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Effort-Related Choice Behavior is Affected by Pharmacological Manipulations Associated with Depression: the Effects of Tetrabenazine

Megan Huizenga

University of Connecticut - Storrs, megan@huizenga.net

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**EFFORT-RELATED CHOICE BEHAVIOR IS AFFECTED BY PHARMACOLOGICAL
MANIPULATIONS ASSOCIATED WITH DEPRESSION: THE EFFECTS OF
TETRABENAZINE**

The University Scholar Honor's Thesis of
Megan Huizenga

Advisor: Dr. John Salamone
Department of Psychology
University of Connecticut, Storrs CT 06269 USA
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II. ABSTRACT

Research indicates that nucleus accumbens dopamine (DA) is an important component of the neural circuitry regulating behavioral activation and effort-related processes. In humans, psychiatric symptoms such as anergia and psychomotor retardation reflect pathologies in behavioral activation. These motivational symptoms are fundamental aspects of depression and other disorders. Drugs such as reserpine and tetrabenazine deplete monoamines, including dopamine, and induce depressive like behaviors in humans. Tetrabenazine inhibits vesicular monoamine transporter-2 (VMAT2), and has been shown to induce depressive symptoms, including psychomotor retardation, lethargy, fatigue and anergia, in some human patients. In rodents, disruptions in activational or effort-related aspects of motivation are sometimes studied using tasks that assess effort-based choice behavior. Organisms are capable of making effort-related decisions based upon assessments of motivational value and response costs. Research involving choice tasks has shown that rats with impaired DA transmission reallocate their instrumental behavior away from food-reinforced tasks with high response costs, and instead select less effortful food-seeking behaviors. The current study investigated the effects of tetrabenazine on effort-related choice behavior. Administration of tetrabenazine at doses that reduce accumbens DA levels (0.5-1.0 mg/kg) alters effort-related choice behavior in rats responding on a concurrent FR5/chow feeding choice task, a concurrent progressive ratio choice task, and T-maze barrier choice procedure. Initial evidence indicates that these effects of tetrabenazine on effort-related choice behavior can be reversed by co-administration of the adenosine A_{2A} antagonist MSX-3. Taken together, these results indicate that administration of low doses of tetrabenazine can alter effort-related choice behavior, biasing animals towards low effort alternatives. These

findings may be related to the ability of monoamine depleting agents such as tetrabenazine to blunt behavioral activation and induce psychomotor retardation, anergia and fatigue in humans, and this research could be useful for the development of drug treatments for effort-related motivational symptoms in humans.

III. BACKGROUND AND SIGNIFICANCE

According to The National Institute of Mental Health, depression is currently the leading cause of disability in the United States (WHO 2004). Major depression is a heterogeneous disease, with symptoms that include, but are not limited to: psychomotor slowing and deficits in emotional processing and cognitive function (APA 2000). The absence of energy (i.e., anergia) is a depressive symptom that is reported more often by depressed patients compared to anxiety-related symptoms (Salamone et al. 2006). Anergia is the single symptom of depression most strongly correlated with a lack of social functioning and thus decreased work productivity due to days in bed and days of lost work (Swindle 2001). As is a particularly difficult symptom to treat, accruing evidence suggests that current first-line pharmacotherapies (e.g., SSRIs) do not adequately address motivational and reward-processing deficits in depression (Dunlop and Nemeroff, 2007; McCabe et al., 2009; Price et al., 2009), and the presence of anergic symptoms is a predictor of poor response to treatment (Spijker et al., 2001).

The specific neural pathology underlying depression is largely unknown, however, depression seems related to decreased transmission of monoamines. Chemical analyses of cerebrospinal fluid in patients suffering from untreated depression, reveals decreases in 5-HIAA (a serotonin metabolite) decreases in total norepinephrine metabolism, and decreases in HVA (a DA metabolite). Additionally, decreasing monoamine synthesis acts to increase depressive symptoms (Meyer et al. 2006). This line of research aided the development of the monoamine theory of depression. This theory postulates that depression is associated with low levels of monoamines, particularly serotonin (5-HT) and norepinephrine (NE) (Maletic, 2007). Imaging studies of patients with untreated depression revealed a high receptor density for monoamine oxidase A (MAO-A), which metabolizes these neurotransmitters (Maletic 2007). A loss

of MAO-A interacts with specific transporter densities (i.e., 5-HT and NE) resulting in depressive illness (Maletic 2007; Meyer et al. 2006). Therefore, the most common prevailing pharmacological treatment for depression is selective serotonin reuptake inhibitors (SSRIs). SSRIs work by increasing the extracellular level of the monoamine 5-HT by inhibiting its reuptake into the presynaptic cell. This effectively increases the level of 5-HT available in the synaptic space to bind with the postsynaptic receptor. However, a major problem with this treatment of depression is the large time gap between starting the medication and the observed therapeutic effect. Working within minutes *in vivo*, SSRIs potently block 5-HT transporters, increasing extracellular levels of 5-HT. Yet, despite these immediate extracellular increases, the therapeutic effects (i.e., mood elevation) are not seen until weeks later. Furthermore, even with remission of some emotional symptoms, patients often report fatigue and psychomotor slowing (Cousins and Salamone 1994; Treadway and Zald 2010).

The lack of effective patient response to the current reigning pharmacological treatment demands further research. It is particularly necessary to elucidate the neuronal mechanisms underlying the pervasive behavioral symptoms: psychomotor slowing and behavior directed motivational tasks. Motivation has been defined as the set of processes that organisms use to regulate the probability, proximity and availability of significant stimuli (Salamone 1992; Salamone and Correa 2002). Motivated behaviors are further broken down to include both directional and activational components (Salamone 1988). Directional aspects refer to motivated behavior as either directed toward or away from a stimulus (Salamone and Correa 2002). Alternatively, the activational aspects refer to the instrumental behaviors often characterized by a high degree of vigor, persistence, and work output (Salamone 1988, 1992; Salamone and Correa 2002; Salamone et al. 2007).

The concept that motivated behaviors have this activational component is not new to the fields of psychology, neurology, or psychiatry. Pathologies that involve effort-related aspect of motivation are seen as an important defining feature of many psychiatric syndromes. In fact, clinical literature emphasizes the importance of motivational symptoms as related to energy and effort-related expenditure (Tylee et al. 1999; Stahl 2002; Salamone et al. 2006; Treadway and Zald 2010). This includes, but is not limited to, the psychomotor slowing, apathy, anergia, and fatigue that typifies major depression, parkinsonism and other disorders. Again, the severity of these symptoms in depressed patients is directly related to difficulties with social functioning, employments and treatment outcomes (Treadway and Zald 2011; Tylee et al. 1999; Stahl, 2002).

The neuronal basis of energy-related impairments in the functioning of depressive patients is still being characterized; however, there is considerable evidence that implicates central dopamine (DA), especially in the nucleus accumbens, as well as the neocortex and limbic system. Research suggests that the compromised DA transmission in the basal ganglia, particularly in nucleus accumbens, is associated with depression and may underlie fatigue, anergia, and problems with behavioral activation. In fact, depleting or blocking DA in these striatal regions can induce psychomotor slowing and parkinsonian motor symptoms (i.e. tremor). Therefore, blocking of depleting DA expression in nucleus accumbens can induce both behavioral inactivation and tremulous movements. Within the striatal regions, DA and adenosine receptors are highly expressed, and have antagonistic interactions. Due to this antagonistic relationship, adenosine A_{2A} antagonists are currently in clinical trials to treat parkinsonian tremors. However, these drugs have yet been evaluated for their potential to reverse the psychomotor symptoms of depression. The literature on Parkinson's disease makes a

strong case for alleviating symptoms clustered around atypical movement and activation. Given the similarities in expression of anergic symptoms between Parkinson's disease and depression, further work is needed to determine how the pathways implicated in Parkinson's disease correlate to those underlying depression. Depression as a common "non-motor" symptom of Parkinson's disease suggests the both disorder share a common neurological substrate, with alterations in the interaction of DA-adenosine neurotransmission as the biological basis of depression.

It was hypothesized that pharmacological manipulations that serve to produce depressive-like motor and behavioral symptoms in humans will also produce effort-related choice impairments in rodents. In fact, this combination of behavioral and pharmacological methods could be employed as an animal model of depression in which to test the efficacy of putative antidepressants, novel treatments, and change the relationship between our understanding of depression and psychomotor retardation. The present study worked to expand upon what is known about nucleus accumbens DA in effort-related processes, by determining if pharmacological manipulations associated with depression-like symptoms can induce effort-based dysfunctions in rats. It is suggested that highly active, instrumental behaviors prompted by conditioned stimuli are those most sensitive to interference with DA systems (Salamone 1991). For instance, instrumental responding for food is affected by accumbens DA manipulations, such as DA antagonism or depletions; however these effects are schedule-dependent. Further, DA antagonism or depletions in these areas have little to no effect on schedules that have low to moderate ratio requirements, such as a fixed ratio of one pellet per single lever press (FR1 schedule). However, increasing the ratio requirement of the operant task from FR1 to an FR5 schedule increases the suppressant effects of an accumbens DA depletion

(Salamone et al. 1991, 2001; Ishiwari et al. 2004a). This evidence suggests that an interference with accumbens DA selectively impairs activational aspects of motivation, while leaving directional aspects intact. Thus, in addition to its role in the exertion of effort, accumbens DA is implicated in the mediation of effort-related choice tasks (Salamone et al. 2003; Ishiwari et al. 2004a; Mingote et al. 2005).

With the body of evidence citing the clinical relevance of fatigue and other forms of energy or effort-related motivation dysfunctions in psychiatric disorders, it is critical to develop animal models of illness. In particular, an animal model of depression would be necessary for evaluating current treatments, identifying therapeutic targets, and investigating the mechanisms involved. Several behavioral tasks have been useful in assessing the effects of antidepressant medications in rodents, such as the forced swim test, tail suspension task, chronic mild stress, and the social defeat paradigm (Duman 2010; Yan et al. 2010). Using these behavioral task to model depression in rodents does not allow for an accurate or reliable approach to the multifaceted disorder. Therefore, the concurrent choice procedure is favored with its focus on modeling specific behavioral depressive symptoms by targeting effort-related choice behavior.

This experiment focused on the behavioral and cellular effects of monoamine-depleting agents that induce or exacerbate depressive symptoms in humans. Monoamine-depleting agents, such as reserpine and tetrabenazine act by blocking monoamine storage to induce behavioral impairments. These pharmacological agents have been used for decades in efforts to create working models of depression in animal research. The drug reserpine was first introduced as a tranquilizing agent to treat hypertension, before removed due to patient report of developing major depression. Subsequent research has found reserpine to induce behavioral depression as a result of depleting all monoamines.

In fact, when administered in high doses, reserpine can induce catalepsy and tremulous movements characteristic of Parkinson's disease. These pharmacological effects could potentially create a rodent reserpine-model of depression to test the efficacy of punitive and novel antidepressant treatments. The drug tetrabenazine was marketed for the treatment of hyperkinetic movement disorders, such as Huntington's chorea, but has a high incidence of inducing depressive symptoms. Similar to reserpine, tetrabenazine-induced depressive symptoms may be due to the degradation of monoamines.

However, preliminary data indicates that tetrabenazine is more consistently effective than reserpine at producing the desired alterations in effort-related choice behavior. Therefore, the proposed experiment sought to characterize the effects of tetrabenazine on effort-related choice behavior. For these reasons, this experiment was designed to study the ability of pharmacological conditions associated with the induction of depressive symptoms in humans to induce grossly similar effort-based dysfunctions in rats.

IV. MATERIALS & METHODS

Subjects:

In this study, adult male Sprague-Dawley rats (n=16; Harlan Sprague Dawley, Indianapolis, IN, USA) were used as subjects. These animals, with no prior drug experience and minimum handling were paired-housed in a colony maintained at 23°C, with a 12 hour light/dark cycle (lights on at 0700). Water was available ad lib in the home cages as all times. However, the rats that were tested in operant boxes were food restricted to 85% of their free-feeding body weight for initial operant training and

allowed modest weight gain during the studies. At the beginning of the experiment the rats weighed between 279-299 grams. These animal protocols were approved by the University of Connecticut Institutional Animal Care and Use Committee, and the studies were conducted according to NIH guidelines for animal care and use.

Pharmacological Agents:

This study used intraperitoneal (IP) injections of TBZ (R&D Systems) and reserpine (Tocris). TBZ was dissolved in an acidified solution and reserpine in 0.3% tartaric acid, which were also used for the vehicle control condition. For the three weeks of the TBZ experiment, the trained rats received the same treatment administered 90 minutes prior to testing: vehicle IP, 0.5 mg/kg TBZ, or 1.0 mg/kg TBZ.

Behavioral Procedure:

To study the effects of a monoamine depleting agent tetrabenazine, subjects were tested on a task that assessed effort-related choice behavior (i.e., the concurrent lever pressing chow intake task, see Salamone et al. 1991). Food restricted rats will be trained on this task in standard operant conditioning chambers (28 cm x 23 cm x 23 cm; Med PC, Inc.) during the light period. Animals were trained in 30 minute sessions, 5 days per week. In the first week of training, all rats were trained to lever press on a fixed ratio 1 schedule, where one lever press results in the animal receiving one 45 mg high carbohydrate food pellet (Research Diets Inc., New Brunswick, NJ). In the second week, animals were shifted to a fixed ratio 5 schedule, where five lever presses results in one

pellet. This schedule was maintained for 3-4 weeks until the rats achieved a stable baseline performance (i.e., >1000 lever presses per session). After performance of the FR5 schedule was stable, weighed amounts of laboratory chow (ProLab, Lab Diet, Brentwood, MO; typically 15-25 g, three large pieces) were concurrently available on the floor of the chamber during the 30 minutes FR 5 sessions. The rats continued to perform on this concurrent feeding procedure for several weeks prior to the introduction of TBZ. At the end of each session, rats will be immediately removed from the operant chambers. Food intake was determined by weighing the remaining food, including collected spillage, while a computer program recorded lever pressing. This experiment used a between-groups design; with each rat receiving only one dose of tetrabenazine once a week carried out for three weeks.

Research Overview:

As previously noted, the behavioral effects of depression are those most often reported as the most debilitating, and consequently result in the most days of lost productivity. Additionally, these motor-related symptoms are the most difficult to treat effectively with putative antidepressant medications. This evidence indicates that the basic animal studies described above are potentially relevant for understanding depression's effort-related dysfunction in humans. Such studies are possible through the strikingly similar brain circuitry involved in effort-related functions in rats and the systems thought to undermine the energy-related dysfunction caused by depression. Capitalizing on this similarity, the proposed animal studies can lead to the development

of animal models for these symptoms to test the efficacy of current pharmacological treatments, as well as novel treatments.

Two pharmacological manipulations will be tested using the same behavioral choice procedure:

Group 1: The drug reserpine was first introduced as a tranquilizing agent to treat hypertension, before removed due to patient reports of developing major depression. The side effect of the monoamine depleting agent reserpine is consistent with the body of literature documenting the effects of interference with nucleus accumbens DA on effort-related choice. This experimental group tested reserpine for its effects on effort-related choice behaviors. Similar to the function of DA antagonists, reserpine also induces psychomotor slowing and parkinsonian motor symptoms by blocking of depleting DA expression. Additionally, subsequent research has found reserpine to induce behavioral depression as a result of depleting all monoamines (Huang 2004). Due to the pharmacological effects of reserpine, it was hypothesized that systemic injections of reserpine would produce a shift in the allocation of effort on the concurrent FR5/chow feeding procedure.

Group 2: The second pharmacological agent tested for its effects on effort-related behaviors was tetrabenazine (TBZ), a VMAT2 inhibitor. Evidence from related animal studies support the idea that pharmacological agents such as TBZ produce depression-like behaviors, including psychomotor slowing, fatigue, and anergia. It was hypothesized that by inhibiting vesicular storage of monoamines, TBZ would decrease

extracellular DA levels, and dose dependently decrease lever pressing and increase the consumption of free feeding chow on the concurrent FR5/chow procedure.

Experiment 1: *Systemic administration of reserpine on the concurrent FR5/chow feeding procedure: a dose response curve*

Rats were trained on the concurrent FR5/chow feeding procedure as described below. The following treatments were used: 0.3% tartaric acid vehicle, 0.625mg/kg reserpine IP (90 min before testing), 0.75mg/kg reserpine (90 min before testing), and 1.0mg/kg reserpine (90 min before testing). Experiment 1 used a within-groups design; with all rats receiving all drug treatments in their particular experiment in a randomly varied order (one treatment per week).

Experiment 2: *Systemic administration of tetrabenazine on the concurrent FR5/chow feeding procedure: a dose response curve*

Rats were trained on the concurrent FR5/chow feeding procedure as described below. The following treatments were used: acidified vehicle, 0.5mg/kg TBZ IP (90 min before testing) and 1.0mg/kg TBZ (90 min before testing). Experiment 1 used a within-groups design; with all rats receiving all drug treatments in their particular experimental in a randomly varied order (one treatment per week).

V. RESULTS

Tetrabenazine produced a consistent behavioral shift from lever pressing to free feeding chow consumption in the first week of testing (Fig. 1). At week one, there was a significant effect of drug treatment on decreasing lever pressing at 0.5mg/kg [$F(2, 26) = 86.643$; $P < 0.05$] and 1.0mg/kg [$F(2, 26) = 43.653$; $P < 0.05$] doses compared to the vehicle. There was also a significant effect of the tetrabenazine treatment on chow intake at 1.0mg/kg dose [$F(2,26) = 22.235$; $P < 0.05$].

In week two, the administration of tetrabenazine maintained the significant shift in lever pressing to chow consumptions at the 1.0mg/kg dose (Fig. 2). Week two, produced a significant effect of the drug treatment on decreasing lever pressing at 1.0mg/kg [$F(2,26) = 86.643$; $P < 0.05$]. There was also a significant effect of the

tetrabenazine treatment on chow intake at 1.0mg/kg [$F(2,26) = 21.327$; $P < 0.05$]. The dose of 0.5mg/kg TBZ no longer produced significant results at week two.

In week three, the administration of tetrabenazine maintained the significant shift in lever pressing to chow consumptions at the 1.0mg/kg dose (Fig. 3). Week three, produced a significant effect of the drug treatment on decreasing lever pressing at 1.0mg/kg [$F(2,26) = 33.641$; $P < 0.05$]. There was also a significant effect of the tetrabenazine treatment on chow intake at 1.0mg/kg [$F(2,26) = 13.911$; $P < 0.05$].

The administration of 0.75mg/kg dose of reserpine suppressed lever pressing with repeated use as compared to week one, but had no significant effect of chow intake across the three week experiment (Fig. 4). There was a significant decrease in lever pressing at week two and three ($P < 0.05$) compared to week one.

VI. DISCUSSION

Motivation is a complex process, and several behavioral approaches have been used to study the impact of drugs administration on performance in effort-related choice procedures. Under these conditions, animals were able to select between two reinforcers that could be obtained through distinct instrumental behaviors (Salamone 2010b; Salamone et al. 1994). In the present study, the rats responded on a concurrent FR5/chow choice task. The monoamine depletion as a result of TBZ administration produced a significant alteration in the relative allocation of behavior, quantified by a decrease in lever pressing, but increase in chow consumption (Fig. 1-3). The present results are consistent with previous studies that determined increased ratio requirements on operant tasks increases the suppressant effect of DA depletions (Salamone et al. 1991, 2001; Ishiwari et al. 2004a). Additionally, previous studies have also supported that modest

doses of DA antagonists, with varying degrees of selectivity, all decrease lever pressing and increase chow intake in rats responding to this same task (Salamone et al. 1991). The findings from the present study are consistent with the hypothesis that pharmacological manipulations that disrupt monoamine storage (i.e. TBZ) can produce effort-related choice impairments, with these behavioral shifts directly related to the actions on nucleus accumbens DA (Salamone et al. 2006, 2007, 2010; Meyer et al. 2011). TBZ reversibly binds with a high affinity to the vesicular monoamine transporter-2 (VMAT-2) (Meyer et al. 2011; Guay 2010). In so doing, TBZ effectively inhibits vehicular storage of cytosolic monoamines, including serotonin, norepinephrine, and dopamine. Although reserpine and TBZ work through a similar mechanism to inhibit monoamine storage, they have different mechanisms of action. Reserpine serves as an irreversible inhibitor of both VMAT-1 and VMAT-2 (Peter et al. 1996). TBZ and reserpine produced effort-related impairments on the concurrent FR5 procedure whereby lever pressing was reduced and chow consumption increased. However, the effect of reserpine sensitizes with repeated administration, and does not provide stable baseline for repeated measures studies. Further, the motor effects of reserpine become severe with repeated administration, as rats show akinesia, incoordination, catalepsy, and tremulous jaw movements (Huang 2004).

This may be related to the difference in the mechanism of action of reserpine as compared to TBZ. It is evident then that TBZ is more consistently effective than reserpine at producing alterations in effort-related choice behavior.

Is it indicated then that these basic animal studies are potentially relevant for understanding the effort-related dysfunctions in. There also is a striking similarity between the brain circuitry involved in effort-related functions in rats, and the systems

thought to be involved in energy-related dysfunction in depression (Salamone et al. 2006, 2007, 2010; Treadway and Zald 2010). This line of evidence suggests there is a degree of efficacy with which TBZ can induce effort-based dysfunctions in rodent models that closely mirror the depression-like symptoms affecting energy acquisition in humans. Future studies will assess the ability of several other conditions that are related to depression, such as pro-inflammatory cytokines, to induce effort-related dysfunctions in rats. Preliminary research indicates that an increase in pro-inflammatory cytokines has been associated with decreases in insulin and glucocorticoid receptor sensitivity, which promotes metabolic and neuroendocrine disruption (Weisler-Frank et al. 2005; Maletic 2007). Symptomatically, these disruptions may be experienced as the fatigue that is associated with decreased behavioral activation experienced with depression. (Tsigos and Chrousos 2002; Maletic 2007). In addition, a TBZ animal model of depression can determine if these dysfunctions are sensitive to experimental and putative pharmacological treatments, such as the adenosine A_{2A} antagonist MSX-3 and bupropion respectively.

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VIII. FIGURE CAPTIONS

Figure 1. The effects of tetrabenazine to dose-dependently induce changes in behavioral performance on the concurrent lever pressing/chow feeding procedure in week one. Rats received IP injections of an acidified vehicle (VEH), 0.5mg/kg tetrabenazine (0.5 TBZ), or 1.0mg/kg tetrabenazine (1.0 TBZ). (A) Mean (\pm SEM) number of lever presses (FR5 schedule during the 30 minutes session). (B) Mean (\pm SEM) gram quantity of chow intake. TBZ significantly suppressed lever pressing activity as compared to vehicle at 0.5mg/kg ($*p<0.05$) and 1.0mg/kg ($*p<0.05$). TBZ significantly increased chow consumption at a dose of 1.0mg/kg ($*p<0.05$).

Figure 2. The effects of tetrabenazine to dose-dependently induce changes in behavioral performance on the concurrent lever pressing/chow feeding procedure in week two. Rats received IP injections of an acidified vehicle (VEH), 0.5mg/kg tetrabenazine (0.5 TBZ), or 1.0mg/kg tetrabenazine (1.0 TBZ). (A) Mean (\pm SEM) number of lever presses (FR5 schedule during the 30 minutes session). (B) Mean (\pm SEM) gram quantity of chow intake. TBZ significantly suppressed lever pressing activity as compared to vehicle at 1.0mg/kg ($*p<0.05$). TBZ significantly increased chow consumption at a dose of 1.0mg/kg ($*p<0.05$).

Figure 3. The effects of tetrabenazine to dose-dependently induce changes in behavioral performance on the concurrent lever pressing/chow feeding procedure in week three. Rats received IP injections of an acidified vehicle (VEH), 0.5mg/kg tetrabenazine (0.5 TBZ), or 1.0mg/kg tetrabenazine (1.0 TBZ). (A) Mean (\pm SEM) number of lever presses (FR5 schedule during the 30 minutes session). (B) Mean (\pm SEM) gram quantity of chow intake. TBZ significantly suppressed lever pressing activity as compared to vehicle at 1.0mg/kg ($*p<0.05$). TBZ significantly increased chow consumption at a dose of 1.0mg/kg ($*p<0.05$).

Figure 4. The effects of reserpine to induce changes in behavioral performance on the concurrent lever pressing/chow feeding procedure, at 0.75mg/kg dose across weeks. (A) Mean (\pm SEM) number of lever presses (FR5 schedule during the 30 minutes session). (B) Mean (\pm SEM) gram quantity of chow intake. Reserpine significantly suppressed lever pressing activity at weeks two and three ($*p<0.05$). Reserpine failed to produce significant increases in chow intake.

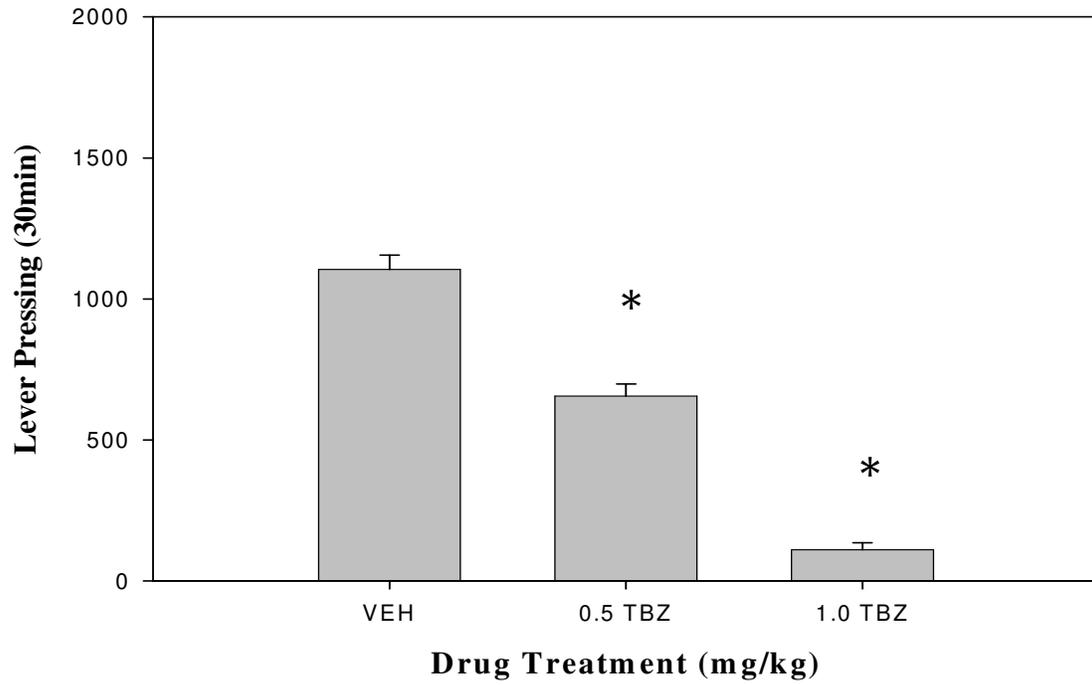
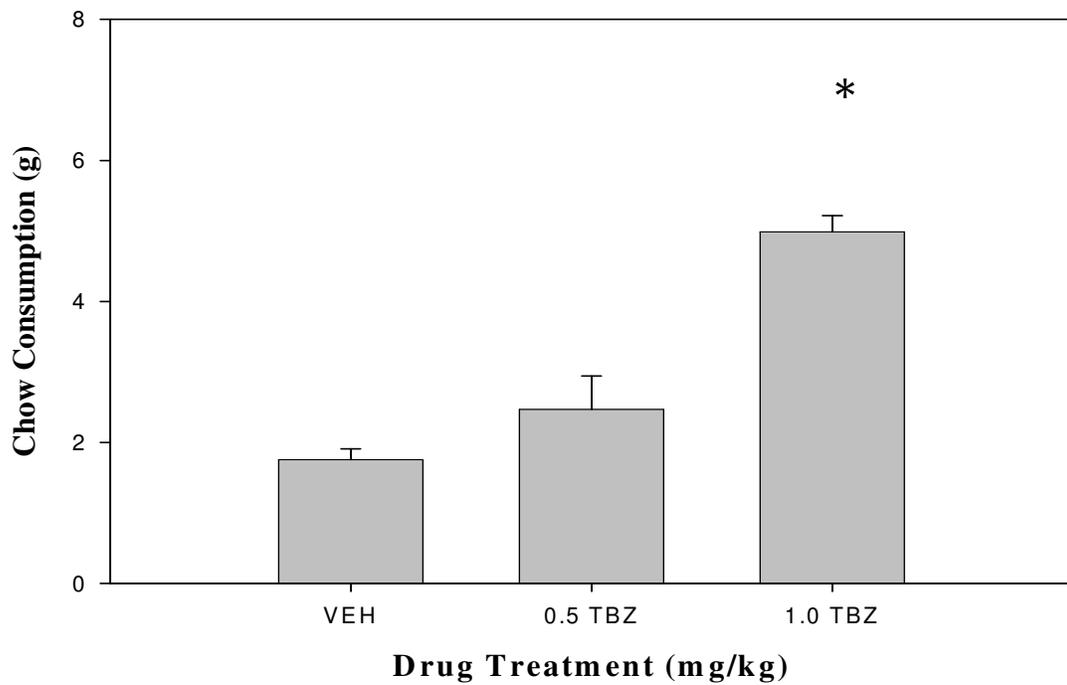
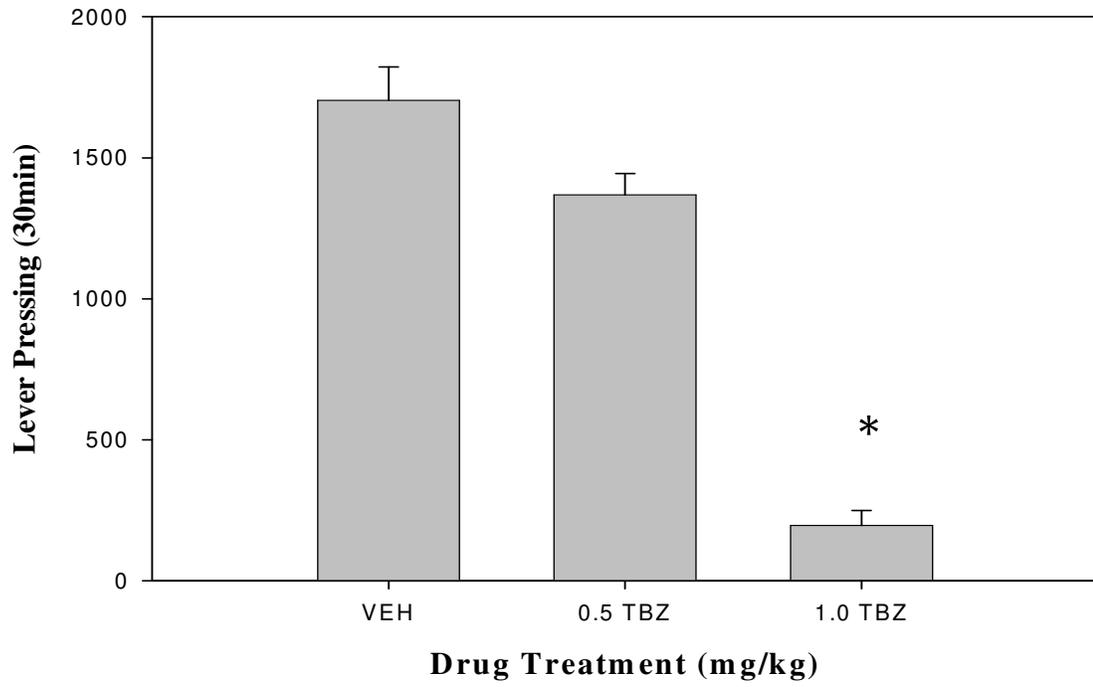
IX. FIGURES**Figure 1.** Week 1 dose-dependent behavioral effects of tetrabenazine**A.****B.**

Figure 2. Week 2 dose-dependent behavioral effects of tetrabenazine.

A.



B.

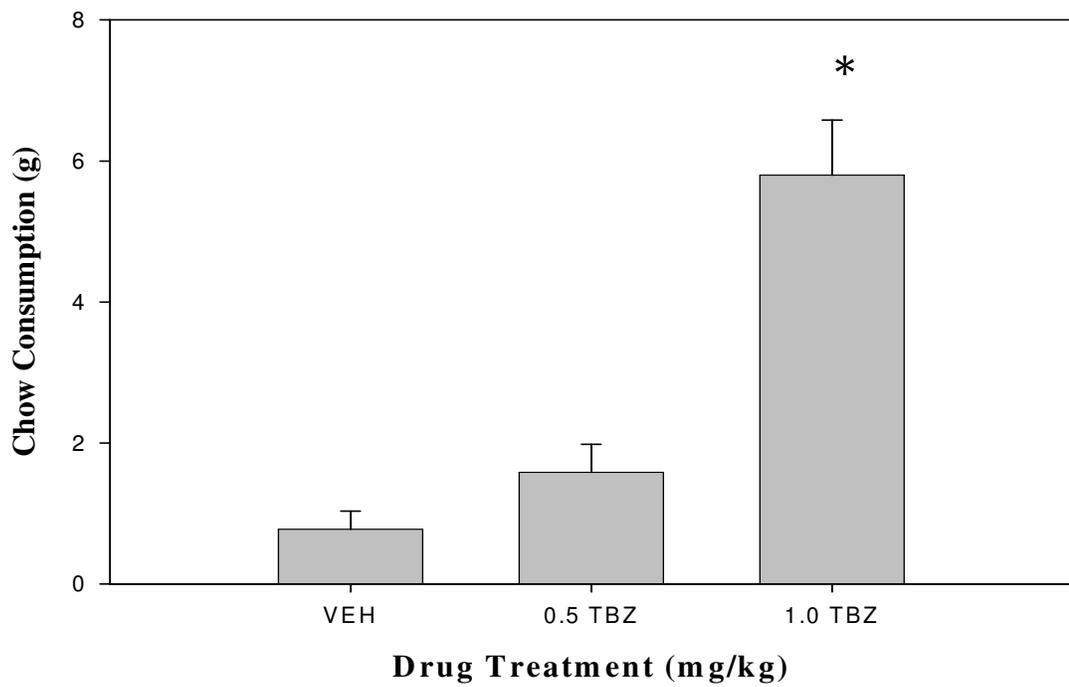
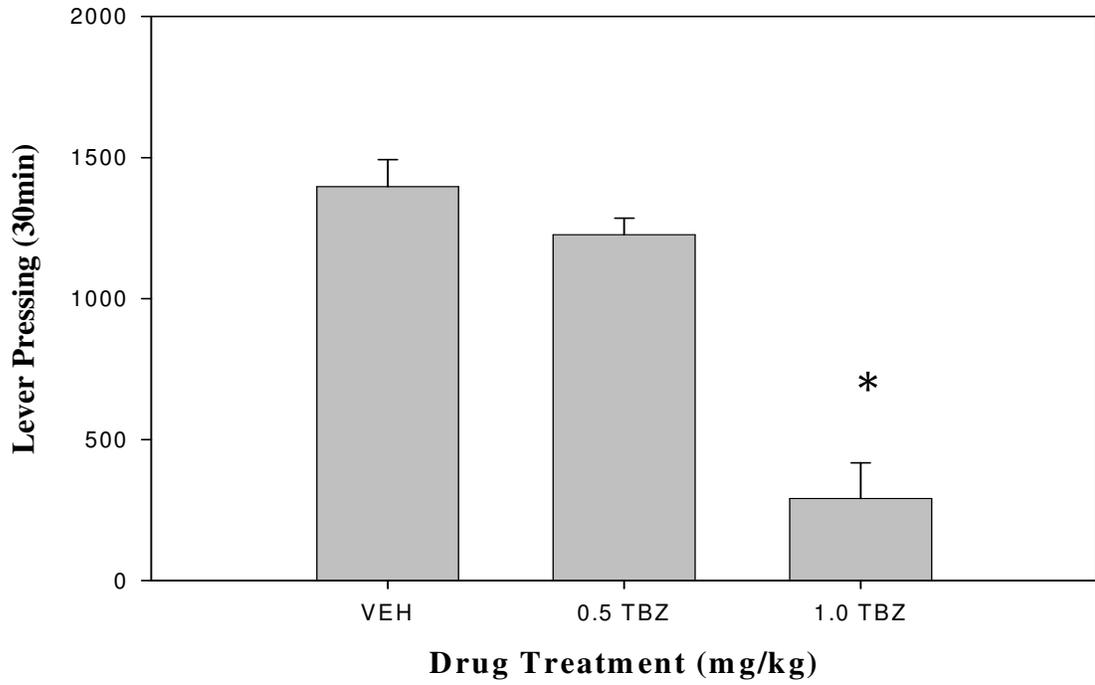


Figure 3. Week 3 dose-dependent behavioral effects of tetrabenazine.

A.



B.

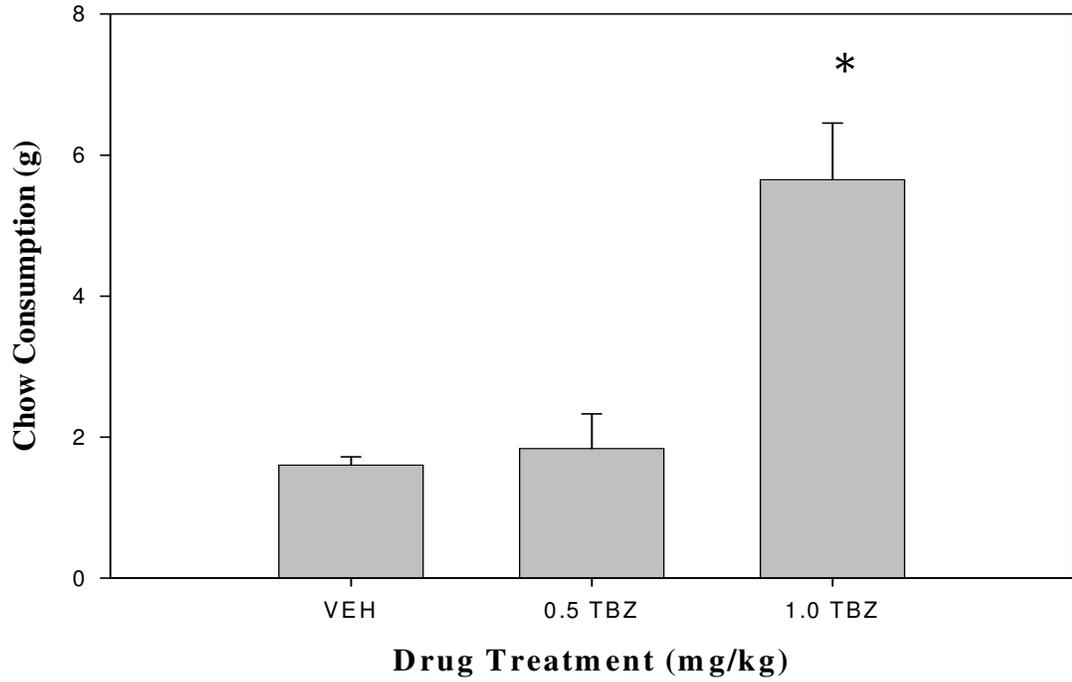
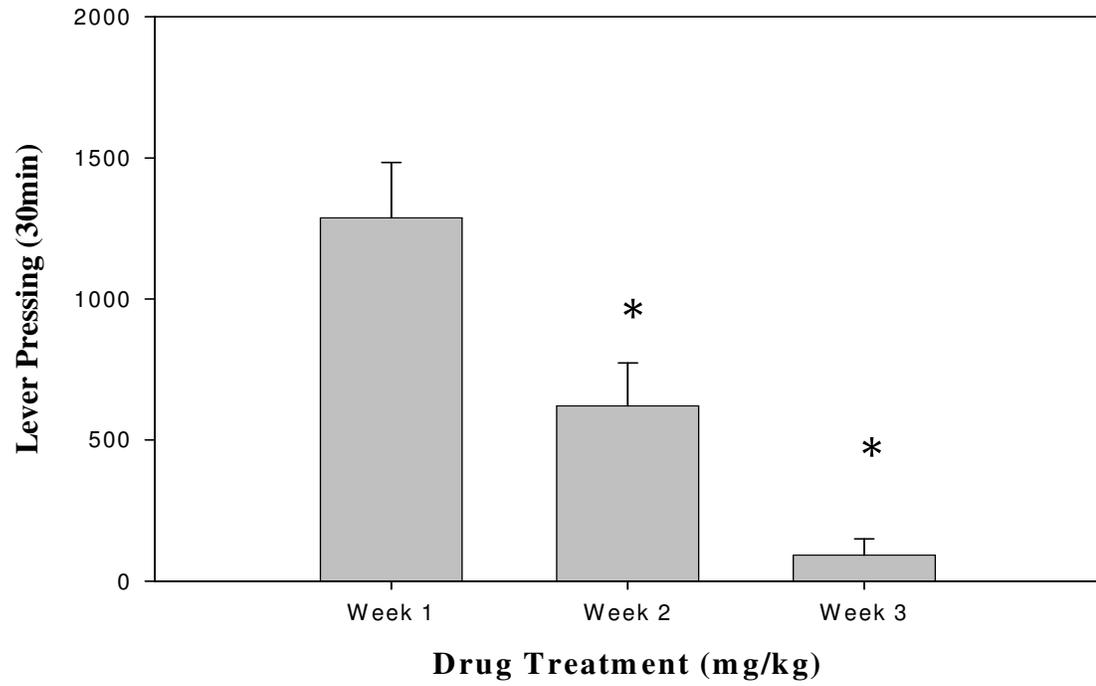


Figure 4. Dose-dependent behavioral effects of reserpine.

A.



B.

