symptom-like Behavioral Measures

SIT. A three-way ANOVA was conducted on exposure to LPS, Yohimbine, and treatment of HU-580 on SI. Results showed a significant main effect of treatment of HU-580 on SI, $F(1,82) = 6.662$, $p = 0.012$. Dunnett's post hoc revealed that mice given HU-580 (M = 1.744, SD = 0.585) had a significantly higher SI than mice given vehicle (M = 1.443, SD = 0.493), MD = 0.301, $q = 2.571$, $p = 0.012$. In males, results showed a significant main effect of Yohimbine on SI, $F(1,34) = 4.172$, $p = 0.049$. Dunnett's post hoc showed that Yohimbine mice (M = 1.761, SD = 0.581) had a significantly higher SI than control mice (M = 1.425, SD = 0.464), MD = 0.336, $q = 2.022$, $p = 0.049$. In females, results showed a significant main effect of treatment of HU-580 on SI, $F(1,40) = 4.910$, $p = 0.032$. Dunnett's post hoc revealed that mice given HU-580 (M = 1.783, SD = 0.601) had a significantly higher SI than mice given vehicle (M = 1.412, SD = 0.524), MD = 0.371, $q = 2.193$, $p = 0.034$. Analysis on time spent with the stranger conspecific showed a significant main effect of exposure to LPS on time spent with the stranger, $F(1,40) = 7.139$, $p = 0.011$. Dunnett's post hoc revealed that mice given LPS (M = 77.797, SD = 21.313) spent significantly less time with the stranger conspecific than mice given saline (M = 95.023, SD = 22.96), MD = 17.226, $q = 2.658$, $p = 0.011$.

FST. A three-way ANOVA was conducted on exposure to LPS, Yohimbine, and treatment of HU-580 on time engaged in escape behavior. Results showed a significant interaction effect between yohimbine and treatment of HU-580 on time engaged in escape behavior, $F(1,82) = 5.36$, $p = 0.023$. Dunnett's post hoc showed that mice given Yohimbine (M = 21.213, SD = 10.133) spent significantly more time engaged in escape behavior than mice given saline (M = 13.163, SD = 10.453), MD = 8.843, $q = 2.684$, $p = 0.009$, but not in Yohimbine mice treated with HU-580.

3.2.3. Cognitive Symptom-like Behavioral Measures

NORT. Results showed a significant difference between groups on difference time with the novel object, $F(7,104) = 3.175$, $p = 0.004$. Dunnett's post hoc revealed that LPSYo (M = -17.972, SD = 42.09) had a significantly lower difference time with the novel object than Ctrl (M = 8.091, SD = 11.389), MD = 26.063, $q = 4.192$, $p < 0.001$, CtrlYoHU (M = 4.63, SD = 7.356), MD = 22.602, $q = 2.788$, $p = 0.04$, and LPSYoHU (M = 5.524, SD = 7.383), MD = 23.496, $q = 3.085$, $p = 0.017$. In females, results showed a significant difference between groups on difference time with the novel object, $F(7,46) = 3.392$, $p = 0.005$. Dunnett's post hoc revealed that LPSYo (M = -25.173, SD = 38.131) had a significantly lower increase in time spent with the novel object than Ctrl (M = 8.28, SD = 9.777), MD = 33.453, $q = 4.333$, $p < 0.001$, CtrlHU (M = 6.867, SD = 10.622), MD = 32.04, $q = 3.152$, $p = 0.017$, CtrlYo (M = 3.198, SD = 10.665), MD = 28.371, $q = 2.966$, $p = 0.028$, CtrlYoHU (M = 2.496, SD = 8.79), MD = 27.669, $q = 2.893$, $p = 0.034$, LPS (M = 3.828, SD = 9.896), MD = 29.001, $q = 3.183$, $p = 0.016$, and LPSYoHU (M = 4.715, SD = 8.78), MD = 29.888, $q = 3.125$, $p = 0.018$ (See *Figure 13*).

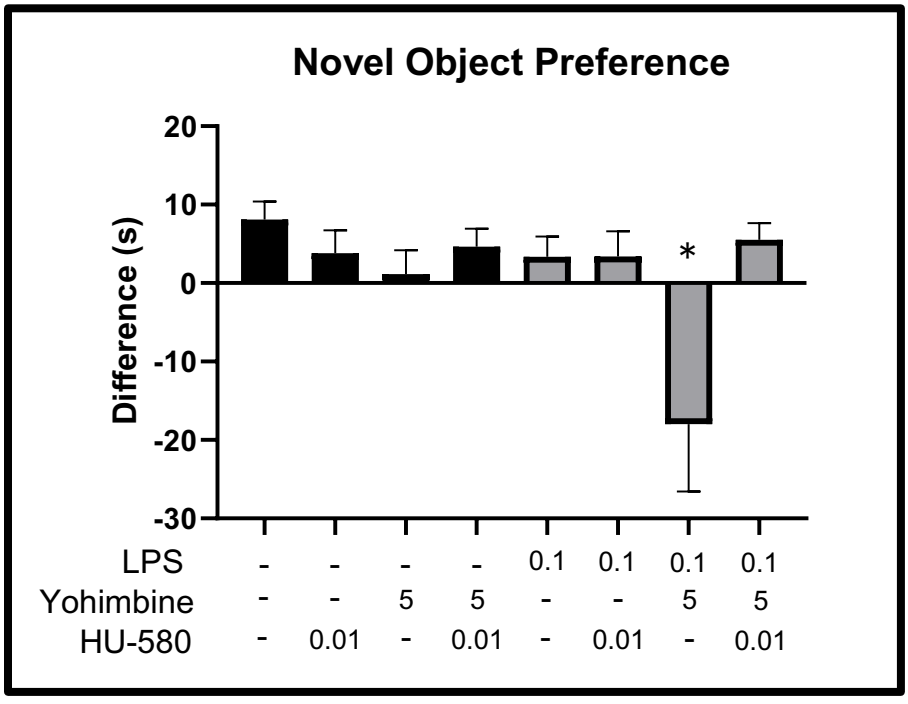

Figure 13. Comparison of the effects of LPS/Yohimbine/HU-580 in the NORT; average (±SEM) difference time (s) with the novel object. Pre-natal exposure of LPS (0.1mg/kg, i.p.) combined with exposure to Yohimbine (5mg/kg, i.p.) at PND 38 induced novel object preference deficits that were attenuated by early (PND 21 – 27) HU-580 (0.01ug/kg, i.p.) treatment.

3.2.4. ELISA

CB1R: Results showed a significant difference between groups in CB1R concentration, $F(3,36) = 8.245$, $p < 0.001$. Dunnett's post hoc revealed that Ctrl (M = 3770.007, SD = 1069.291) had a significantly higher CB1R concentration than LPSYo (M = 2602.539, SD = 516.285), MD = 1167.468, $q = 3.303$, $p = 0.007$, LPSYoHU (M = 2548.214, SD = 539.274), MD = 1221.793, $q = 3.457$, $p = 0.005$, and trended towards a higher CB1R concentration than LPS (M = 3056.21, SD = 446.639), MD = 713.798, $q = 2.226$, $p = 0.088$. In females, results showed a significant difference between groups in CB1R concentration, $F(3,16) = 5.514$, $p = 0.009$. Dunnett's post hoc revealed that Ctrl (M = 4165.183, SD = 1305.696) had a significantly higher CB1R concentration than LPSYo (M = 2579.916, SD = 506.358), MD = 1585.267, $q = 3.213$, $p = 0.014$, and LPSYoHU (M = 2312.284, SD = 481.895), MD = 1852.90, $q = 3.755$, $p = 0.005$. In males, results showed a marginally significant difference between groups in CB1R concentration, $F(3,16) = 2.86$, $p = 0.07$. Dunnett's post hoc revealed that Ctrl (M = 3374.832, SD = 690.913) had a significantly higher CB1R concentration than LPSYo (M = 2990.272, SD = 443.479), MD = 903.291, $q = 2.595$, $p = 0.05$, and trended towards a higher CB1R concentration than LPSYoHU (M = 2564.453, SD = 549.755), MD = 810.379, $q = 2.328$, $p = 0.083$ (See *Figure 14*).

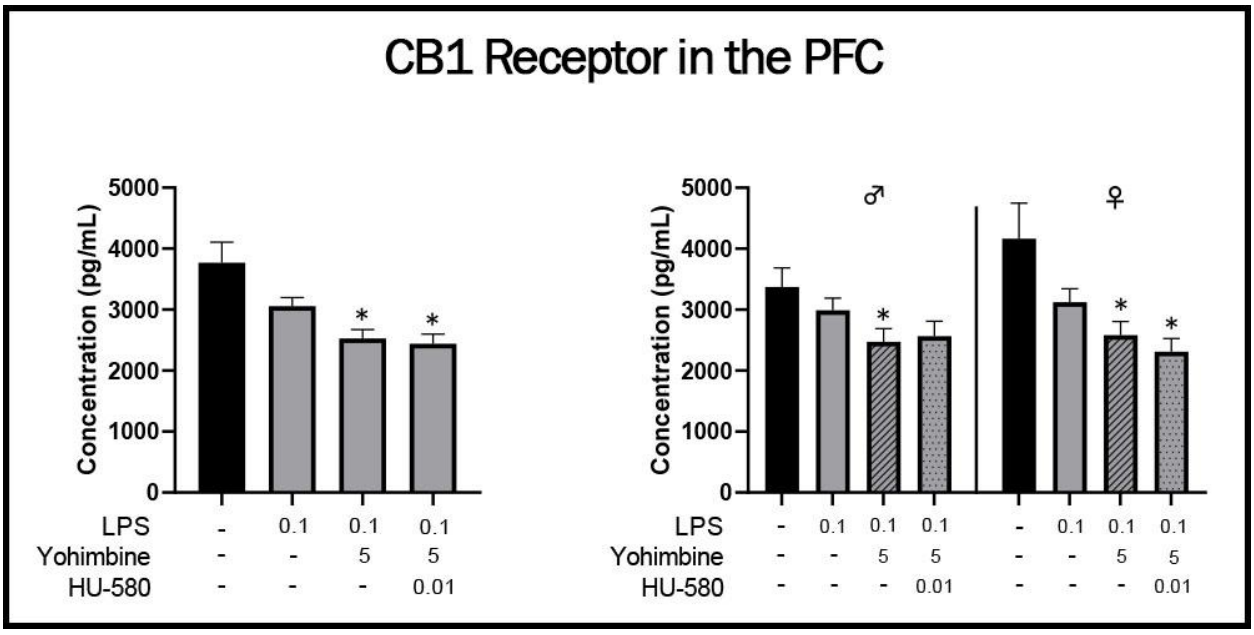

Figure 14. Comparison of the effects of LPS/Yohimbine/HU-580 in the CB1R ELISA in pooled (left) and sex separated (right) analysis; average (±SEM) concentration (pg/ml). Pre-natal exposure of LPS (0.1mg/kg, i.p.) combined with exposure to Yohimbine (5mg/kg, i.p.) at PND 38 induced down regulation of the CB1Rs in the PFC.

5-HT1AR: Results showed a significant difference between groups in 5-HT1AR concentration, $F(3,36) = 6.909$, $p < 0.001$. Dunnett's post hoc revealed that Ctrl (M = 237.345, SD = 21.099) had a marginally significantly lower 5-HT1AR concentration than LPSYo (M = 260.401, SD = 18.282), MD = 23.056, $q = 2.338$, $p = 0.064$. Both LPS (M = 215.805, SD = 16.692), MD = 44.595, $q = 4.523$, $p < 0.001$, and LPSYoHU (M = 233.718, SD = 29.774), MD = 26.682, $q = 2.706$, $p = 0.028$, had a significantly lower 5-HT1AR concentration than LPSYo. In females, results showed a significant difference between groups in 5-HT1AR concentration, $F(3,16) = 4.468$, $p = 0.018$. Dunnett's post hoc revealed that LPSYoHU (M = 213.856, SD = 28.318) had a significantly lower 5-HT1AR concentration than Ctrl (M = 253.038, SD = 16.945), MD = 39.182, $q = 2.622$, $p = 0.047$, and LPSYo (M = 256.234, SD = 24.096), MD = 42.378, $q = 2.836$, $p = 0.031$. LPS (M = 218.038, SD = 16.945) trended towards a lower 5-HT1AR concentration than Ctrl, MD = 34.572, $q = 2.314$, $p = 0.085$, and LPSYo, MD = 37.769, $q =$

2.528, $p = 0.057$. In males, results showed a significant difference between groups in 5-HT1AR concentration, $F(3,16) = 25.474$, $p < 0.001$. Dunnett's post hoc revealed that LPSYo (M = 264.567, SD = 11.314), MD = 42.915, $q = 6.196$, $p < 0.001$, and LPSYoHU (M = 253.581, SD = 14.365), MD = 31.929, $q = 4.61$, $p < 0.001$, had significantly higher 5-HT1AR concentration than Ctrl (M = 221.652, SD = 9.943; See *Figure 15*).

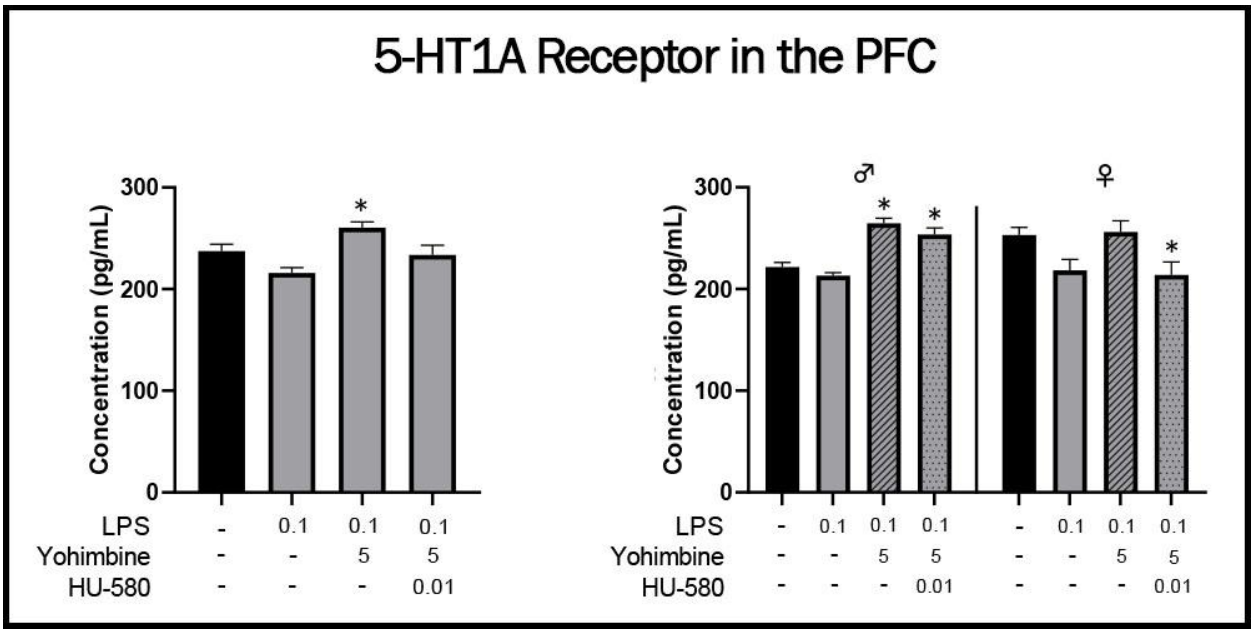

Figure 15. Comparison of the effects of LPS/Yohimbine/HU-580 in the 5-HT1AR ELISA in pooled (left) and sex separated (right) analysis; average (±SEM) concentration (pg/ml). Pre-natal exposure of LPS (0.1mg/kg, i.p.) combined with exposure to Yohimbine (5mg/kg, i.p.) at PND 38 induced up-regulation of the 5-HT1ARs in the PFC, primarily in males. In females, early (PND 21 – 27) HU-580 (0.01ug/kg, i.p.) treatment down-regulated 5-HT1AR in the PFC.

Overall, LPS and/or yohimbine induced social deficits, latency to enter a lit box compartment, novel object preference deficits, and escape behavior. LPS and yohimbine down-regulated CB1R and up regulated 5-HT1AR. HU-580 blocked cognitive deficits and 5-HT1AR up-regulation.

Chapter 4: Discussion

This study investigated the antipsychotic potential of HU-580 in two preclinical mouse models of schizophrenia. These models targeted specific aspects of schizophrenia pathology and

development and provide insights into how the eCB and serotonin systems can modulate typical pathologies of schizophrenia. Overall, we showed that HU-580 provides therapeutic potential against MK-801 and preventative potential against MIA in relieving symptom behaviors and normalizing pathology. Our results show that HU-580 normalizes behavior and receptor sensitization of the NDMAR antagonist model and in the MIA model of schizophrenia. Dependencies found (e.g., sex and dose) suggest that further studies are needed for a greater confidence in the application of HU-580 as a treatment. However, results are promising thus far.

4.1. MK-801 and HU-580 Treatment

MK-801 was effective in inducing schizophrenia-like behaviors consistent with previous literature. Indeed, hyperlocomotion (Irifune et al., 1995; Chartoff et al., 2005; Hakami et al., 2009; Mabunga et al., 2019), social deficits (Moy et al., 2013; Zou et al., 2008), immobility (Langen et al., 2012**;** Kawaura et al., 2015), and cognitive deficits (Nilsson et al., 2007; Rajagopal et al., 2014) that were shown in this study are consistent effects from NMDAR antagonists as a pharmacological model of schizophrenia (Lee & Zhou, 2019). These behaviors are hypothesized to be related to MK-801 inducing positive-like (i.e., hyperlocomotion), negative-like (i.e., social withdrawal, immobility), and cognitive-like (i.e., memory impairment) symptoms of schizophrenia (Powell & Miyakawa, 2006). Contribution to these behavioral deficits come from hypofunction of the NMDAR on PV GABAergic interneurons that impairs cortical activity (Balu, 2016). In turn, several regions and pathways in the brain are either hypo- or hyper-activated and result in altered dopamine, serotonin, and glutamate signaling (Balu, 2016). This results in behavioral changes seen in this study.

The effects of MK-801 were dependent on treatment length and sex. Some studies have shown that MK-801 effects may be dose and approach dependent in that a high dose (0.5mg/kg),

but not a chronic low dose (0.1mg/kg) increases locomotor activity (Eyjolfsson et al., 2006). Indeed, previous literature does show sex-dependent effects of MK-801 (D'Souza, Harlan, and Garcia, 2002). One example of this is the motor-induced differences of MK-801. In females, it is typical of MK-801 to cause increased activity measured as hyperlocomotion (Feinstein & Kritzer, 2013). However, males do not exhibit the same effects. Instead, males show deficits in other aspects of motor-coordination not expressed as hyperlocomotion (Feinstein & Kritzer, 2013). Therefore, it is without confidence that we could conclude that MK-801 didn't induce the motor-related effects in males as females; only that the OFT was more sensitive in detecting deficits in females. However, unexpectedly our results showed a synergistic-like effect of MK-801 and HU-580 in the OFT, but only in males. Previous literature shows that cannabinoids can effect locomotive activity in the OFT (Kasten, Zhang, & Boehm, 2019), and effects of cannabis in C57BL/6 can be sex-dependent (Peterson et al., 2023). In addition, stress has been shown to have sex-dependent effects in rodents that can increase locomotive activity in males (Jakovcevski, Schachner, & Morellini, 2008; Franceschelli et al., 2014). It is possible that the synergistic effect observed here is a complex set of sex-dependent effects building upon each other. For example, stress has been shown to alter eCB signalling, increasing the presence of endogenous cannabinoids (Rademacher et al., 2008). However, in the presence of endogenous cannabinoids, compounds such as CBD and CBDA tend to convert into a CB1R inverse agonist (Navarro et al., 2020; An et al., 2020), likely producing an anxiogenic effect (Sink et al., 2010).

As expected, HU-580 attenuated hyperlocomotion, immobility, and cognitive-deficits. This is consistent with previous studies that showed CBD can block effects of MK-801 (Kruk-Slomka & Biala, 2021). While CBD and CBDA alone do not seem to affect locomotor activity (Calapai et al., 2022), its regulation of NDMAR via CB1R and 5-HT1AR is likely the

mechanism to reverse hyperlocomotion (Rodríguez-Muñoz et al., 2016; Yuen et al., 2005). Previous research was able to show that NMDAR antagonism can induce immobility in the FST (Langen et al., 2012 Kawaura et al., 2015), and our study corroborates the findings that compounds such as CBD and HU-580 can significantly reduce immobility behavior (Sales et al., 2019; Sales et al., 2020; Dlugosz et al., 2023). Moreover, CBD (Felipe et al., 2013; Osborne et al., 2017; Leweke et al., 2021) and CBDA (Kim et al., 2023) have been shown to improve or rescue cognitive performance in psychiatric and neurological disorders. It is difficult to assign behavioral deficits to disruptions in individual receptor systems. CB1R and 5HT1AR are both implicated in positive, negative, and cognitive symptom functioning of schizophrenia as potential therapeutic targets or pathologies (Dickens et al., 2020; Ceccarini et al., 2013; Borgan et al., 2019; Kim, 2021; Kishi, Meltzer, & Iwata, 2013; Ohno, 2011; Švob Štrac, Pivac, & Mück-Šeler, 2016). Therefore, further conclusions cannot be made until follow-up studies isolate the therapeutic mechanisms for each behavior in HU-580.

MK-801 induced powerful decreased responses of EEG ERP in the MMN oddball paradigm. Previous literature appears to consistently show similar deficits in MMN oddball paradigms from NMDAR antagonists (Javitt et al., 1996; Umbricht 2000; Harms et al., 2018; Koshiyama et al., 2020). Our results, in corroboration with Lee et al. (2017), show there is an overall decrease response to auditory stimuli suggesting disrupted inputs to the auditory cortex. Both deviant and standard response amplitude are greatly deceased from MK-801. NMDAR are glutamatergic receptors that contribute to neural excitability. Therefore, antagonism at the NMDAR site should decrease neuron excitability and activation. However, it is unclear which type of neuron and in which brain structure this occurs (Cohen et al., 2015). Auditory stimuli pass through several paths before transduction is encoded into a neocortical experience. Due to

the global administration of MK-801, the NMDAR could be hypofunction from cochlea through the thalamus and into auditory cortex dampening response. Indeed, similar thalamocortical and corticocortical connections that are impacted have been linked to deficits in schizophrenia (Lee et al., 2017; Lakatos et al., 2020; Tada et al., 2019). Moreover, there is a significant change in the difference response amplitude as well. Although overall stimulus response is dampened, significant divergence of groups in difference response amplitude suggests that mechanisms specific to stimuli-type differentiation are disrupted as well. Otherwise, results would show no ability to differentiation between stimuli-type (i.e., deviant and standard) shown by the difference response. Further, this suggests promise that the effects of MK-801 are related to that of schizophrenia. However, the overall dampening effect of MK-801 may indicate deficits that preclude sensation making it difficult to pin-point at which point is NMDAR hypofunction occurring.

HU-580 did not block the effects of MK-801 in the oddball paradigm. Previous research has shown that co-administration of CBD and THC attenuates the effects of THC induced enhancements in MMN intensity (Greenwood et al., 2022), suggesting that CBD may dampen MMN processes. Indeed, past studies have shown that CB1R antagonism induces MMN deficits (Roser et al., 2011). Currently, the literature on the effects of cannabinoids in MMN paradigms is somewhat mixed with some findings indicating enhancements (Juckel et al., 2007; Greenwood et al., 2022), and others indicating impairments (Roser et al., 2011; Greenwood et al., 2022). The use of cannabis has been associated with some impairment of MMN (Greenwood et al., 2014), however there is a demand for more investigation of the role of the eCB to accurately elucidate its role in neural transmission in MMN mechanisms. Alternatively, studies have shown that 5-HT1AR agonism enhances MMN response (Guille et al., 2011; Wienberg et al., 2010; Todd et

al., 2006). Although unclear, what may be occurring is opposing effects of HU-580 negating the overall effect we expected to see. This might be why we see no change in MMN measures, rather than impairment from CB1R antagonism (Roser et al., 2011; Greenwood et al., 2022) or an enhancement from 5-HT1AR agonism (Guille et al., 2011; Wienberg et al., 2010; Todd et al., 2006).

MK-801 down-regulated both the CB1R and 5-HT1AR in the PFC. One such explanation for this is that MK-801 causes a disruption of E/I balance by hypofunction of NMDAR and thus recruits CB1R regulation to restabilize E/I balance (Sánchez-Blázquez, Rodríguez-Muñoz, & Garzón, 2014). Such dysregulation causes both stress-related responses (Liang, Chen, & Cheng, 2022) and the employment of regulatory receptors (Sánchez-Blázquez, Rodríguez-Muñoz, & Garzón, 2014). Stress induced by MK-801 could be inducing an increase in eCB production and/or release (e.g., 2-AG; Hillard, 2014; Morena et al., 2016). Such increase would agonize CB1Rs, and if done so chronically, should induce receptor desensitization (Hillard, 2014). Additionally, it is possible that MK-801 is down-regulating CB1R via oxidative stress pathways as chronic stress is known to downregulate CB1R (Liang, Chen, & Cheng, 2022; Morena et al., 2016).

HU-580 blocked the downregulation of CB1R from MK-801. NMDAR and CB1R have a complex relation, and CB1R are known to regulate glutamatergic activity (Sánchez-Blázquez, Rodríguez-Muñoz, & Garzón, 2014). Thus, it is likely that CB1R antagonism mitigated some of the impacted NMDAR hypofunction to prevent internalization and down-regulation (Rodríguez-Muñoz et al., 2016). By introducing an antagonist to mitigate downregulation, it is possible that receptor sensitization is kept normal, and effective regulation of dysfunctional NMDAR activity is maintained. Alternatively, it is possible that by antagonizing CB1R, the oxidative stress

response of MK-801 and CB1R are being mitigated and preventing down-regulation (Liang, Chen, & Cheng, 2022; Mukhopadhyay et al., 2010). However, there are limited studies on this topic and further research is needed to elucidate the relationship between NMDAR dysfunction, and eCB synthesis, production, and release.

Our finding of increased 5-HT1AR in the PFC of mice corroborates past literature that showed MK-801 increases 5-HT1AR in the rat brain (Wedzony et al., 1997). While our findings were counter to some schizophrenia pathology, it speaks to the limitations of the NMDAR model. Although the pathology of 5-HT1AR in schizophrenia is generally understood to have an increased presence of 5-HT1AR, the sensitization of 5-HT1AR appears to be regionally specific and the literature has mixed results (Nikolaus, Müller, & Hautzel, 2016; Razakarivony, Newman-Tancredi, & Zimmer, 2021). Inconsistent findings of 5-HT1AR sensitization may be a cause for heterogeneity and/or differential manifestation of schizophrenia symptomatology. There may be a difference in 5-HT1AR sub-types. 5-HT1AR heteroreceptors and autoreceptors are sub-types of 5-HT1AR that mediate serotoninergic signalling and could be differentially sensitized in schizophrenia (Albert, 2012). Another possible explanation for 5-HT1AR down regulation from MK-801 is that mice in this study began as healthy adults with an already established serotonin system. Serotonin receptors, especially 5-HT1AR, regulate both NMDAR and stress responses (Biswal et al., 2015; Flügge et al., 1998; Yuen et al., 2005). Similar to the explanation of CB1R down regulation, 5-HT1Rs are likely over activated in attempt to regulate NMDAR dysfunction and cause internalization (Yuen et al., 2005).

However, this may not be the best explanation as the serotonin mechanism of HU-580 is counterintuitive to this explanation. If our results are due to 5-HT1AR over-activation by MK-801, then 5-HT1AR agonism should exacerbate downregulation of 5-HT1AR synergistically

with MK-801. However, there is extremely complex crosstalk between serotonin, eCB, and glutamatergic systems (Haj-Dahmane & Shen, 2011). Although for explanatory purposes it is simpler to discuss each receptor independently, its also possible that there is an interaction occurring between CB1R and 5-HT1AR via HU-580 (Haj-Dahmane & Shen, 2011). However, due to the dual mechanism of HU-580, it is difficult to draw conclusions about specific mechanisms. Thus, follow-up studies are needed with challenges to the receptor systems (i.e., opposing agonism/antagonism) to investigate precise mechanisms involved in sensitization.

4.2. MIA and HU-580 Treatment

The MIA model of schizophrenia is an animal model that has been shown to induce schizophrenia-like behaviors in animals by disrupting typical neurodevelopment via immune, inflammatory, and stress mechanisms (Talukdar et al., 2020). Exposure to compounds or organisms that activate an immune response increases inflammatory cytokines in the mother that is passed to the fetus, disrupt immune response, and/or cause immune failure leading to possible epigenetic modifications and neurodevelopmental disruption (Shimizu et al., 2023). Consistent with schizophrenia pathology, the MIA model is known to decrease PV interneurons (Vojtechova et al., 2021). Our results show that aspects of the MIA model (i.e., LPS and/or yohimbine) induced positive-, negative-, and cognitive-like behavioral changes and differential receptor sensitization.

Regarding positive-like symptoms, our study showed increased anxiety-like behaviors in some, but not all measures. The HPA activator, yohimbine, decreased locomotive activity overall. In the context of schizophrenia-like behaviors, the OFT is used to measure anxiety-like behavior using the parameter of distanced traveled, indicating increased locomotor activity. However, decreased locomotive activity may be indicative of other possible parameters such as

apprehension or fear-related freezing. While Yohimbine is thought to be an anxiogenic compound (Rawleigh, Gibson, & Kemble, 1990; Simon, Dupuis, & Costentin, 1994), it has also been shown to impair locomotor activity in intrathecal administration (Majczyński et al., 2006) However, the effects of yohimbine on locomotion may differ depending on methodology, such as intraperitoneal injection compared to intrathecal administration. Yohimbine also acts as a 5-HT1AR agonist in doses greater than 1mg/kg (Zaretsky et al., 2015). Indeed, it appears that Yohimbine works in a dose dependent manner and reduced locomotor effects can be seen in higher doses (Zaretsky et al., 2015). However, studies investigating the effects Yohimbine do so shortly after administration. Long term effects of Yohimbine appear to be dependent on stress (Davidson & Lucki, 1987). Regarding anxiety measures, the OFT may be tainted with some aforementioned confounds. Our results show that the MIA model induced anxiety-like behavior via light dark box test and Yohimbine induced potential anxiety behaviors via FST. Pre-natal exposure of LPS combined with peri-adolescent exposure to Yohimbine increased latency to leave the dark box and exposure to LPS alone increased time spent in the dark box. This corroborates many animal studies showing anxiety behaviors in the MIA model (Quagliato, de Matos, & Nardi, 2021). Moreover, increased latency to leave the dark box only occurred in the LPS+Yohimbine group. Indeed, pre-natal exposure to LPS increases stress mechanisms and these results likely speak to the prerequisite of stress for yohimbine to induce anxiety (Davidson & Lucki, 1987; Lin, Lin, & Wang, 2012). It is worth noting that although escape behavior in the FST is not standard, anxiety-like behavior of the light dark box test provides corroborative evidence to its validity. The FST is a gold standard depression-related test for learned helplessness, despair-like behavior, or passive coping strategies (Can et al., 2012). However, it is possible that both extremes of rodent behavior (i.e., escape and immobility) during this test are

indicative of different aspects of psychological disorders. Indeed, some literature is now surfacing to suggest that extreme escape behavior in the FST may be indicative of anxiety (Anyan & Amir, 2018). Regarding negative symptoms, the effects of pre-natal and/or peri-adolescent exposure to Yohimibine were dependent on sex. LPS decreased time spent with a stranger conspecific suggesting social withdrawal behaviors. However, this only occurred in females. Interestingly, Yohimbine increased spontaneous sociability in males. It is known that the MIA model can induce sex-dependent effects where female mice exhibit a unique set of responses to the model, including altered social behavior (Braun et al., 2019; Vojtechova et al., 2021). In addition, one reason why we see sex-differences in social behavior in our results is that Yohimbine may promote sexual behavior in males (Clark, Smith, & Davidson, 1984). Although mice were sex-matched during SIT, it could be that Yohimbine generally increased social exploration via increased sexual behavior. While it is possible that pheromones may have facilitated this response (Matsuo et al., 2015), all apparatuses were cleaned well between each trial. Regarding cognitive symptoms, the effects of the MIA model were robust. The MIA model decreased the difference time spent with the novel object, more so in females, with a trend towards a deficit in males. Cognitive deficits induced by the MIA model in the NORT is consistent across other studies (Swanepoel, Möller, & Harvey, 2018; Simões et al., 2018). Moreover, while it is usually more likely to see cognitive deficits in male rodents more so than females (Gogos et al., 2020), our dual-hit component using Yohimbine is unique and therefore not easily comparable. For example, Yohimbine has been shown to be more impactful in females in its stress-inducing effects (Li et al., 2014).

The current study found that the MIA model of schizophrenia induces CB1R down-regulation and 5-HT1AR up-regulation. These results indicate that MIA creates receptor changes

slightly more consistent with schizophrenia pathology, with regards to 5-HT1A, than MK-801. While the CB1R down-regulation was robust across both sexes, only males seen a marked increase in 5-HT1AR. This could be due to injection timing, as females are known to have some pre-natal resilience, and earlier gestational injections (i.e., LPS injections during gestational day 12) may be more effective in inducing inflammatory response in females (Braun et al., 2019). Indeed, the MIA model has been shown to alter eCB signaling and sensitivity to cannabinoid compounds (Santoni et al., 2023). A similar study also showed that the MIA model induces marked increases of 5-HT1AR (Dalton et al., 2012). However, this study was only done in male rats, so sex differences were not investigated. Moreover, differences seen between receptors and sex may be due to variability in the effects of the MIA model. The impact of the MIA model depends on factors such as stress, gestational period, and inflammatory reaction in magnitude and type (Shimizu et al., 2023). Thus, future studies should focus on elucidating sex-different mechanisms occurring in the MIA model to better understand effective treatment options between sexes (Braun et al., 2019).

HU-580 was able to reduce cognitive deficits induced by LPS and Yohimbine. Cannabinoid compounds are known to prevent effects of LPS and MIA (Suryavanshi et al., 2022; Osborne et al., 2019). Moreover, HU-580 in general increased sociability, and down regulated 5-HT1AR in females. Recent literature has shown dose-dependent differences across sexes for the anti-depressant effects of CBDA (Hen-Shoval et al., 2023). Sex differences are novel in the context of HU-580, but they are to be expected. While CB1R activation has been shown to enhance the inflammatory effects of LPS (Joffre et al., 2020), CB1R antagonism has shown to mitigate a myriad of effects in the context of inflammatory models with over expressed CB1R (Nam et al., 2012; Schaich et al., 2014). Interestingly, one possible influence occurring is

HU-580s action at the site of cannabinoid receptor type 2 (CB2R) to mitigate hyperactive inflammatory and immune responses. Indeed, CB2Rs have received much of a spotlight in inflammatory research (Turcotte et al., 2016; Guindon & Hohmann, 2008). Recently, CBDA has been reported to have anti-depressant effects that was blocked by AM-630, claimed to be an antagonist at the site of CB2R (Hen-Shoval et al., 2023). However, studies show that the action of AM-630 is complex and suggest it may be a CB2R inverse-agonist as well as a CB1R agonist (Ross et al., 1999). Due to HU-580s novelty, much of its pharmacological action is unclear. However, its similarities with CBD and CBDA suggest that it is likely to have CB2R actions related to anti-inflammatory processes and future studies are needed to unravel these mechanisms. Overall, HU-580 blocked the up-regulation of 5-HT1AR in the MIA model, but it did not block the downregulation of CB1R. This is likely due to HU-580s strong affinity for 5-HT1AR (Navarro et al., 2020). It is possible that to prevent CB1R down-regulation, a higher treatment dose of HU-580 is required. However, research on higher doses of HU-580 are needed, as too high of a dose may have toxic-like effects (Volpi-Abadie et al., 2013; Nakayama et al., 2014). Alternatively, stress responses between models may be different. While CB1Rs are responsible for mediating stress response, it may differ depending on specific stress mechanisms. For example, MK-801 may induce CB1R down-regulation via oxidative stress (Liang, Chen, & Cheng, 2022; Mukhopadhyay et al., 2010), MIA stress effects involve glucocorticoid over expression (Maganga-Bakita et al., 2022; Hillard, 2014). Indeed, MK-801 appears to have different effects on glucocorticoid receptors than MIA (Lefevre et al., 2017; Maganga-Bakita et al., 2022). HU-580 may not be able mediate MIA stress-specific effects on the CB1R. Further, the MIA model induces early developmental changes that are likely more established and difficult to reverse as compared to the MK-801 effects. Thus, further investigations should test

HU-580 at different time points of development to see if CB1R down-regulation can still be reversed.

Both models produced schizophrenia-like behaviors of anxiety and cognitive deficits, down-regulated CB1R receptors, and disrupted 5-HT1AR expression. Although it isn't entirely clear, the consistency between these models further suggests a strong role of PFC CB1Rs and 5-HT1ARs in anxiety and cognition. Consistent with the literature, CB1Rs are known to be involved in anxiety, depression, and cognitive function (Patel & Hillard, 2009; Saravia et al., 2017). Although 5-HT1ARs were differently disrupted from each model, they are also implicated in anxiety and cognition (Albert, Vahid-Ansari, & Luckhart, 2014; Meltzer & Sumiyoshi, 2008). Moreover, in both models HU-580 was able to reverse the effects of the model on 5-HT1ARs, highlighting the robustness of HU-580 and suggests that the behavioral deficits may be more related to 5-HT1AR disfunction. However, this is only conjecture as there is no way to parse the effects seen. Indeed, 5-HT1ARs have subunits that may have localized pathology in schizophrenia (Albert, 2012; Albert, Vahid-Ansari, & Luckhart, 2014). Therefore, further studies are needed to tease out which subunits are involved in each behavior and in what structure.

The results of this study has several implications. First, the pharmacological mechanism of HU-580 (i.e., CB1R antagonism, 5-HT1AR agonism) are relevant for the prevention of schizophrenia-like behavior deficits in the context of NMDAR antagonism and the inflammatory MIA model. Second, the time in which treatment is administered is important. Our studies show that both late and early treatment of HU-580 can block some effects of the model. However, some effects (e.g., behavior, MMN, sensitization) were not effectively blocked. Therefore, further research is needed to continue to identify the most effective aspects of HU-580 treatment in the context of schizophrenia (e.g., dose, timing, length).

4.3. Strengths and Limitations

The pharmacological approach using MK-801 is unfortunately stricken with limitations such as half-life and tolerance, that are difficult to control. The most obvious limitation is that administration of MK-801 is an artificial model of schizophrenia in which intraperitoneal injections may not be ecologically valid to its natural development. Although a single or relatively small number of mechanisms involved in a pharmacological model provide greater precision in mechanism detection, it doesn't accurately recapitulate pathology. As an example, 5-HT1AR expression downregulated in MK-801 modeling but may be upregulated in schizophrenic patients. Indeed, there are many receptors and systems involved in schizophrenia pathology. Although NMDAR antagonism provides an efficient look into schizophrenia-like behavior in rodents, these models are typically administered in adult mice after presumably healthy development. As we know, schizophrenia is now seen as a neurodevelopmental disorder that likely originates in early or pre-natal development, it's difficult to generalize the effects seen in this study as mechanisms and behavior may be different in rodents that developed something equating to schizophrenia. Pharmacological models hold their place in research but ultimately come with drawbacks. However, the MK-801 model is one frequently used, and it provided this study with the ability to find a therapeutic effect of HU-580 may be more applicable to the real world.

Due to some of the drawbacks of NMDAR antagonist models, we used two mouse models of schizophrenia to induce schizophrenia-like behaviors. While MK-801 is administered in adults, the MIA model allowed us to test the neurodevelopmental similarities in MIA and schizophrenia pathology more accurately. This triangulated approach is more advantageous than using only one model as each model inevitably has their weaknesses. By more closely

recapitulating the proposed pre-natal environment, MIA is more likely to induce expected pathological effects as seen in our data. The MIA model provides a more ecologically valid model of the likely neurodevelopment of schizophrenia. Moreover, by using two models, this study highlights a heterogeneous nature of schizophrenia. For example, by targeting NMDAR directly, we can see somewhat different effects as compared to MIA. Although each model may provide slightly different effects, such results are still consistent with schizophrenia. For this reason, we can see a level of heterogeneity in the suggested schizophrenia-like behaviors (e.g., different behavioral effects of each model) and the robustness in the treatment potential of HU-580.

4.4. Conclusions

HU-580 is a potentially effective anti-psychotic compound that shows promising results in mouse models of schizophrenia. Further investigations are needed to continue to elucidate its effects and find the best fit method for its application. Sex-differences on the effects of both the models used and HU-580 highlight the complex nature of schizophrenia animal modeling and treatment but do so in a relevant manner. Animal models at best only model some aspects of the disorder but remain useful tools in the preclinical screening of novel treatments. This study showed that NDMAR hypofunction and MIA induce schizophrenia-like behaviors, and CB1R and 5-HT1AR sensitization. HU-580 was robust in preventing behaviors and receptor expression changes across both models. HU-580 provides mechanistic insight (i.e., CB1R antagonism/5-HT1AR agonism) in its preventative ability and supports the involvement of CB1R and 5-HT1AR in the PFC of schizophrenia. These findings will provide converging evidence and guide future research in further understanding the involvement of these receptors, ultimately leading to

aiding in identifying relevant treatment options (e.g., HU-580) for those diagnosed with schizophrenia.

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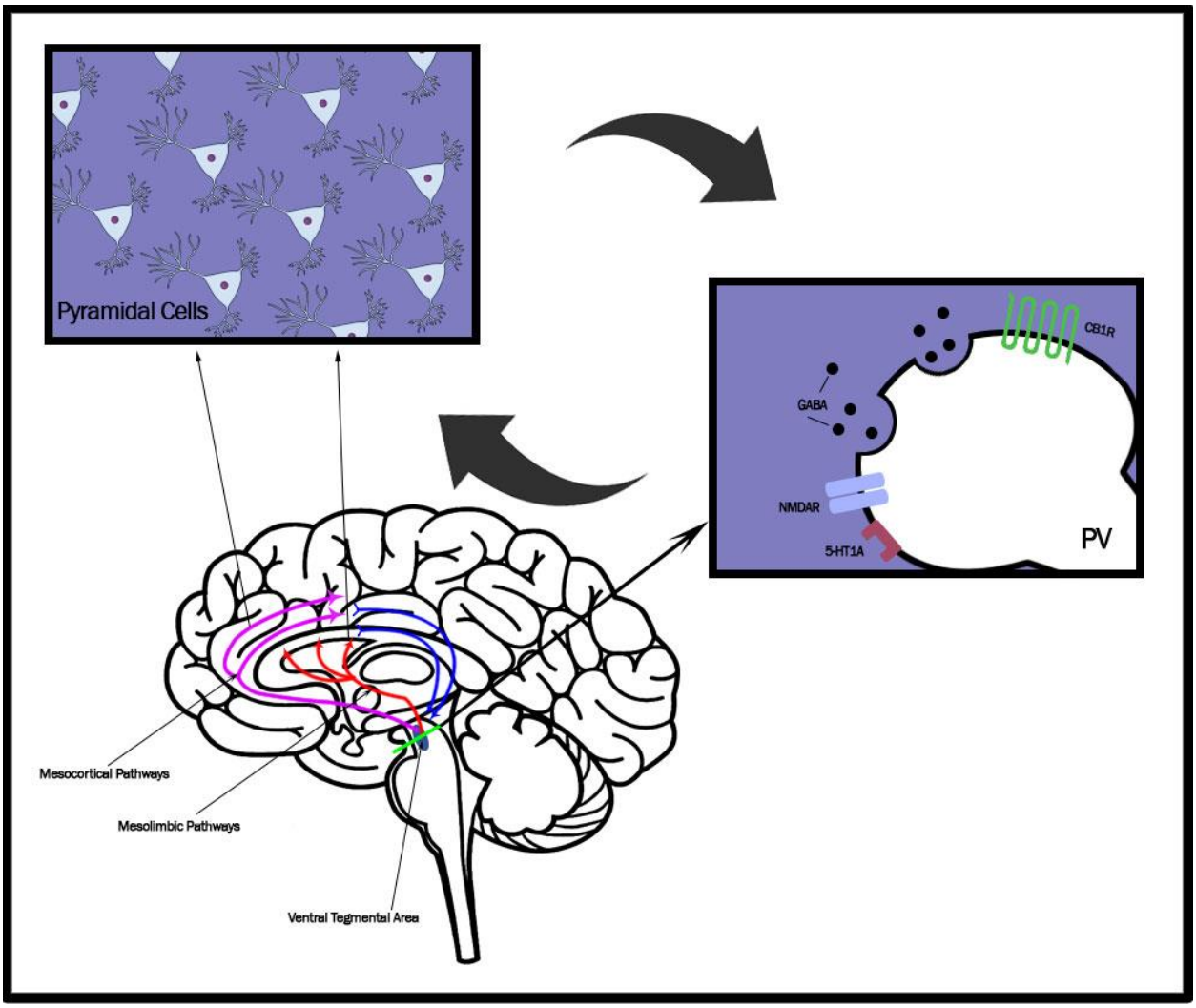
Supplementary Tables and Figures

Supplemental Table 1

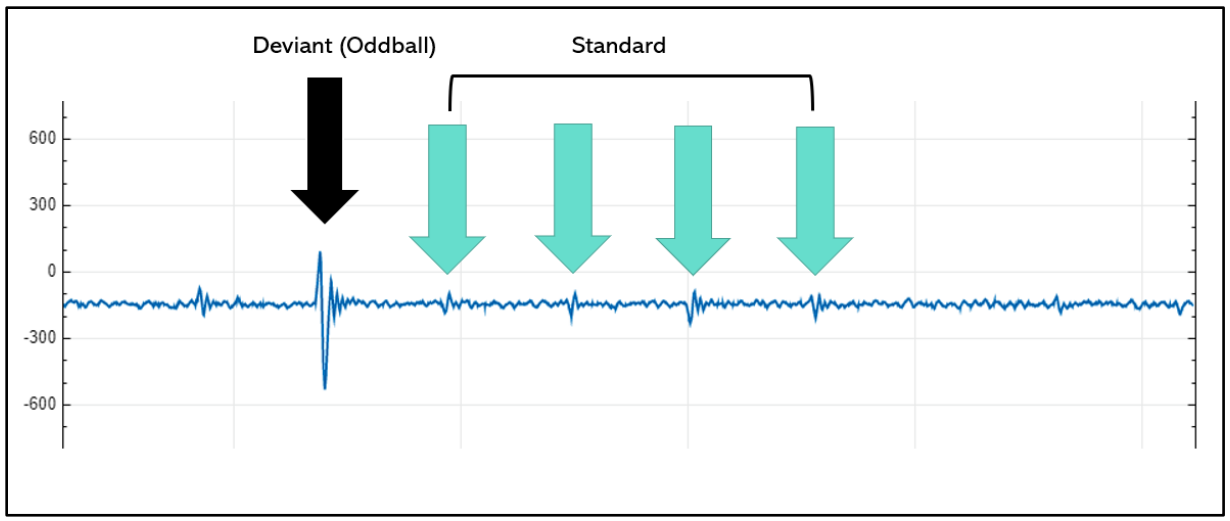
Comparison of deviant amplitude with standard amplitude of EEG mismatch negativity measure

Group	**Sex**	**Deviant (M/[SD])**	**Standard (M/[SD])**	**p-value**
Ctrl				
	Female	665.516(550.917)	266.682(157.959)	0.29
	Male	1325.138(205.964)	308.255(37.998)	< 0.001*
	Both	1042.443(496.684)	290.438(97.636)	0.002*
MK				
	Female	193.151(44.947)	151.033(38.336)	0.204
	Male	**149.451(34.775)**	**130.337(44.102)**	0.2
	Both	**171.301(43.929)**	**140.685(39.822)**	0.16
MK+0.01				
	Female	169.399(29.947)	119.183(33.432)	0.066
	Male	**168.488(16.436)**	**116.5(27.49)**	0.0175*
	Both	**168.944(22.369)**	**117.841(28.372)**	0.001*
MK+0.05				
	Female	221.17(74.7)	135.814(53.378)	0.11
	Male	**453.431(485.052)**	187.691(141.297)	0.41
	Both	**320.71(310.851)**	**158.047(94.066)**	0.063

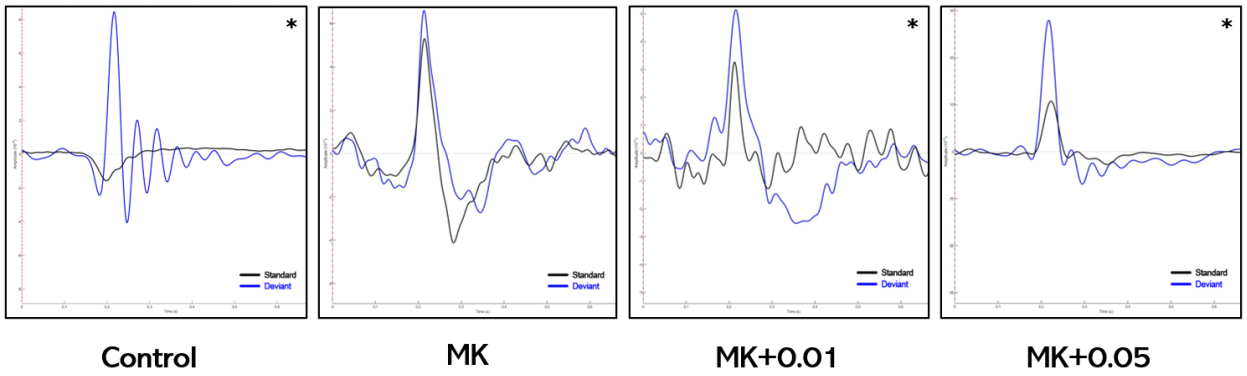
Note. Comparison of the difference between deviant response amplitude and standard response amplitude as an indication of stimuli-type differentiation. Statistical significance indicates the ability to differentiate between novel (deviant) and trivial (standard) auditory stimuli. Bold font indicates significantly different from control.



Supplemental Figure 1. Schizophrenia Meso-circuitry: The dopamine hypothesis suggests hypo-activation of dopamine pathways in the PFC and hyper-activation of dopamine pathways in the meso-limbic circuitry. The VTA projects through these pathways and PV GABAergic interneuron stimulation in the VTA silences downstream pyramidal neurons. Irregularities of PV interneurons are believed to be a primary pathology of schizophrenia and when PV GABAergic interneurons in the VTA are stimulated, the projected signals result in silencing of pyramidal neurons. With fewer PV GABAergic interneurons silencing pyramidal neurons, hyperactive feedback signals influence VTA activity. CB1R and 5-HT1AR regulate the activity of PV interneurons and pyramidal neurons making them an excellent pharmacological target.



Supplemental Figure 2. Deviant and Standard ERP Waveform Output: Using MATLAB EDF Reader, ERPs were identified, and amplitude was recorded. Averages were taken across groups for comparison. This figure depicts an expected response of increased deviant response amplitude (black arrow) and lower standard response amplitude (green arrows).



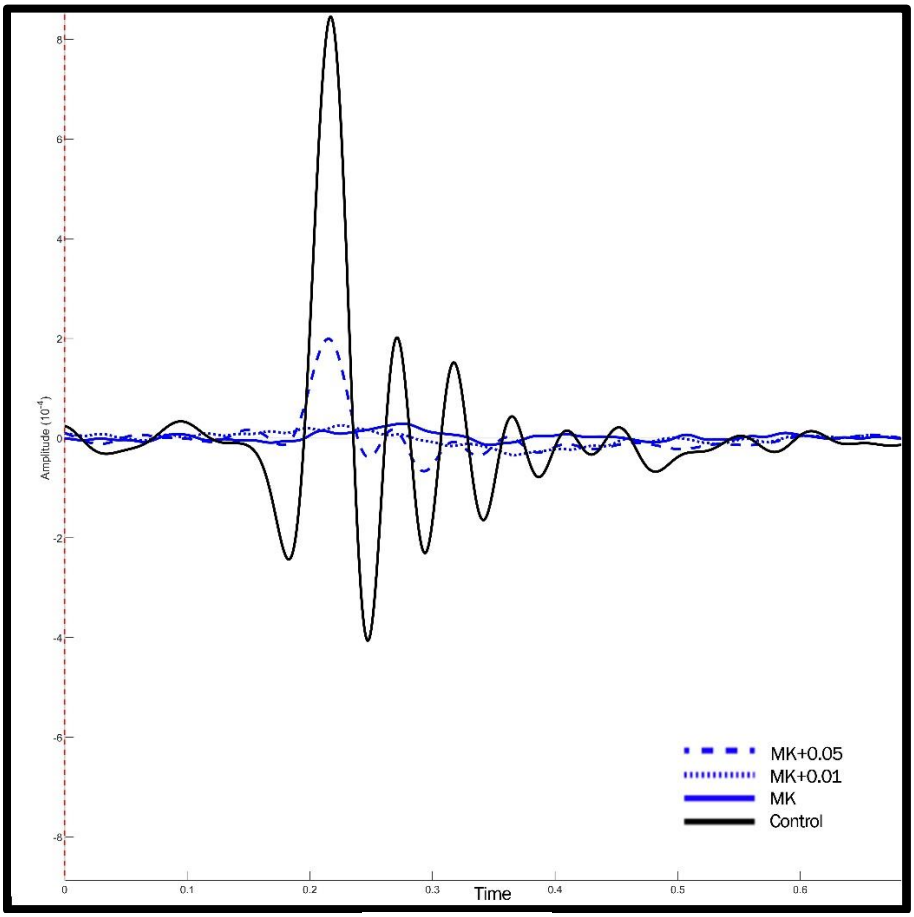


Figure 10. Average deviant, standard, and difference ERP response waveforms: using MATLAB plugins, ERPs were segmented in epochs and averaged across animals and groups to produce deviant and standard response waveforms. Top: Deviant and standard response amplitudes were compared across groups and sex (see *Supplemental Table 1*). The deviant response amplitude of Control and MK+0.01 were significantly higher than their respected standard response amplitude. There was a marginally similar effect in MK+0.05, but not MK. Bottom: Difference response waveforms were averaged across groups and overlayed. Difference response amplitude was significantly higher in Control.