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Effects of Systemic Administration of 8-OH-DPAT on Agonistic Social Behaviors in Male Syrian Hamsters

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Abstract

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In male Syrian hamsters. social avoidance of other hamsters is produced when an individual is defeated by another larger hamster. Social avoidance produced by this social defeat stress is mediated in part by serotonin (5-HT). 24 hours after social defeat, increasing extracellular 5-HT levels by the systemic administration of the selective serotonin reuptake inhibitor (SSRI), fluoxetine, prior to social avoidance testing increases social avoidance. However, 24 hours after social defeat, site-specific microinjection of 8-OH-DPAT, a 5-HT1a receptor agonist, into the anterior hypothalamus decreases social avoidance. Thus, there is a discrepancy between the systemic and site-specific effects of 5-HT on social avoidance. The goal of this study is to determine if the anxiolytic effects of 5-HT1a receptor activation after social defeat and prior to avoidance testing are specific to the anterior hypothalamus or if systemic activation of 5-HT1a receptors prior to avoidance testing reduces social avoidance. Our data suggest that systemic activation of 5-HT1a receptors after social defeat and prior to avoidance testing does not affect social avoidance. Therefore, the ability of 5-HT1a receptors to reduce social avoidance in male hamsters is site-specific, at least at the level of the anterior hypothalamus

Key Words:	*Conditioned Defeat*
Avoidance	*8-OH-DPAT*
Anxiolytic	*5-HT (Serotonin)*
Anterior Hypothalamus	*5-HT1A receptor*

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By Corey Andrews

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Introduction

Syrian hamsters (*Mesocricetus auratus*) are an excellent model species to study the effects of serotonin (5-HT) on social avoidance because they display robust aggressive and dominance behaviors. The specific model used in these hamsters is called the resident-intruder model. Hamsters are solitary in the wild, and in turn, are territorial and spontaneously attack intruders (Olivier & Young, 2002). When an unfamiliar intruder hamster is introduced into the home cage of another hamster, both hamsters investigate each other almost immediately. Shortly after, they exhibit aggressive posturing and flank marking behaviors to establish dominance (Olivier & Young, 2002). This phenomenon has been utilized in the conditioned defeat model, in which a resident aggressor (RA) hamster, who already possesses a lot of fighting experience and is typically large in body mass, defeats an intruder hamster that has been placed in the RA's cage (McCann & Huhman, 2012). For days, and even weeks, after being defeated by the RA, the intruder hamster displays a significant psychological change that can be easily observed and scored for behavior (Huhman, 2006). The behavioral indices that define this psychological shift in the defeated hamster include heightened HPA-axis activity, increased anxiety-like behavior in the elevated plus maze, altered circadian rhythmicity, reduced body weight, and reduced locomotor activity (Bader, Carboni, Burleson, & Cooper, 2014). Additionally, hamsters who have experienced social defeat will show submissive and defensive behaviors even when a smaller, non-aggressive intruder is placed inside their cage (Bader, Carboni, Burleson, & Cooper, 2014).

There is a lot of promise in the utilization of agonistic, or dominant-subordinate, hamster models for studying human pathologies. These pathologies include, but are not limited to, post-

traumatic stress disorder (PTSD) and major depressive disorder. Similar responses seen between humans and rodents towards pro-aggressive (i.e. ethanol, benzodiazepines) and anti-aggressive (i.e. serenics) psychopharmacological agents confirm that there is a significant similarity that is not exclusive to hamsters (Olivier & Young, 2002).

A drug that can be used to manipulate these differential aggression responses is 8-OH-DPAT. 8-OH-DPAT, referred to simply as DPAT, is an agonist to the 5-HT1A serotonin transmembrane receptor. Serotonin, also known as 5-HT, is a neurotransmitter that is synthesized from the amino acid tryptophan. All but one of the serotonin receptor subtypes are G-protein coupled receptors, and the 5-HT1A receptor is among this larger subtype set (Ito H, 1999). Serotonin cells originates from the raphe nucleus of the pons, a brainstem region that projects heavily to the structures of the midbrain and limbic system (Cooper MA, 2008). The 5-HT1A receptor is one of the most commonly found serotonin receptors found throughout the limbic system (Ito H, 1999). This receptor modulates not only learning and memory, but also agonistic behaviors and establishing dominance or subordinance, as demonstrated through the conditioned defeat response (Terranova, et al., 2016).

Due to the variety of different regions that possess 5-HT1A receptors, there are differential behavioral response to DPAT administration depending on the region where the drug is injected. Throughout the various scientific studies that have been conducted with agonistic behaviors using the conditioned defeat model, the two areas that have been pinpointed as the areas most responsible for mediating the behavioral responses that manifest from the social interactions of resident and intruder hamsters are the basolateral amygdala (BLA) (Bader, Carboni, Burleson, & Cooper, 2014), and importantly for this study, the anterior hypothalamus (Terranova, et al., 2016). In Bader et al (2014), administration of DPAT *prior* to social defeat

reduces social avoidance inside of a Y-maze test. This, and the fact that DPAT-treated males are less aggressive than controls when receiving stereotaxic administration of DPAT directly to the anterior hypothalamus, was also confirmed in Terranova et al. (2016). This experiment is intended to expound more on the data from these two experiments, particularly in regards to the manner in which DPAT is received.

Interestingly, there is a discrepancy between the site-specific actions of 8-OH-DPAT and the global actions of fluoxetine with regards to social avoidance exhibited after social defeat stress. Microinjection of DPAT into the anterior hypothalamus of a hamster defeated 24 hours prior, results in a decrease in duration of avoidance in male hamsters. Conversely, peripheral administration of fluoxetine 20 minutes before social avoidance testing, increases duration of avoidance in male hamsters. before a second resident-intruder encounter with a different resident aggressor hamster. Thus, there is a discrepancy between the site-specific effects of 5-HT1a receptors in the anterior hypothalamus and the global effects of serotonin on anxiety behavior after social defeat stress. The goal of this thesis is to investigate whether the effects of 5-HT1a receptors on duration of avoidance are site-specific, at least at the level of the anterior hypothalamus, or if they are global throughout the brain. We hypothesize that 5-HT1a receptor activation throughout the brain decreases social avoidance. We predict that systemic injection of DPAT into defeat hamsters, 20 minutes prior to a second encounter with an aggressor hamster, should be sufficient for the dampening of avoidance behaviors in comparison to vehicle treated hamsters. If DPAT is shown to have anxiolytic effects when injected intraperitoneally, demonstrated in this experiment by a lower duration avoidance, then DPAT can potentially be used as a pharmaceutical, like fluoxetine, to counteract the negative effects of social stress.

Methods

For this experiment, 25 male Syrian hamsters were housed individually in poly-carbonated (24 x 43 x 20) cages for two weeks in the Animal Research Facility at Georgia State University, in 14:10 light/dark cycle conditions with free access to food and water. After two weeks had elapsed, all of the hamsters were handled for a week. On the fourth week, all the hamsters were separated into a group and a subgroup. The main group was determined by whether the hamsters would be defeated by a resident aggressor (RA) hamster, or become a no-defeat control. The subgroup was determined by what type of injection the hamsters would receive before avoidance testing, with the injection being either a) 0.5 mg/kg DPAT or b) saline vehicle. Thus, the total number of groups used for data analysis equaled 4.

The experiment itself spanned across two days. The hamsters were first weighed, to determine the injection volume needed for the avoidance testing the next day. Next, the defeat group hamsters were placed in the cage of a RA hamster for a 15-minute defeat period on the first day. The non-defeat groups were placed inside of an RA cage with an absent RA for 15 minutes as well, with a caged mesh placed inside as a control. The RAs that were used were recorded for both groups.

On day 2, all of the hamsters were injected with either DPAT (0.5 ml/kg) or saline vehicle 20 minutes before avoidance testing. Hamsters were then tested in a neutral arena with a novel RA behind a caged mesh. Hamsters could investigate with the RA behind the caged mesh but there was no physical social interaction. The RA utilized for avoidance testing was always different from the RA used for the defeat/no-defeat control the previous day. The hamsters would be placed on the opposite side of the cage facing away, then would be observed with an

overhead camera for 5 minutes and scored for avoidance behavior. Avoidance behavior in this

experiment was determined by the duration of time that the hamster spent on the side of the cage

opposite of the seclusion box that contained the RA hamster. A video camera mounted over top

of the cages provided the means by which the behaviors were observed and recorded.

Results:

A two-tailed t-test was used to compare the DPAT and saline treated hamsters for both the defeated and no defeat controls. Two bar graphs (figures 1 and 2) display the mean avoidance time, or the average time spent in the opposite end of the cage from the resident aggressor hamster, for each group. The n values for the DPAT and saline defeat, and DPAT and saline no defeat groups respectively were 8, 7, 4, 4. For the defeated group, there was a trend of drug treatment towards a significant decrease in avoidance ((13) = 1.311, p=.213). For the no defeat groups, there was no effect of drug treatment on duration of avoidance (t(6) = .583; p=.581; p>.05).

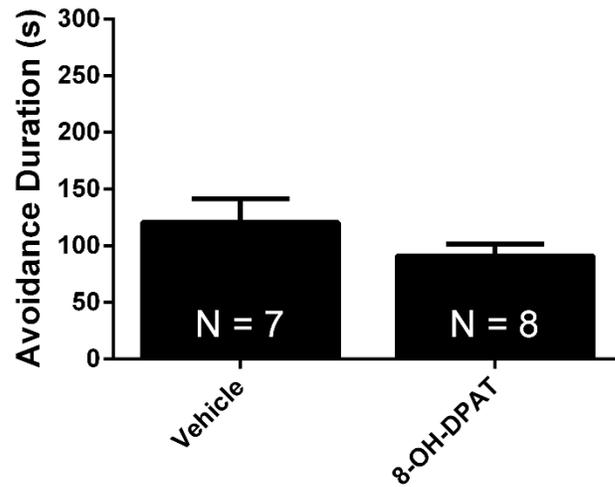## 8-OH-DPAT Injection (IP) Prior to Avoidance

FIGURE 1 – AVOIDANCE DURATION (s) FOR BOTH DPAT AND SALINE DEFEAT GROUPS (WITH SEM BARS) INJECTED 20 MINS BEFORE AVOIDANCE TESTING

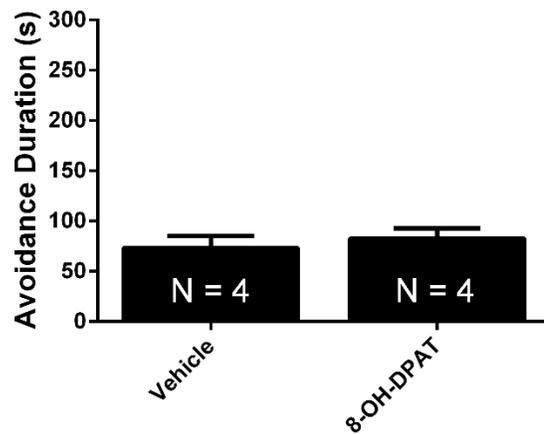## 8-OH-DPAT Injection (IP) Prior to Avoidance
(No Defeat controls)

FIGURE 2 – AVOIDANCE DURATION (s) FOR BOTH DPAT AND SALINE, NO DEFEAT CONTROLS (NDCs) (WITH SEM BARS) INJECTED 20 MINS BEFORE AVOIDANCE TESTING

Discussion

Although many controls for confounding variables (e.g. no defeats, using new cages and avoidance boxes to eliminate flank marking stimuli, etc) were used, there was no effect of systemic administration of DPAT on duration of avoidance. While we found a trend towards a decrease, the behavior of the DPAT-treated hamsters was indiscernible from the vehicle-treated hamsters. There are other indices of subordinate behavior, like being chased, posturing, and flank marking, that can be observed in addition to general avoidance, but those were not looked at in this study (McCann & Huhman, 2012). Perhaps DPAT treatment does not affect avoidance behavior *per se,* but it could affect subordinate behaviors directed towards another hamster when there is no barrier of separation (such as the avoidance box). Measuring these behaviors is a worthwhile future direction from this study.

A possible explanation for the observed results arises considering the ubiquity of the 5-HT1A receptor. They are present throughout numerous brain regions, such as the raphe nucleus, the amygdala, and the hypothalamus (Ferris, Stolberg, & Delville, 1999). With so many possible receptors to bind to, the effects of 5-HT1A receptor stimulation in different regions may cancel itself out. DPAT also has a partial affinity for 5-HT7 receptors as well (Eriksson TM, 2008). Another limitation is a dose response curve was not used in this study. Although a 0.25 mg/kg DPAT injection was shown to be more effective than a 0.5 mg/kg injection in Bader et al. (2014), it is not certain whether the same would hold true for our experiment. A dose response study would be valuable in future replications of this experiment.

This experiment's design assumes that the acquisition of social defeat behavior is an acute and instantaneous process following a social defeat encounter. Augmenting the social

defeat by using several rounds of RA defeats could create more robust effects than what was observed in this experiment. This experiment observed the effects of social defeat from an acute defeat encounter, but with this design, one could see how chronic stress affects avoidance instead. Perhaps having the hamsters go through three separate trials of 5 minute defeats instead of one, prolonged 15 minute trial could demonstrate a more robust effect of avoidance behavior unlike observed in the first experiment. Additionally, a Y maze test, which essentially scores for the same variables as observed in this study without the avoidance box, might also facilitate prospective results.

If we are able to show anxiolytic effects of DPAT after a social defeat experience, then this suggests that DPAT could potentially be used as a pharmacological agent that assists in the treatment of psychosocial disorders such as PTSD. Many PTSD patients show comorbidity with other anxiety disorders whose symptoms may or may not entail violent behaviors (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). If DPAT can mitigate anxiety in rodents, it could possibly be used as a potent psycho-pharmaceutical in patients with PTSD and other psychiatric disorders. Moreover, further academic discoveries from this study could be applied to female hamsters, although their more cyclical nature of aggressive behavior according to their estrus cycle would have to be considered in the experimental methods. As the psychiatric data on PTSD suggests, the implications of seeing the results of this experiment on females may be even more worthwhile, considering the more common prevalence of PTSD in females than in males (Terranova, et al., 2016).

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