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Regaining Effort-Based Food Motivation: The Drug Methylphenidate Reverses the Depressive Effects of Tetrabenazine in Female Rats

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REGAINING EFFORT-BASED FOOD MOTIVATION

The drug methylphenidate reverses the depressive effects of tetrabenazine in female rats

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ABSTRACT

Tetrabenazine (TBZ), a vesicular monoamine transporter type 2 (VMAT-2) inhibitor, depletes dopamine and induces motivational deficits and other depressive symptoms in humans. Methylphenidate (MPH) is a dopamine transport blocker that is used to enhance motivational function. Previous studies have shown that in male rats, TBZ induces a shift in effort-related choice such that a low-effort bias is induced. In male rats this occurs at a dose range of 0.75-1.0 mg/kg TBZ, and this effect is reversible with co-administration of MPH. Recent studies have shown that females need a higher dose of TBZ (2.0 mg/kg) to show the low-effort bias. The present study tested the ability of MPH to reverse the effects of 2.0 mg/kg TBZ in female rats using an effort-based choice task. Food-restricted female rats (n=8) were trained on a fixed-ratio (FR) 5/chow feeding choice task in which they can choose between the high effort/high reward option (FR5 lever pressing for preferred food, which was Bioserve pellets) or the low effort/low reward option (consuming the concurrently available but less preferred lab chow). After initial training, rats were tested in a repeated measure design in which they received combined treatments of either a vehicle control solution, 2.0 mg/kg TBZ, or TBZ plus various doses of MPH ranging (0.5 - 4.0 mg/kg MPH) prior to testing. TBZ significantly reduced lever pressing and increased chow intake, and this effect was reversed by 2.0 mg/kg MPH. This study shows that MPH can treat motivational deficits induced by TBZ in female rats as well as male rats.

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INTRODUCTION

MOTIVATION

It is crucial for the survival of any organism to be able to overcome obstacles or environmental constraints in order to gain access to necessary stimuli (such as food, water, or appropriate shelter). For example, animals under prey will have heightened vigilance and physiological mobilization necessary to escape and survive a predator (Löw *et al.*, 2008) and the phenomenon of motivation is key to responses such as this. Motivation is the set of processes that allow organisms to regulate internal and external environments and control the probability, proximity, and availability of stimuli (Salamone 1992, Salamone *et al.* 2016) . There are many aspects of motivation, but two main facets are directional and activational. Directional aspects of motivation refer to the fact that behavior can be directed towards or away from certain stimuli, whereas activational aspects of motivation refers to the energetic component and is characterized by an ability to initiate and maintain rapid or vigorous responses over time (Salamone *et al.* 2016, Nunes *et al.* 2013b). Activational aspects of motivation are clinically important in humans, as deficits in this type of function span multiple psychiatric disorders. Thus, studying the neural mechanisms underlying dysfunctions in activational aspects of motivation is critical for finding relevant treatments.

According to Demyttenaere *et al.* (2005), fatigue is one of the main depressive symptoms reported in the psychiatric literature. Fatigue (referred to as central fatigue, rather than muscle fatigue) is characterized by reduced self-reported energy and impaired goal-directed activity, and is debilitating to normal human functions and is present in a wide variety of psychiatric disorders. While major depressive disorder is most

commonly associated with a lack of motivation, other psychiatric and neurological disorders have a high comorbidity with this symptom including schizophrenia, parkinsonism, bipolar disorder, and multiple sclerosis (Demyttenaere *et al.* 2005, Salamone *et al.* 2016). Given the importance and relevance of motivational problems among several mental disorders, it is critical to develop novel treatments and animal models for these symptoms. One commonly used rat model is utilizing operant effort-based choice behavior, which assesses the tendency of animals to select high-effort activities when given a choice between multiple alternatives.

EFFORT BASED CHOICE TASKS

Motivation can be measured by various operant choice tasks, such as a T-maze procedure developed by Salamone *et al.* (1994), an effort-discounting procedure developed by Bardgett *et al.* (2009), and a concurrent lever-pressing/chow procedure developed by Salamone *et al.* (1991). With the concurrent lever-pressing/chow procedure used in this study, rats are placed into operant boxes and given the option to press a lever in order to obtain small but preferred pellets (high effort/high reward) or to eat given and standard lab chow (low effort/low reward). Thus, the amount of times the lever was pressed in contrast to the amount of lab chow eaten can be considered a suitable measure for the motivation of the rats. The operant box can be put onto multiple schedules, including: an FR1 schedule in which every time the lever is pressed the rat is given a pellet, which is typically used for pre-experimental training; an FR5 schedule in which every five times the lever is pressed the rat is given a pellet; and a progressive ratio (PROG) schedule, which gradually increases the ratio lever pressing requirement over the course of the session. The baseline behavior pattern for most rats on the

FR5/chow feeding choice task is to have high amounts of lever pressing and low amounts of chow consumption, whereas the baseline for most rats on the PROG/chow feeding choice task is marked by relatively lower amounts of lever pressing and relatively higher amounts of chow consumption, due to the PROG schedule being more difficult (Randall *et al.* 2012). Because of the difference in baseline activity between FR5 scheduling and PROG scheduling, operant boxes are programmed on the FR5/chow feeding choice task in order to observe depressive effects from drug intervention (i.e., a drug that shifts behavior from lever pressing to chow consumption), and they are programmed to run on the PROG/chow feeding choice task schedule in order to more easily observe increased selection of the high-effort PROG lever pressing activity, which is a marker of increased exertion of effort.

After extensive research in rodent models, effort-based decision making procedures were developed in humans. In a study conducted by Treadway *et al.* (2009), a task called the Effort-Expenditure for Rewards Task (EEfRT) was developed, and it was conducted on a variety of human subjects. Patients with major depressive disorder, along with healthy controls, were given a task wherein they could let the subject choose between pressing a button 100 times with a non-dominant pinky to receive a higher monetary reward (ranging from $1.24-$4.30) or press a button 30 times with the index finger of a dominant hand within 7 seconds to receive a lower monetary reward ($1.00). There is a striking similarity between this task and that of the rat pressing a lever for a higher reward. The EEfRT task has also illustrated a correlation of individual differences in willingness to exert greater effort for further rewards with dopamine transmission in the left striatum and the ventromedial prefrontal cortex (Treadway *et al.* 2012). This trend of having greater dopamine transmission in these brain areas and being more willing to choose a higher effort/reward option has been shown to be consistent in rats as well (Randall *et al.*

2012, Salamone *et al.* 2016). Thus, the molecular and behavioral basis of fatigue as a result of depression or other psychiatric illness in humans can be reliably demonstrated and studied through rat choice procedures. The neurotransmitter dopamine is highly involved in these procedures (Salamone *et. al* 2018), and thus studying the molecular mechanisms of dopaminergic involvement in effort-related aspects of motivation is important.

DOPAMINE

Although the dopamine system is often seen as a "reward system," this view is largely oversimplified; dopamine is responsible for a much wider variety of psychological processes such as effort exertion, decision making, reinforcement learning, and habit formation (Salamone & Correa 2012). The mesolimbic dopamine system in the brain is the key neural circuitry in mediating motivational processes (Salamone et al. 2016, Nunes et al. 2013, Salamone et al. 2018). The dopamine neurons for this system originate in the ventral tegmental area in the midbrain, and terminate within the nucleus accumbens in the ventral striatum.

Nucleus accumbens dopamine is key for motivational processes, and dysfunctions in the nucleus accumbens contribute to a wide variety of psychopathologies involving lack of motivation such as major depressive disorder. Mesolimbic dopamine is crucial within the nucleus accumbens. Dopamine transport (DAT) blockers such as methylphenidate have been shown to heighten levels of mesolimbic dopamine within the nucleus accumbens, such as methylphenidate and modafinil (Rotolo *et. al* 2020).

Anatomical studies cited in Nunes *et al.* (2013b) have shown that adenosine A_{2A} receptor

subtypes are colocalized with dopamine transmission, with them being expressed mainly in the nucleus accumbens and other neostriatal areas of the brain. Adenosine-dopamine interactions take place at the signal transduction level inside accumbens neurons that receive dopamine inputs, and thus many A_{2A} antagonists such as MSX-3 and KW-6002 have been observed reversing the effects of fatigue (Nunes *et al.* 2013b). It has also been observed that dopamine receptors in the nucleus accumbens are different in male and female rats; according to Williams *et al.* 2021, adult male rats have an overproduction of dorsal striatal D1 receptors in the nucleus accumbens in comparison to female rats.

Tetrabenazine (TBZ), an inhibitor of vesicular monoamine transporter-2 (VMAT-2), was used in the present study to induce depressive effects. TBZ presents itself as a reserpine-type antipsychotic and is used to treat Huntington's, Parkinson's, and other movement disorders, but its main side effect is the induction of depressive symptoms (Salamone *et al.* 2016, Nunes *et al.* 2013b). The greatest impact of TBZ is shown in the blockage of striatal dopamine, thus reducing motivation. It was shown in a study by Nunes *et al.* (2013a) that injection of 20.0 μg of TBZ directly into the nucleus accumbens of rats significantly altered lever pressing and chow intake by decreasing the likelihood of them choosing the high effort/high reward option and increasing the likelihood of choosing the low effort/low reward option. This, in addition to having the comparison of injection of TBZ to a control area next to the nucleus accumbens and having no significant effect, shows that TBZ has effects directly in the nucleus accumbens.

TBZ REVERSAL

Depressive effects of TBZ have been reversed by certain types of antidepressants. While

SSRIs, such as fluoxetine or citalopram, as well as the NE transport inhibitor desipramine have no effect on TBZ reversal (Salamone *et al.* 2018, Yohn *et al.* 2016), dopamine uptake inhibitors have a significant effect. These include bupropion, lisdexamfetamine (Vyvanse), modanofil, pilocarpine, and, as talked about in this study, methylphenidate (MPH) (Salamone *et al.* 2018, Nunes *et al.* 2013b, Yohn *et al.* 2016). MPH, which has been reported to increase self-reported energy and psychomotor activity within hours after administration (Stotz *et al.* 1999), can be used to induce motivational effects in patients with Parkinson's, major depressive disorder, narcolepsy, and most commonly ADHD (Salamone *et al.* 2016, Mayo Clinic 2022).

In Salamone *et al.* 2016, TBZ reversal was observed with MPH in a group of eight male rats on the FR5/chow feeding choice task. A dosage of 0.75 mg/kg of TBZ was sufficient to induce depressive effects in this group. Rats that were given solely a vehicle, or control, dose, had high lever presses and low chow consumption (preference towards high effort/high reward option) and rats that were given 0.75 mg/kg TBZ without MPH had relatively much lower lever presses and higher chow consumption (preference towards low effort/low reward option). All rats were given different doses of MPH after being given the standard dose of TBZ on random days, and all doses (ranging from 0.5 to 4.0 mg/kg MPH) produced a significant effect compared to rats who were administered TBZ but not MPH.

Even though TBZ reversal with MPH has been extensively studied in male rats, there has been a lack of knowledge on how this phenomenon may be different from females. In humans, mental disorders vary widely between males and females, such as in major depressive disorder. Females have an earlier age-at-onset than their male counterparts, as well as exhibit more depressive episodes, symptoms, and atypical depressive features

(Smith *et al.* 2008). While reasoning behind these differences likely has many factors, reasons for differences between males and females are likely molecular. Studying rats as a model for the phenomenon of these sex differences in depression is crucial. Therefore, the present study finds a different ideal dosage of TBZ for females and examines its reversal with MPH.

MATERIALS AND METHODS

ANIMALS

Eight adult female Sprague Dawley rats (Harlan-Sprague Dawley) were used throughout this study. They were pair housed, and both temperature and humidity conditions were consistently monitored. They were given 12 hour light/dark cycles where lights were turned on at 7:00 am and turned off at 7:00 pm. Rats initially weighed between 275 and 299 grams, and were food restricted to 85% of their free feeding body weight. They were allowed a modest weight gain, where each rat's weight was monitored daily and nightly lab chow feeding was administered appropriately. They were also given water constantly and conditions and animal protocols were approved by the University of Connecticut institutional animal care and use committee, which followed guidelines from the National Institute of Health.

PHARMACOLOGICAL AGENTS

Tetrabenazine [(R,R)-3-Isobutyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-pyrido[2,1-a]iso-quinolin-2-one] was obtained from Tocris Bioscience. It was dissolved in a 20% dimethyl

sulfoxide (DMSO) solution, and small amounts of hydrochloric acid (HCl) were used to bring the solution to a pH level between 4.0 and 4.5. The vehicle control used in this study is the same DMSO and HCl solution used to dissolve the tetrabenazine. Methylphenidate was obtained from the Cayman Chemical Company, and was dissolved in 0.9% saline. The dosages of TBZ were initially based on previous studies in our lab with male rats (Salamone et al. 2016) but, as is discussed later in the paper, upon understanding that female rats need a higher dose of 2.0 mg/kg of TBZ it was found to be effective and was thus used throughout the rest of the study.

BEHAVIORAL PROCEDURE: FR5/CHOICE

FR5/chow feeding choice task utilizing operant chambers (28 x 23 x 23 cm3; Med Associates, Fairfax, VT) were used to conduct behavioral sessions. Eight female rats were introduced to high carbohydrate pellets (45 mg, Bio-Serv, Frenchtown, NJ). They then went through magazine training for two days, which consisted of one pellet being received every thirty seconds while on an FR1 reinforcement schedule where one lever press is always rewarded with one pellet. Rats were then put on an FR1 reinforcement schedule without the magazine training for three days and then moved onto the FR5 schedule (five lever presses are needed to be rewarded with one pellet). Once this lever pressing training period was completed, rats were introduced to a choice food option of lab chow (Laboratory Diet, 5P00 Prolab RMH 3000, Purina Mills, St. Louis, MO; about 17-21 g) for five weeks. After every operant session (30 minutes), the number of lever presses as well as the weight of the chow that was consumed (including spillage) was recorded. Drug testing began after this training period was over. Rats were weighed every day and given supplemental food as necessary in order to allow rats a modest

weight gain. Most often, chow food was only given after weekly drug trials and over weekends in order to supplement feeding.

BEHAVIORAL EXPERIMENT

Rats were trained on the FR5/chow feeding procedure, as described above, and behavioral sessions were conducted five days per week (Monday-Friday). Drug trials were run once per week. During the first part of the study, eight rats (n=8) were given different doses of TBZ (either vehicle control, 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg, or 1.0 mg/kg) in a randomized order for six weeks, so that each rat had each dose at least once. These doses were based off of the doses in male rat studies from Salamone *et. al* 2016. After no effect was observed, rats received either 2.0 mg/kg TBZ or the vehicle control for two weeks. Because 2.0 mg/kg TBZ was found to be an effective dose for inducing depression in female rats, this dose was used during the second portion of the study. Two hours before behavioral procedures, rats were either given vehicle control or 2.0 mg/kg TBZ. After 1.5 hours, rats were then given different doses of MPH (a vehicle control, 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, or 4.0 mg/kg). After operant procedures, lever presses were recorded and excess chow was weighed as described above.

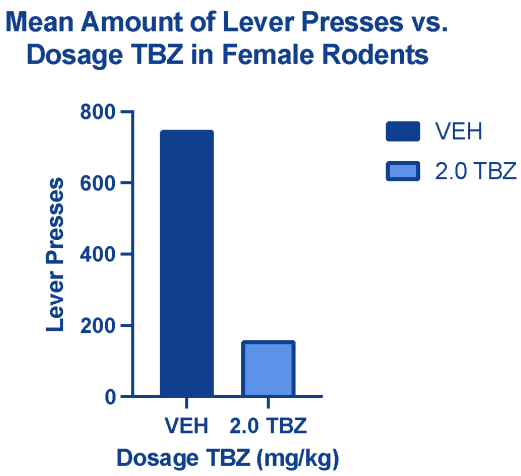
STATISTICAL ANALYSIS

Results were analyzed with repeated-measures analysis of variance (ANOVA) by using SPSS version 28 (IBM, US). For the significant ANOVA results, Tukey's pairwise comparisons were used.

RESULTS

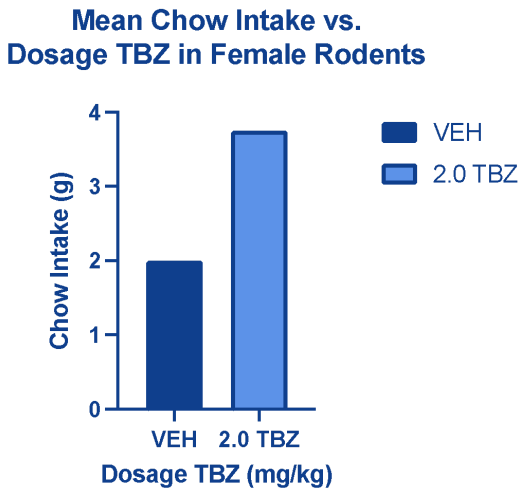
Figure 1.

A



L.P. VEH vs. 2.0 mg/kg TBZ $t(7) = 6.34$, $p < 0.001$

B

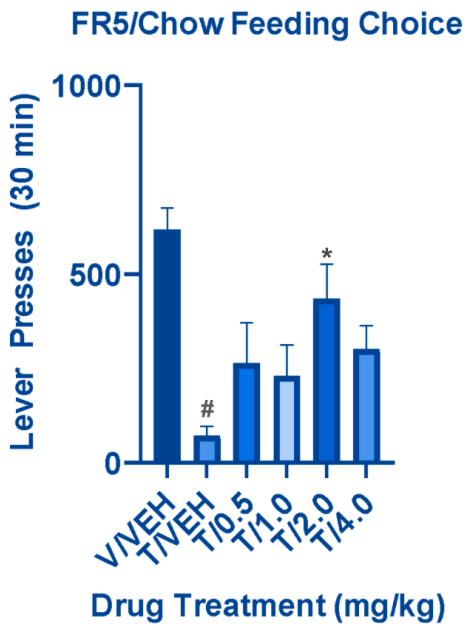


Chow VEH vs. 2.0 mg/kg TBZ $t(7) = -5.11$, $p < 0.001$

Figure 1. Deciphering appropriate TBZ doses to induce depressive effects in female rats. The first vehicle dose as well as low doses of TBZ were given in random order to a group of female rats (n=8). All low doses did not significantly differ from the first vehicle dose with both lever pressing and chow consumption. A second vehicle dose was then given and 2.0 mg/kg TBZ were administered via IP injection. **A**, Mean (±SEM) number of lever presses (FR5/chow schedule) during the 30 minute session. **B**, Mean (±SEM) gram quantity of chow intake during the 30 minute session. This dose of TBZ was found to be significantly different from the initial dose with $p < 0.001$ for both lever pressing and chow consumption. Data are from Ecevitoglu et al. in preparation).

Figure 2.

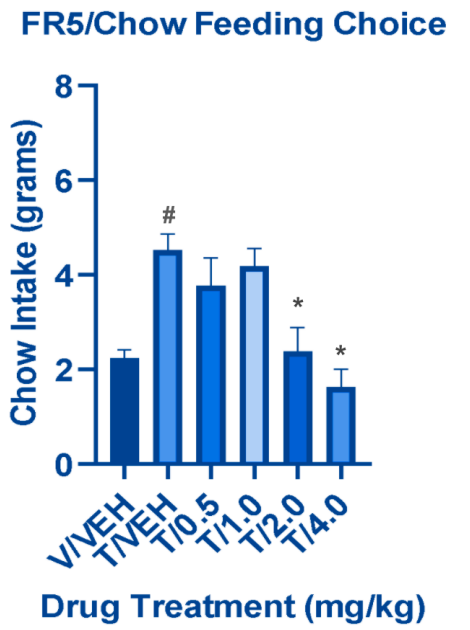
A



L.P. VEH/VEH vs TBZ/VEH $F(1,7)=29.56$, $p < .05$

L.P. T/VEH vs T/2.0 $F(1,7)=13.05$, $p < .05$

B



Chow VEH/VEH vs TBZ/VEH $F(1,7)=20.35$, $p < .05$

Chow T/VEH vs T/2.0 $F(1,7)=17.98$, $p < .05$

Chow T/VEH vs T/2.0 $F(1,7)= 32.71$, $p < .05$

Figure 2. The effect of TBZ reversal with MPH on female rats. Female rats (n=8) were either given two vehicle doses in succession to each other, TBZ followed by a vehicle, or TBZ followed by either 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, or 4.0 mg/kg MPH. These dosages were received randomly and each rat received each dose at least once. **A**, Mean (±SEM) number of lever presses (FR5/chow schedule) during the 30 minute session. **B**, Mean (±SEM) gram quantity of chow intake during the 30 minute session. The VEH/VEH dose was found to be significantly different than the TBZ/VEH dose with $p < 0.05$ for both lever pressing and chow consumption. The TBZ/VEH dose was found to be significantly different than the TBZ/2.0 dose with $p < 0.05$ for both lever pressing and chow consumption with $p < 0.05$. The TBZ/VEH dose was found to be significantly different than the TBZ/4.0 dose for only chow consumption with $p < 0.05$.

The results of the first part of the experiment are shown in **Figure 1.** The higher dose of TBZ in comparison to the second vehicle had a significant effect in both lever pressing ($t(7) = 6.34$, $p < 0.001$) and chow consumption ($t(7) = -5.11$, $p < 0.001$).

The results of the second part of the experiment, in which TBZ was reversed with MPH, was shown in **Figure 2.** There was a significant difference between rats who received both vehicle doses (V/VEH) and rats who received the TBZ and the vehicle (T/VEH) both the amount of lever presses ($F(1,7)=29.56$, $p < .05$) and the amount of chow consumption ($F(1,7)=20.35$, $p < .05$), which indicates that the presence of TBZ has a significant effect in decreasing lever pressing and increasing chow consumption. The dose of 2.0 mg/kg TBZ combined with 2.0 mg/kg MPH (T/2.0 compared to T/VEH) was found to significantly reverse the effects of lowered lever pressing ($F(1,7)=13.05$, $p < .05$) and raised chow consumption ($F(1,7)=17.98$, $p < .05$). The dose of 2.0 mg/kg TBZ combined with 4.0 mg/kg MPH (T/4.0 compared to T/VEH) did not significantly alter lever pressing but did significantly alter chow consumption ($F(1,7)= 32.71$, $p < .05$).

DISCUSSION

This study focused on the depression-like motivational effects of the VMAT-2 inhibitor TBZ in females in order to determine if those effects could be reversed by administration of the DAT inhibitor methylphenidate. A concurrent FR5 lever pressing/chow procedure can be used to measure motivation in rats (Salamone *et al.* 1991). This procedure was used in the present study to establish the effort-related effects of TBZ in female rats, and to determine if MPH could reverse the effects of TBZ. As discussed above, a dose of 2.0 mg/kg TBZ is necessary in female rats for producing the shift in effort-based choice,

because female rats are less sensitive than male rats (Ecevitoglu et al. in preparation). In the present study, the low-effort bias was observed with a dose of 2.0 mg/kg TBZ, as by the fact that lever pressing was reduced by TBZ compared to vehicle (**Figure 1**), and chow intake was increased. This greatly contrasts with previous studies of male rats. In these studies, low-effort bias was induced by lower doses of TBZ (Nunes et al. *2013*; Salamone *et al.* 2016). It is not clear why female rats are less sensitive to the effects of TBZ compared to male rats. The reasoning behind this may be due to different molecular mechanisms of dopamine and dopamine antagonism between males and females. According to Williams *et al.* (2021), adult male rats have an overproduction of dorsal striatal D1 receptors in the nucleus accumbens in comparison to female rats. Since TBZ has been shown to target the nucleus accumbens (Nunes *et al.* 2013a), TBZ having less effect on dopamine depletion in the nucleus accumbens in females may be due to their lack of D1 dopamine receptors in this area. Thus, a higher dose of TBZ was required to induce effort-related motivations dysfunctions in female rats compared to male rats. Determining this was critical for determining if MPH could reverse the effects of TBZ in females.

It was found in **Figure 2** that the DAT inhibitor MPH was able to partially but significantly reverse the effects of TBZ, increasing lever pressing and decreasing chow intake in TBZ-treated rats. The most effective dose for reversing the lever pressing effects of TBZ was 2.0 mg/kg of MPH. This is the only dose at which lever pressing was found to be significantly higher than doses 2.0 mg/kg TBZ condition. Chow consumption was also found to be significantly lower than vehicle doses for both the 2.0 mg/kg and 4.0 mg/kg doses of MPH. The reason why 4.0 mg/kg MPH induced significantly lower chow consumption but statistically similar lever pressing in comparison to the vehicle dose of MPH is that the higher dose of 4.0 mg/kg MPH induced appetite-suppressing effects. High

doses of MPH are known to cause appetite suppression (Davis *et al.* 2007).

Since MPH is able to reverse the decrease in motivation caused by TBZ, it may prove to be a promising treatment for patients who are suffering with motivational dysfunctions. While other antidepressants, such as SSRIs, may help with improving mood, they are relatively ineffective in comparison to DAT inhibitors such as MPH, which may be used to reverse motivational deficits in patients across many pathologies (Salamone *et al.* 2018, Yohn *et al.* 2016). Further understanding of dopamine and its differences between males and females in rats may directly translate into molecular mechanisms of dopamine in humans, and may be vital in clinical settings (Salamone *et al.* 2018).

Future directions of these studies may include testing effects of TBZ on other operant-based schedules, such as PROG rather than FR5. These experiments may also be repeated using other DAT inhibitors to counter TBZ, such as bupropion, lisdexamfetamine (Vyvanse), modanofil, and pilocarpine (Salamone *et al.* 2018, Nunes *et al.* 2013b, Yohn *et al.* 2016). This may allow us to further our understanding of dopamine transmission across both males and females and translate our knowledge into vital clinical practice for human patients.

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