Spring 5-1-2014

An animal model of the motivational symptoms of depression: Testing the antidepressant desipramine on an effort-related choice task

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May 2014

A. Abstract

Patients with depression, schizophrenia, and other related disorders often show effort-related motivational symptoms such as anergia, psychomotor slowing, lassitude, and fatigue. Several studies have indicated that dopamine (DA) within the nucleus accumbens (NAc) is involved in the regulation of effort-related behavior. Interference with NAc DA alters response allocation in effort related choice procedures, biasing animals towards the alterative that can be obtained with minimal effort. Previous studies have shown that administration of the vesicular monoamine transporter-2 (VMAT-2) inhibitor tetrabenazine (TBZ) shifts behavior in rats responding on the FR5/chow choice procedure causing a decrease in lever pressing and a compensatory increase in chow consumption. By inhibiting VMAT-2, TBZ affects monoamine storage, but studies indicate that the greatest effects are on striatal DA. The deficits induced by TBZ can be successful attenuated through co-administration of the adenosine A2A antagonist, MSX-3, and the dopamine (DA) and norepinephrine (NE) reuptake inhibitor, bupropion. While considerable evidence implicates DA systems in effort-related functions, no previous studies have demonstrated the role of NE in effort-related choice behavior. Therefore, the current studies investigated the ability of tricyclic antidepressant desipramine, which blocks NE uptake, to attenuate TBZ induced shifts in choice behavior. Co-administration of desipramine does not successful reverse the shift in behavior induced by TBZ. In fact the highest dose of desipramine further suppressed lever pressing and chow consumption compared to TBZ-treated animals. The results of this study indicate that NE uptake blockade does not reverse the effects of TBZ, which suggests that DA, rather than NE, is the catecholamine that is most closely involved in effort-related decision making.

B. Acknowledgments

First and foremost, I would like to graciously thank Dr. John Salamone, for not only allowing me to be a part of his team, but also for always having my back with my research project, and putting his whole being into his work. I have taken a handful of classes with Dr. Salamone, and his love for teaching is only amplified when he is hands on in the laboratory. I would also like to thank Samantha Yohn, who was the graduate student that was the magic behind the curtain – all of her hard work and dedication to my project, along with other undergraduate projects she was helping out with, will forever stick with me. My project ended up being switched halfway through the semester, and it was Sam and Dr. Salamone that made sure I was still able to graduate with a thesis! Moreover, I would like to thank any and all undergraduates in the Salamone Lab the past year, whose help I am eternally grateful for. Finally, I would like to thank my honors advisor, Dr. Crystal Park, whose guidance made my success with this project possible.

1. Introduction

Many psychiatric disorders, including Parkinson's disease (PD), schizophrenia, major depressive disorder (MDD), multiple sclerosis, and drug addiction, are associated with the dopamine (DA) systems within the brain. Although there are four major DA systems, research has placed particular emphasis on the motivational functions of the mesolimbic DA system, which originates in the ventral tegmental area (VTA) and projects to the nucleus accumbens (NAc). Considerable evidence indicates that NAc DA is associated with motivational (e.g. effort-related) dysfunctions in many psychiatric disorders (Salamone and Correa, 2002, 2012; Salamone et al. 2007, 2009).

Environmental obstacles often separate organisms from motivationally significant stimuli, such as food or water. Organisms need to exert effort to overcome constraints through effort-related decision making revolving around cost/benefit analyses (Salamone and Correa 2002; Van den Bos et al., 2006). Motivation has been defined as the set of processes through which organisms regulate the probability, proximity, and availability of significant stimuli (Salamone, 1992; Salamone and Correa, 2002). Motivationally significant stimuli can have directional or activational aspects (Coffer and Appley, 1964; Salamone, 1988). The directional component of motivation denotes behavior that is directed towards or away from a particular stimulus (Salamone and Correa, 2002). For example, an organism may be directed towards food when hungry, or may be directed away from an aversive stimulus, such as an electric shock. Alternatively, activational aspects of motivation refer to the notion that motivated behaviors often are characterized by a high degree of work output, vigor or persistence (Salamone, 1988; Salamone and

Correa 2002). In a complex environment, organisms frequently must exert different effort in to overcome work-related costs that separate them from significant stimuli.

Substantial evidence indicates that NAc DA is involved in regulating behavioral activation and effort-related processes, such as overcoming work-related response obstacles in reinforcement-based behavior (Barbano and Cador, 2007; Phillips et al., 2007; Salamone et al., 1997, 2005, 2007). Interference with NAc DA transmission impairs activational aspects of food motivation, but actually leaves directional aspects (e.g. food intake, appetite) intact (Barbano and Cador, 2007; Salamone, 1992; Salamone et al. 1993). Operant tasks with minimal work requirements attached tend to be relatively insensitive to interference with DA transmission, such as FR1 schedules (Ishiwari et al., 2004; McCullough et al., 1993; Salamone et al., 2001). In contrast, tasks that require greater work output (i.e., progressive ratio, FR5, FR16, or FR64 schedules) are sensitive to DA manipulations (Aberman and Salamone, 1999; Ishiwari et al., 2004; Salamone et al., 1993). There is little to no evidence indicating that performance on high work output schedules is impaired due to deficits in primary food reinforcement or motivation. The effects of accumbens DA depletion do not resemble the effects of extinction (withdrawal of reward) reinforcer devaluation by pre-feeding (Aberman and Salamone, 1999; McCullough et al., 1993; Salamone et al., 1995, 1997), or appetite suppressant effects (Salamone et al., 1991). Substantial evidence indicates that interference with DA transmission by systemic or local administration of low-to-moderate doses of DA D_1 or DA depletions can alter the behavior in animals responding on tasks that assess effort-based choice behavior, biasing animals towards the lower effort alternative (Floreso et al., 2008a,b; Hauber and Sommer, 2009; Salamone et al., 2003, 2005, 2007).

There is a growing emphasis on motivational symptoms in the human clinical literature. Human pathologies involving activational or psychomotor impairments can be maladaptive. Moreover, these motivational dysfunctions are among the most common and difficult to treat in modern medicine (Demyttenaere et al., 2005). The severity of effort-related symptoms has been correlation with problems with social function, employment, and response to treatment (Tylee et al., 999; Stahl 2002). Patients with major depressive disorder (Treadway et al., 2012) and schizophrenics with a preponderance of negative symptoms (Gold et al., 2013) have impairments in exertion of effort during reward seeking. These impairments in exertion of effort are not due to problems experiencing pleasure in response to primary motivational stimuli (Treadway and Zald, 2011; Treadway et al., 2012). For these reasons, it is imperative to assess effort-related impairments in rodent models to further understand the underlying mechanism and to develop novel treatments.

Tests of effort-related choice behavior offer animals choices between a more highly valued reward that can only be obtained by a high degree of effort vs. a low effort/low reward option. One procedure that is used to study the effects of dopaminergic manipulations on effort-related choice behavior is the concurrent FR5/chow feeding choice task. This operant choice task offers rats the option of lever pressing to obtain a more preferred food (Bioserve high carbohydrate pellets), or approaching and consuming a concurrently available less preferred standard lab chow. Under baseline or control conditions, when the FR requirement is relatively low (i.e., FR1 or FR5), trained rats will receive most of their food from lever pressing and consume only a small quantity of the lab chow (Cousins et al., 1993; Nowend et al., 2001; Salamone et al., 1991, 1997). Low-

to-moderate doses of DA antagonists with varying selectivity profiles, including haloperidol, cis-flupenthixol, SCH-23390, SKF-83566, ecopipam, raclopride, and eticlopride, and NAc DA depletions produce a dramatic shift in response, such that lever-pressing is significantly decreased and consumption of the lab chow is increased (Cousins and Salamone, 1994; Koch et al., 2000; Nunes et al., 2010; Salamone, 1996; Salamone et al., 1991, 2002; Sink et al., 2008; Worden et al., 2009). Recently our laboratory has studied the effects of the reversible VMAT-2 (vesicular monoamine transporter-type 2) inhibitor tetrabenazine (TBZ) using the concurrent FR5/chow feeding choice task. Previous studies have shown that the reversible VMAT-2 inhibitor TBZ blocks the storage of and depletes, monoamines, with its greatest effects on striatal DA (Pettibone et al., 1984; Tanra et al., 1995). Moreover, TBZ also affects DA-related signal transduction in a manner consistent with reduced accumbens D_1 and D_2 receptor transmission (Nunes et al., 2013). Additionally, postmortem tissue studies of humans receiving clinical doses of TBZ reported that the only significant depletions of DA were in the caudate and hippocampus (Guay, 2010). Similar to the effects seen with DA antagonism, TBZ produced a significant reallocation of behavior, causing rodents to select an alterative food source with minimal work requirements (Nunes et al., 2013a; Randall et al., submitted; Yohn et al., submitted).

Reversal studies (e.g., co-administration of another compound) are used as pre-clinical assessment of potential treatments. Co-administration of the adenosine A_{2A} antagonist, MSX-3, was able to attenuate the shifts in behavior induced by TBZ (Nunes et al., 2013). Additionally, the widely used antidepressant drug bupropion, a catecholamine uptake blocker, and l-deprenyl, a monoamine oxidase-B (MAO-B) inhibitor, also reversed the effort-related effects of TBZ (Nunes et al., 2013; Randall et

al., submitted). Because bupropion acts on both DA and norepinephrine (NE), it is unclear which catecholamine neurotransmitter is most involved in mediating the effort-related effects of bupropion. While considerable evidence implicates DA in effort-related processes, little is known about the potential role of NE. NE is a monoamine (more specifically, a catecholamine) that is located in several brain areas; the larges NE system in the brain originates in the locus ceruleus (brainstem), and via the dorsal NE bundle, these neurons project to a wide variety of brain regions including prefrontal cortex, limbic system, and anterior cingulate (Kolb & Whishaw, 2009). NE is also an integral part of the stress response, is released by the sympathetic nervous system, and is critical for the production of the "fight or flight" response. Not only is NE associated with the stress response, it has been shown that stressors that are more "psychological" in nature (e.g. social pressures, emotional distress) are more likely to alter NE reactivity compared to stressors of the physical nature (e.g. being constrained, free falling); moreover, it is still unclear whether the stress response induces an increase in brain NE, or rather a decrease, which causes an upregulation of NE receptors (Goddard et al., 2010). In any case, these unknowns contribute to the neurochemical underpinnings of depression that are still being studied.

In accordance with the many neurotransmitters that may be involved in depression, there are a number of antidepressants on the market today that are suggested to lessen the degree of depressive symptoms. The two primary families of antidepressants are selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). SSRIs are the most commonly prescribed when it comes to depression, however a lot of adverse side effects can be experienced, such as decreased appetite, dry mouth, tremors, and sexual problems (Mika et al., 2013). The second family

of antidepressants, TCAs, are commonly prescribed in adjunct with an SSRI or other form of antidepressant in order to maximize the effect. Moreover, TCAs can range in their selectivity for different neurotransmitters, so there is some uncertainty in each drug's efficacy (Mika et al., 2013).

Some studies have already suggested that NE uptake inhibition by desipramine can cause a range of antidepressant-like effects. Desipramine has been shown to possess antidepressant-like effects in animal models commonly employed to screen antidepressants, such as the forced swim and tail suspension test. For instance, in these paradigms co-administration of desipramine with DA depleting agents such as reserpine decreased immobility time. For example, Zangen et al. (2001), used a depressive phenotype anima line Flinders Sensitive Line (FSL) and found that after chronic desipramine treatment (i.e., 14 days of daily treatment with 5 mg/kg per day), FSL rats had restored both the dopamine-serotonin interaction as well as the behavioral deficits seen using the forced swim test (Zangen et al, 2001.). Moreover, a study done by Poldinger (1962) showed that depressed patients who were unresponsive to desipramine could be made responsive by co-administration of either tetrabenazine or reserpine, both V-MAT2 (vesicular monoamine transporter-2) inhibitors.

Previous studies have shown that 5-HT is not involved in mediating effort-related choice behavior (Salamone et al., unpublished data), however, the involvement of NE is unknown. The current study aimed to focus on the role of NE individually in its efficacy in treating the motivational deficits of depression. For this reason, the secondary amine tricyclic, desipramine was chosen based on its high selectivity for NE (Ravindran et al., 1995). It has been noted that desipramine acts as a NE uptake inhibitor, and to a lesser extent a 5-HT uptake inhibitor. Moreover, in one study, desipramine was found to be 25

times more selective for NE than it is for 5-HT (Deupree et al., 2007). In total, desipramine blocks the uptake of NE back into the presynaptic cell, allowing it to stay in the synapse for a longer period of time, and subsequently increasing the amount that is able to activate post-synaptic receptors (Deupree et al., 2007; Ravindran et al., 1995). Therefore, the motivational effects of desipramine were assessed by studying its ability to reverse TBZ induced shifts in behavior in rodents responding on the concurrent FR5/chow choice task.

2. Materials and Methods

2.1 Animals

Adult male, drug-naïve, Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN, USA) were housed in a colony maintained at 23°C with 12-h light/dark cycles (lights on at 0700 hours). The rats (n=6) weighed 300-350 grams at the beginning of the study and were food-deprived to 85% of their free-feeding body weight for the experiment. Rats were fed supplemental chow to maintain the 85% free-feeding body weight throughout the course of the study with ad libitum water available in their home cages. Animal protocols were approved by the University of Connecticut Institutional Animal Care and Use Committee and followed NIH guidelines.

2.2 Pharmacological agents and dose selection

Tetrabenazine (9,10-dimethoxy-3-(2-methylpropyl)-1,3,4,6,7, 11b hexahydrobenzo[a]quinolizin-2-one), the VMAT-2 inhibitor, was purchased from Tocris Bioscience (Bristol, UK). Tetrabenazine (TBZ) was dissolved in a vehicle solution of 0.9% saline (80%) and DMSO (20%). 1N HCl /mL volume was then added to adjust the pH and get the drug completely into solution. The final pH of TBZ was 3.5. The saline with 20% DMSO vehicle solution was administered as the vehicle control. **Desipramine**

(desipramine hydrochloride), the tricyclic antidepressant, was purchased from Sigma Aldrich (Enzo Life Sciences Inc., Farmingdale, NY). Desipramine (DES) was dissolved in a vehicle solution of 0.9% saline, with light heat added with the use of a hot plate in order to fully dissolve the drug in solution. Desipramine's binding affinity ratio for the NE and 5-HT transporters, respectively, is 25:1 (Deupree et al., 2007.) Desipramine shows no affinity for DA. The 0.9% saline was administered as the vehicle control.

The 0.75 mg/kg dose of TBZ used for the operant choice task was based on extensive pilot work done in our laboratory (Nunes et al., 2013; Randall et al., *In press;* Yohn et al., 2014*)*. Doses higher than 0.75 mg/kg (e.g. 1.0 mg/kg) have been shown to induce motor deficits. The four doses of DES used (2.5, 5, 10, 20 mg/kg) were based off previous literature. The range of doses seen in previous research has spanned from 5 to 25 mg/kg DES, with 20 mg/kg having the most robust effects, without having prominent side effects (Crews & Smith, 1978; Roth-Deri et al., 2009; Sulser et al., 1968; Thangathurai et al., 2010). The current study aimed to cover a wide enough dose range, so as to not overlook any dose-dependent effects. All drugs were administered through intraperitoneal injections (IP).

2.3 Behavioral Paradigms

Concurrent FR5/chow-choice paradigm: Behavioral sessions were conducted in operant conditioning chambers (28x23x23 cm^3, Med Associates, Georgia, VT, USA) during the light period. Rats were initially trained to lever press on a continuous reinforcement schedule (30 minute sessions, 5 days/week) to obtain 45mg pellets, (Bioserve, Frenchtown, NJ, USA), and then were shifted to the FR5 schedule (30 minute sessions, 5 days/week) and trained for several additional weeks until reaching a predetermined

baseline number of lever presses (i.e., consistent responding ≥ 1,200 lever presses). Animals needed to consistently reach baseline criteria for the course of approximately one week before being introduced to the concurrent FR5/chow-feeding choice procedure. In this task, weighed amounts of laboratory chow (Laboratory Diet, 5P00 Prolab RHM 3000, Purina Mills, St. Louis, MO, USA; typically 20-25 grams, four-five large pieces) were concurrently available in the chamber during the 30 min FR5 session (Figure 1). At the end of the session, rats were immediately removed from the chambers, lever-pressing totals were recorded, and amount of chow consumed was determined by weighing the remaining food and spillage. Rats were trained until reaching and maintaining stable levels of baseline lever pressing and chow intake. Once animals achieved baseline rates, one experimental testing day per week began. For most baseline days, rats did not receive supplemental feeding. However, over weekends and after drug tests, animals received supplemental chow in the home cage. On baseline days, rats mainly consumed pellets that were delivered from lever pressing during the 30 min session.

2.4 Experimental Procedures

This experiment used a within-group design in which each rat received all doses of drug or vehicle treatments in their particular experiment in a randomly varied order (one treatment per week; no treatment sequence repeated across different animals in the experiment). Baseline training sessions (i.e. non-drug) were conducted four days per week for the operant choice task. Once a week for 6 weeks, a drug run was conducted. Trained rats (n=6) received the following treatments IP, all TBZ injections administered 90 minutes and DES injections 45 minutes prior to testing – TBZ vehicle plus DES vehicle (VEH/VEH), 0.75 mg/kg TBZ plus DES vehicle (TBZ/VEH), 0.75 mg/kg TBZ

plus 2.5 mg/kg DES (TBZ/2.5), 0.75 mg/kg TBZ plus 5 mg/kg DES (TBZ/5.0), 0.75 mg/kg TBZ plus 10 mg/kg DES (TBZ/10), or 0.75 mg/kg TBZ plus 20 mg/kg DES (TBZ/20). After the allotted lead-time, rats were placed in the operant chamber that they had been trained in on non-drug days, and were allowed to either lever press, or eat the concurrent lab chow for 30 minutes. Immediately after the 30-minute session, rats were removed from the chambers, total lever presses were recorded, and chow consumed was calculated.

2.5 Statistical Analyses

For this experiment, total number of lever presses and gram quantity of chow consumption from the 30 min session were analyzed using repeated measures analysis of variance (ANOVA). A computerized statistical program (SPSS 21.0 for Windows) was used to perform all analyses. When there was a significant ANOVA, non-orthogonal planned comparisons using the overall error term were used to assess the differences between each treatment and the control condition. The number of comparisons was restricted to the number of treatments minus one (Keppel, 1991).

3. Results

The effects of the VMAT-2 inhibitor TBZ on effort-related choice behavior was not attenuated by co-administration of the tricyclic antidepressant DES. Repeated measures ANOVA indicated that there was an overall significant effect of drug treatment on lever pressing [$F(5,25) = 19.277$; $p < 0.001$]. Non-orthogonal planned comparisons revealed that TBZ significantly reduced lever pressing relative to vehicle-control treated animals (Figure 2; planned comparisons, $p < 0.01$). Planned comparisons also revealed that co-administration of DES at the 2.5-10.0 mg/kg doses failed to reverse the effects of

TBZ, while 20 mg/kg DES further decreased lever pressing as compared to TBZ-treated animals ($p < 0.05$). The overall treatment effect for chow consumption was also statistically significant [$F(5,25) = 5.593$, $p < 0.001$]. Non-orthogonal planned comparisons revealed that chow consumption was significantly increased by TBZ relative to vehicle-vehicle condition ($p < 0.01$). Chow consumption was significantly reduced at 20 mg/kg DES relative to TBZ-treated animals (planned comparisons, $p < 0.01$). Thus, co-administration of DES does not attenuate TBZ-induced shifts in choice behavior, and the highest dose of DES appears to produce further behavioral impairments.

4.0 Discussion

The current study aimed to expand upon research that has been done involving animal models of the motivational symptoms of depression using an effort-related choice task, and the assessment of drug treatments for reversal effects. For the first portion of the experiment, using TBZ, it was hypothesized that it would shift rat's behavior from the high effort option to the lower effort alternative that can be obtained with minimal work effort. These motivational deficits that are seen in animal models of effort-related choice behavior are similar to the motivational symptoms seen in human pathologies. TBZ, a VMAT-2 inhibitor, blocks storage of catecholamines, with strongest affinity for striatal DA (Pettibone et al., 1981; Nunes et al., 2013). Recently, a study conducted by our laboratory showed that TBZ reduced DA neurotransmission at both NAc DA D_1 and D_2 receptors (Nunes et al., 2013). In addition, postmortem tissue analysis of patients receiving clinical doses of TBZ reported there was substantial DA depletions within the caudate (Guay, 2010). Although TBZ mainly effects DA, studies have shown that TBZ reduced NE within the amygdala and hippocampus (Guay, 2010). Administration of TBZ produces effects similar to DA depletions or administration of DA D1 or D2 family

antagonists in tasks assess effort-related decision making. In maze procedures (Yohn et al, submitted) and operant tasks (Nunes et al., 2013; Randall et al., submitted) administration of TBZ reduces selection of the high effort option and increases selection of the low effort alternative. Consistent with previous studies, administration of TBZ reduced lever pressing and increasing chow consumption. The effects of TBZ are not due to a reduction in primary food motivation or appetite suppressant effects (Nunes et al., 2013; Randall et al., submitted).

The shifts in choice behavior induced by TBZ can be attenuated through various compounds that have different selectivity profiles. For example previous studies have shown that, co-administration of the adenosine A2A antagonist MSX-3 successfully reversed TBZ induced shifts in the concurrent FR5/chow choice task (Nunes et al., 2013). Moreover, the behavioral deficits caused by administration of TBZ are also attenuated by the MAO-B inhibitor deprenyl as well as the catecholamine uptake inhibitor bupropion (Nunes et al., 2013; Randall et al., submitted; Yohn et al., submitted). Studies that are currently being conducted in our lab show that 5-HT is not involved in modulating effort-related choice behavior (Salamone et al., unpublished observations). Administration of the commonly prescribed SSRI, Prozac, also fails to reverse the effects of TBZ, and in fact makes animals worse on choice tasks compared to TBZ-treated animals. That observation is consistent with clinical studies showing that SSRIs are generally ineffective at treating motivational symptoms such as fatigue, and in fact, can exacerbate them (Fava et al. 2013). Since bupropion has action on both DA and NE, it could be postulated that NE may be involved in regulating effort-related choice behavior. Therefore, the purpose of the current study was to investigate the tricyclic antidepressant

desipramine. This drug has been shown to be 25 times more selective for NE than it is for 5-HT; however, this study also suggests that one of DES's metabolites (desmethyldesipramine) has an affinity for 5-HT, similar to that of DES for NE (Deupree et al., 2007). Additionally, Dekeyne et al. (2001a), found that 20 mg/kg increased preferentially catecholamines, and to a lesser extent, 5-HT.

The results of the present study indicate that co-administration of DES does not attenuate TBZ induced shifts in choice behavior. In fact, TBZ plus 20 mg/kg DES further suppresses lever pressing and chow intake compared to TBZ-treated animals. Interestingly, all doses of DES co-administered with the VMAT-2 inhibitor TBZ seem to further impair animals responding on the concurrent FR5/chow choice task. Therefore, co-administration of desipramine with TBZ does not produce a behavior profile similar to the DA/NE reuptake inhibitor, bupropion. At the highest doses of DES chow consumption although not statistically significant was reduced even more so than vehicle-control conditions. Along with the FR5 results, adverse side effects were noted throughout the course of the study. About 20-30 minutes after DES injections, 93 % of rats who were administered higher doses (i.e., 10 or 20 mg/kg) showed signs of sedation/catatonia. Mika et al. (2013) found that adverse side effects of DES include sedation, constipation, and dry mouth. Moreover perhaps, DES is exacerbating the TBZ-induced effects. Rousseau et al. (1998), found that chronic administration of 30 mg/kg DES decreased T_4 thyroid serum levels. Moreover, there was an accumulation of DES within the thyroid it. Therefore, future studies should also investigate blood serum concentrations of TBZ and DES to determine system levels. Human clinical studies found that many subjects had to withdraw due to DES-related adverse side effects. Both

desipramine and sertraline (an SSRI) were tested, and patients in the DES group were more likely to withdraw (2:1 to sertraline) due to adverse side effects including vision disturbances, dry mouth, sweating, cardiovascular and GI effects (Ravindran et al., 1995).

Dekeyne et al. (2001a) used a differential-reinforcement of low-rate (DRL) operant task that measured response rate (lever pressing) and reinforcement rate (eating pellet) in order to assess a variety of antidepressants. Similar to the results generated by this study, DES was shown to gradually decrease response rate, while increasing reinforcement rate; however, the trend for reinforcement rate was biphasic, as reinforcement peaked with 20 mg/kg, and then both responding and reinforcing dropped drastically with 40 mg/kg desipramine. Another study using DRL showed that DES also decreased response rate and increased reinforcement. On the contrary, DA depletion with DES caused reinforcement rate to decrease (O'Donnell and Seiden, 1984). In another study, which employed a continuous reinforcement (CRF) schedule, rats treated with 10 mg/kg DES showed reduced lever pressing and lever-pressing rates compared to controls. It was also found that 10 mg/kg DES caused reduced body weight in both free-feeding and food-restricted animals. (Lucki and Frazer, 1985). Moreover, this reduction even lasted a few days after treatment ended (Lucki and Frazer, 1985). Taken together, these studies lend support to the idea that the roles of NE are not as clear cut as other neurotransmitters such as DA in reinforcement response rates.

DES was also found to reduce running wheel time. Physical activity on a voluntary running wheel has been shown to produce antidepressant-like effects in mice tested on the forced swim and tail suspension test (Cunha et al., 2013). A previous study which studied both locomotor activity and active running wheel time found that 30 mg/kg

DES decreased significantly decreased both activities (Weber et al., 2009). The behavioral profile of DES was different from SSRI's. Together with previous studies, these results suggest that tricyclic antidepressants may reduce behavioral activation and induce sedation compared to other antidepressant subfamilies (Weber et al., 2009).

Future research should continue to focus on the assessment of drug treatments using a variety of effort-related paradigms. In doing so, new treatments for a variety of neurological disorders, from depression to PD, can be discovered and evaluated. The idea for the current study emerged out of the significance found by Nunes et al. (2013b) with bupropion (DA/NE uptake blocker) on the concurrent FR5/chow-choice operant task. Focus on simply NE uptake inhibition with desipramine was the goal in order to broaden the knowledge already known on effort-related behavior. Another study, done by Dekeyne et al. (2001a), ran dialysis in the frontal cortex for certain neurotransmitters during different drug treatments; they found that 20 mg/kg desipramine actually showed the largest increase in DA, then NE, and an even smaller increase in 5-HT. This study suggests that no assumptions should be made in the underlying mechanisms of these drugs, and further research should continue to monitor brain levels of neurotransmitters during drug treatment. In a review by Mika et al. (2013), tricyclics have been suggested to have no direct affect on dopamine, however indirect effects by adrenergic receptors and desensitization of D_2 receptors could be occurring. These effects could be clues as to why the current study saw such a dramatic decrease in responding with higher doses of DES. Moreover, despite the lack of significance found in terms of desipramine's ability to reverse TBZ's effort-related dysfunctions, NE should not be completely disregarded.

Future research should focus on new drugs with different neurotransmitter affinities, which can be assessed for novel effects on effort-related tasks.

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Figures

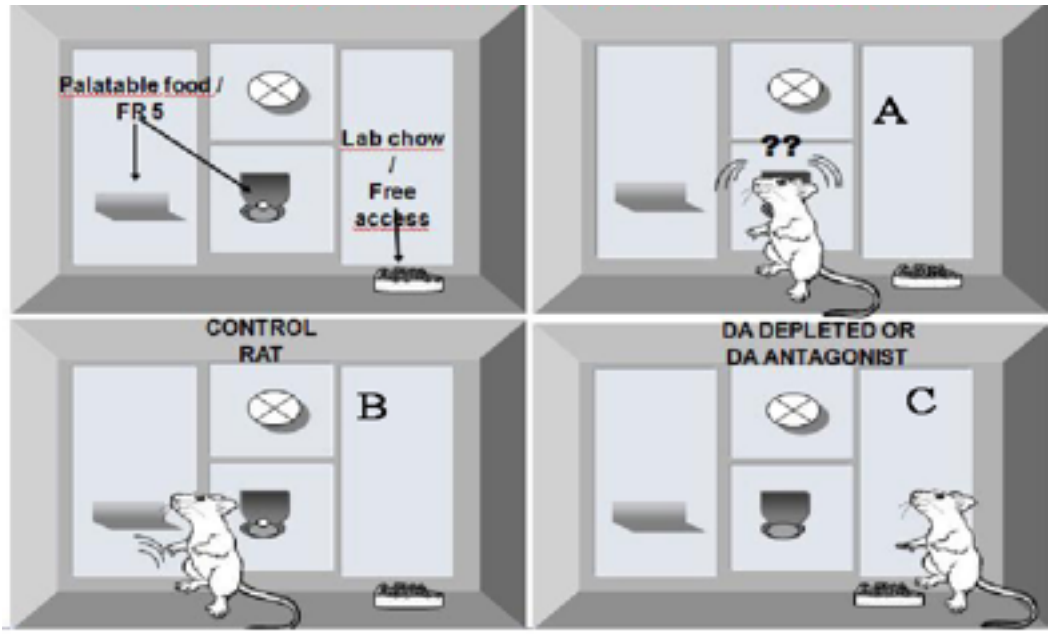

Figure 1: Concurrent FR5/chow-choice operant procedure. (A) The animal has the choice of pressing the lever for the more preferred Bio-serv pellets, or consuming the less-preferred, freely available lab chow. (B) A rat under control conditions (high-responder) will obtain their food by pressing the lever for the more preferred Bio-serv pellets. (C) A rat with DA antagonism/DA depletions in NAc (low-responder) will choose to consume freely available, less-preferred lab chow.

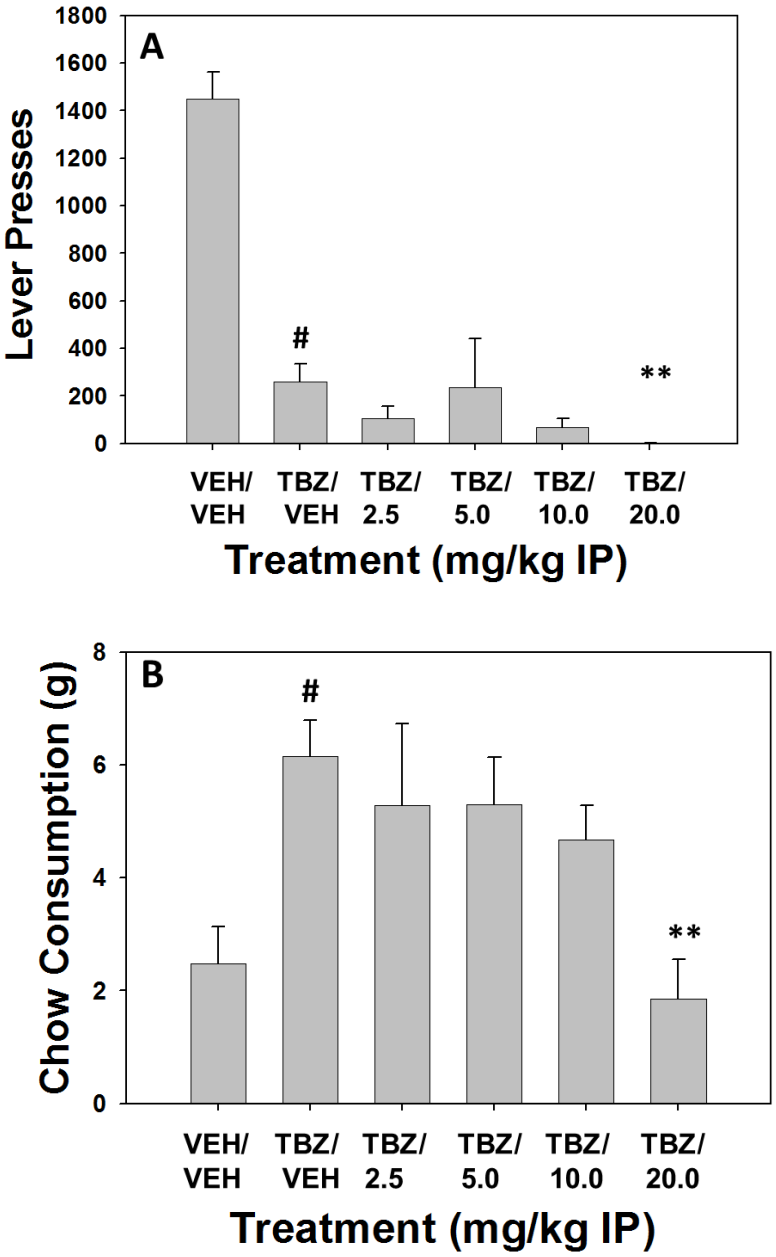

Figure 2: The effects of the tricyclic antidepressant desipramine on TBZ-induced changes in rats responding on the concurrent FR5/chow choice task. Rats received IP injections of vehicle or 0.75 mg/kg of TBZ 90 minute and DES 45 minutes prior to testing. (a) Mean (± SEM) number of lever presses (FR5 schedule) during the 30 minute session. (B) Mean (± SEM) gram quantity of chow intake. TBZ significantly decreased lever pressing and increased chow consumption relative to vehicle control animals (# $p<0.01$). Co-administration of 20.0 mg/kg DES further suppressed lever pressing and decreased chow consumption relative to TBZ-treated animals (** $p<0.01$).