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Differential Effects Of The MAO Inhibitors Deprenyl, Moclobemide And Pargyline on Effort- Related Choice Behavior

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Differential Effects Of The MAO Inhibitors Deprenyl, Moclobemide And Pargyline On
Effort-Related Choice Behavior

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Master of Science Thesis

Differential Effects Of The MAO Inhibitors Deprenyl, Moclobemide And Pargyline On
Effort-Related Choice Behavior

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Chapter 1: General Introduction

1.1 Motivated Behavior; effort-related processes

Although motivation has been defined in different ways, a useful working definition is to state that motivation is ‘the set of processes through which organisms regulate the probability, proximity and availability of stimuli’ (Salamone 1992; Salamone and Correa, 2002). The survival of organisms depends upon their ability to seek and obtain access to some stimuli, while avoiding others. Furthermore, effort-related motivational processes are crucial for the success of an organism in being able to overcome obstacles in order to gain access to stimuli like food, water and sex, or to get away from predators and other harmful situations. The effort or work an organism has to allocate to obtain or to avoid a stimuli can differ substantially, and these requirements can vary along several distinct dimensions (e.g. numbers of responses, force or distance; Collier and Jennings, 1969; Aberman and Salamone, 1999; Ishiwari et al., 2004a; van den Bos et al., 2006).

1.2 Neuroanatomy and neuropharmacology of effort-related choice behavior

In the last few years there has been an increase of research focused on motivation, including studies specifically focusing upon effort-related processes (i.e, effort-decision making, cost-benefit analysis, work-requirements, among others) and their underlying neural mechanisms. One important reason for this increased emphasis is the evidence demonstrating that effort-related symptoms are seen in various psychiatric disorders. For instance, clinicians have emphasized symptoms like psychomotor slowing, apathy, anergia and fatigue in major depression, Parkinsonism, multiple sclerosis and other

disorders (Tylee et al. 1999; Stahl 2002; Demyttenaere et al. 2005, Salamone et al. 2006; Treadway and Zald 2011). Modeling effort-related motivational dysfunctions in animals had provided details about the neural circuitry, neurotransmitters and neuromodulators involved in such processes. For instance, several studies has linked effort-related dysfunctions with the interfering of dopamine transmission, specifically in the nucleus accumbens (Salamone 1986, 1988; McCullough and Salamone 1992, Salamone et al., 1991, 1997, 2007, 2012), which is one of the major terminal fields for the mesolimbic pathway.

The mesolimbic pathway is one of four DA pathways in the brain; mesolimbic DA neurons go from the ventral tegmental area (VTA) to medial neostriatum, olfactory tubercle, and the nucleus accumbens. Caudate and putamen collectively are known as the neostriatum, and nucleus accumbens also is considered to be part of the striatal complex. Thus, neostriatum is sometimes referred to as “dorsal striatum”, while nucleus accumbens and olfactory tubercle are sometimes referred to as “ventral striatum”. The dorsal division of the basal ganglia is primary associated with motor whereas the ventral is more related to “limbic” (i.e. motivational) functions (Tepper et al, 2007). The accumbens is the largest component of the ventral striatum, and it is an important target of the mesolimbic dopaminergic pathway; thus, studies have focused in transmission and interference with DA and its involvement in behavior. In rats, increased activity induced by scheduled presentation of food pellets is accompanied by increases in accumbens DA release, and is reduced by DA antagonism and accumbens DA depletions (Salamone 1986, 1988; McCullough and Salamone 1992). Furthermore, in effort-related decision making tasks in which animals have the choice between the selection of high effort

instrumental behaviors that lead to more highly valued reinforcers, vs. low effort/low value alternatives, DA antagonism or interference with accumbens DA alters response allocation (Salamone et al., 1991, 1997, 2007, 2012). Animals with impaired DA transmission shift their response towards the selection of low effort alternatives, rather than spending more effort for the highly valued reinforcer.

Several studies have also investigated other structures (e.g. amygdala, anterior cingulate cortex, ventral pallidum) and neurotransmitters (e.g. GABA, adenosine, Ach, 5-HT) and found that these areas also are involved in regulating effort-related aspects of motivation (Asadi et al., 2009; Denk et al., 2005; Farrar et al., 2008; Floresco et al., 2007, 2008; Hauber and Sommer, 2009; Mingote et al., 2008; Schweimer and Hauber, 2006; Walton et al., 2002, 2003). Connections exist between anterior cingulate cortex (ACC) and striatal areas, including the nucleus accumbens. Furthermore, the accumbens projects back to the ACC indirectly through its connections with ventral pallidum, which in turn projects to the mediodorsal (Ongur and Price, 2000; Ray and Price, 1993; Yeterian and Pandya, 1988) and anteroventral nuclei of the thalamus (Xiaob and Barbas, 2004; Zikopoulos and Barbas, 2007). These regions have several connections to other structures, including DA-enriched area in the VTA (Baleydier and Mauguiere, 1980; Floresco and Ghods-Sharifi, 2007; O'Donnell and Grace, 1995).

In rats, studies employing T-maze task developed by Salamone et al. (1994a) showed that DA depletion in the ACC-NAc circuit leads to changes in effort-related decision-making. In the T-maze task rats had a choice between climbing a barrier to obtain a large reward in one arm vs. running into the other arm without any barrier in order to obtain a small reward. Under control or baseline conditions, rats will choose the

arm with the highest valued reinforcer even though they have to spend more effort by climbing the barrier compared to the low effort/low value alternative. However, lesions to the ACC (Schweimer and Hauber, 2005; Walton et al., 2003; or NAc (Hauber and Sommer, 2009), disrupting ACC-NAc connection (Hauber and Sommer, 2009) and DA depletion or blockade in the ACC (Schweimer and Hauber, 2006; Schweimer et al., 2005) or NAc (Cousins et al., 1996; Salamone, 1994; Salamone et al., 2003) dramatically biased the rats towards the low effort/low value alternative. It is important to note that while lesions to the ACC impair effort-related processes similarly as NAc DA antagonism or DA depletions in T-maze task, this is not seen when animals are tested with an operant choice task (Schweimer and Hauber, 2005).

1.3 Tetrabenzine; a pharmacological model of the motivational symptoms of depression

Further understanding of the neurochemistry of effort-related processes has been gained by the use of pharmacology agents like tetrabenzine (TBZ) in combination with behavioral paradigms that assess effort-related processes and decision making. TBZ deplete monoamines by inhibiting vesicular monoamine transport (VMAT), selectively blocking VMAT-2, and its greatest impact is upon striatal DA (Pettibone et al., 1984; Tanra et al., 1995; Nunes et al., 2013; Randall et al., 2014). In Huntington's disease (HD), TBZ is often used to treat the hyperkinetic symptoms (e.g., chorea) that accompany this disease. Although symptoms of depression are common in HD, these can be further aggravated by the use of TBZ (Frank et al., 2014). Experiments done by Nunes et al. (2013) have shown that administration of 0.75mg/kg and 1.0 mg/kg TBZ in rats trained on the concurrent fixed ratio 5 (FR5)/chow feeding choice task leads to a shift in their response allocation; they reduce selection of the higher effort option (lever pressing) and increase selection of chow

intake. Moreover, the effort-related dysfunctions produced by TBZ were attenuated by co-administration of the adenosine A2A antagonist MSX-3 and the catecholamine uptake blocker bupropion, which is a commonly used antidepressant (Nunes et al. 2013). A follow up study by Randall et al. (2014) using the concurrent progressive ratio (PROG)/choice feeding task found that an administration of 0.5, 0.75 and 1.0mg/kg TBZ was able to shift behavioral response biasing the animals toward the lower effort/lower reward option (i.e., reduced lever pressing and increased chow intake). Results of this experiment seem to indicate that lower dose of TBZ can produce the shift in behavior as a result of an increased response demand. Furthermore, as seen in Nunes et al. (2013) study, MSX-3 and bupropion were able to attenuate the effects of TBZ but this time in a more demanding task like the PROG/choice feeding task. Taking these results together, it validates the hypothesis that effort-related choice behavior can be impaired by administration of TBZ, and that some of these motivational impairments can be attenuated by co-administration of putative or known antidepressants. Moreover, these results, as well as those of Yohn et al. (2015a) with the T-maze barrier task, suggest that the effort-related impairments induced by TBZ can be used for the assessment of drugs for their potential utility as treatments for effort-related dysfunction.

1.4 Monoamine Oxidase Inhibitors: history, discovery and downfall

Monoamine oxidase (MAO), a flavin-adenosine-dinucleotide (FAD)-containing enzyme, is located primarily on mitochondrial membranes (Denney & Denney 1985). The enzyme is active in different tissues, including organs (i.e., heart, liver, blood vessels) and the brain (Chen and Weyler 1988; Markoglou et al., 2004 ; Rodríguez et al., 2001). MAO is responsible for the oxidative deamination of primary, secondary and

tertiary amines, including the monoamines DA, noradrenalin (NA) and serotonin (5-HT; Markoglou et al., 2004). Both enzymes have specific and overlapping preferences in oxidizing amines. For instance, MAO-A preferentially oxidizes 5-HT, NA and epinephrine while MAO-B enzyme preferentially oxidizes phenethylamine and benzylamine. However, both enzymes oxidize DA (Cashman, 1995). The structures, functions, and mechanisms of action of the different isozymes of MAO have been the focus of extensive investigations mainly due to its involvement in psychiatric and neurological disorders, specifically depression and Parkinson (Edmondson et al., 2007).

The discovery of MAO inhibitors as a possible treatment for depression was accidental. Emil Fischer discovered phenylhydrazine in 1874 while working in the laboratory of Adolfo von Baeyer in Strasbourg (Lichtenthaler, 2002). From this discovery, Hans Meyer and Josef Malley, of the German Charles-Ferdinand University (Prague), synthesized isonicotinyl hydrazine (Meller and Malley, 1912). It was not till the early 1950s, 40 years after Meller and Malley synthesis of isonicotinyl hydrazine (isoniazid), that the compound was considered important due to its efficacy in tuberculosis (Grunberg and Schnitzer, 1952; Sneader, 1985; Sneader, 2005). However, before the discovery of the antitubercular properties of hydrazines, in 1928 Mary Bernheim for the first time described an enzyme capable of oxidizing biogenic amines in the liver (Hare, 1928). Later on, this same enzyme was named monoamine-oxidase by two groups of researchers; Herman Blaschko and Derek Richter (Blaschko and Richter 1937) at the Physiology Department of Cambridge University and Caecilia E. Pugh and Juda H. Quastel (Pugh and Quastel, 1937), at the Biochemical Laboratory of Cardiff City Mental Hospital (López-Muñoz and Alamo, 2009). Further studies looking at alternative

treatments for tuberculosis brought different derivatives of isoniazid, including an isopropyl derivative called iproniazid (1-isonicotinyl-2-isopropyl-hydrazine). Erns Albert Zeller observed for the first time inhibition of MAO with the use of iproniazid (Zellert et al., 1952). Moreover, iproniazid proved to have a superior tuberculostatic activity compared to isoniazid in humans (Fox and Gibas, 1953). The discovery of the MAO inhibitory properties of isoniazid, together with the amine hypothesis of depression proposed a year later (Freis, 1954), made iproniazid an attractive drug for treating mood disorders like depression. Iproniazid showed what was reported to be a remarkable antidepressant action; unfortunately, its clinical relevance was short due to serious side effects such as liver toxicity (Youdim and Bakhle, 2006). This side effect was the product of the hydrazine structure and was resolved by the development and use of other MAO's inhibitors, specifically tranylcypromine (Youdim et al., 1988). This new wave of MAO inhibitors also brought another problem; the "cheese effect". Cheese reaction or "cheese effect" is induced by tyramine and other indirectly acting sympathomimetic amines, such as tyramine, which are present in several foods and drinks, including some cheeses, beers and wines. Under normal circumstances, MAO enzymes metabolize tyramine and related amines in the gut wall and the liver, preventing them from entering the systemic circulation (Blackwell, 1963, 1964, 1965; Youdim and Bakhle, 2006; Rao and Yeragani, 2009). Thus, inhibiting these enzymes will prevent these amines from being metabolizing, leading to their accumulation and entrance into systemic circulation. As a result, increased tyramine levels induce a significant release of noradrenaline from peripheral adrenergic neurons (Finberg et al., 1981; Finberg and Tenne, 1982). In turn, this increased released of noradrenaline will cause a severe hypertensive response that can be

fatal (Youdim and Bakhle, 2006). Serious side effects like liver toxicity due to the hydrazine structure, and the cheese effect, slowed down the use of MAO inhibitors as the primary treatment for depression. This prompted the search of new alternative drugs like uptake inhibitors; tricyclic antidepressants (TCAs), and 5-HT selective re-uptake inhibitors (SSRI), like Prozac (Youdim and Bakhle, 2006). However, in basic research, there was still interest in understanding the underlying mechanisms of the MAO inhibitors.

1.5 Monoamine oxidase enzymes isoforms and brain location

Research done with MAO inhibitors has been a key factor in coming to understand the functions of MAO. For example, research on MAO inhibitors led to the discovery that MAO enzymes existed in two isoforms; MAO-A and MAO-B. Experiments by Johnston (1968) showed that the propargyl inhibitor clorgyline had preference towards the inhibition of the deamination of NA and 5-HT. At this same concentration, it only slightly inhibited the deamination of benzylamine (BZ) and 2-phenylethylamine (PE). Meanwhile, experiments using another MAO-inhibitor, deprenyl (selegiline) showed that this compound selectively inhibited the deamination of BZ and PE at concentrations that only slightly reduced the deamination of NA and 5-HT (Knoll and Magyar, 1972). Hence, the isoform, which showed greatest activity towards 5-HT and NA was termed MAO-A, while the isoform showing greatest activity towards BZ and PE was termed MAO-B (Finberg, 2014). The classic MAOIs (iproniazid, phenelzine and tranylcypromine) irreversibly inhibited both isoenzymes (López-Muñoz and Alamo, 2009). However, the “cheese reaction” was found to be due to the inhibition of MAO-A. MAO-A is the major enzyme form associated with sympathetic neurons; inhibition of the

enzyme causes potentiation of the sympathomimetic effects of tyramine whereas selective inhibition of MAO-B does not (Finberg and Tenne, 1982; Finberg and Gillman, 2011).

In order to further understand the pharmacology potential that MAO-inhibitors have for treating psychiatric and neurological disorders, it is important to understand where MAO is located in the brain. The links made between specific MAO isoform and particular neuronal types or glial cells have been possible by using methods such as immunohistochemistry, enzyme histochemistry, radioligand binding, and other techniques. An early study with rats found evidence of MAO-B immunoreactivity in the raphe and in the hypothalamus, specifically in serotonergic cells (Levit et al, 1982). Localization of MAO-B to serotonergic neurons is controversial since 5-HT behaves as a selective substrate of MAO-A, both in vitro and in vivo (Finberg, 2014). Furthermore, there is evidence that MAO-A and B mRNA changes during development, which gives some insight as to why MAO-B can be found in 5-HT neurons. A study done with mice showed that embryonic and early-postnatal raphe neurons express both MAO-A and MAO-B, but the MAO-A component disappears during development (Vitalis et al., 2002). It has been hypothesized that the disappearance of the MAO-A expression in adulthood is due to the trafficking of mitochondria expressing MAO-A to axon terminals (Denney and Denney, 1985), however currently there is no experimental evidence of this trafficking (Fingberg, 2014). While it is still unknown why 5-HT cells and adjacent areas contain MAO-B, since it has low affinity for 5-HT, it seems unlikely that this enzyme could contribute significant changes in physiological levels of 5-HT in these cells. Meanwhile, if high levels of 5-HT were present in these serotonergic cells, these

differences in substrates affinity may not be significant (Levitt et al., 1982). In this situation, MAO-B could be important in metabolizing the substrates in these cells. Although Levit and colleagues (Levit et al, 1986) failed to detect MAO-B activity in catecholamine-rich areas, and in turn concluded that such enzymes have no important role in affecting transmitter levels in these neurons, other studies yielded different results. For example, a study using MAO-A deficient transgenic mice and deprenyl (DEP) showed significant MAO-B activity in the striatal structures, the nucleus accumbens, and in particular its dorsal shell (Ikemoto, 1997). The majority of cells found in the striatum are medium spiny neurons, which express D1 and D2 receptors. These two receptors are associated with distinct G proteins, which exert different intracellular signaling pathways leading to different biochemical responses and in turn behavioral outcome when activated (Calabresi et al, 2014). Another study using PET and MRI and monkeys showed MAO-B activity in many catecholamine-rich areas of the brain An injection of fluororasagiline (analogue of rasagline) radioligand revealed significant brain uptake by MAO enzymes in the striatum. Furthermore, this MAO enzymatic activity was halted after pretreatment of DEP (0.5mg/kg) by intravenous administration (Nag et al.,2013) .

Another study with Sprague- Dawley rats and Macaca monkeys found evidence of MAO-A immunoreactivity in large locus coeruleus neurons, in pallidostriatum neurons and in a few neurons in the substantia nigra pars reticularis lateralis dopaminergic neurons (Westlund et al., 1993). Moreover, no significant MAO activity was found in this area using histochemical methods (Arai et al., 1988). These results are surprising considering that microdialysis experiments have suggested that DA is metabolized by MAO-A in the rat striatum in vivo (Wachtel and Abercrombie, 1994), however, this

study employed only a single, low dose of DEP (1mg./kg) to test for the effects of MAO-B inhibition. A more recent study with squirrel monkeys found that treatment with L-Dopa preceded by clorgyline (MAO-A) or DEP (MAO-B) counteracted the increase in the DOPAC and HVA levels and DOPAC/DA ratio induced by L-DOPA in the substantia nigra (Di Monte et al., 1996). The reduction of DA metabolites is evidence of MAO activity in the substantia nigra. A possible explanation of the negative finding in the histochemical study could have been that the isoform localized on axon terminals may be different from that in perikarya and dendrites, if different populations of mitochondria are transported along the axons (Arai et al., 2002; Denney and Denney, 1985; Fingberg, 2014). Furthermore, if the MAO isoforms were located in the axonal varicosities, it would be difficult to identify them by using the light microscope together with colorimetric or fluorescent markers (Fingberg, 2014). In addition, there could be problems with the suitability of the antibodies used for some of the studies, because variation in antibody selectivity can affect the findings of immunohistochemical studies.

1.6 Clinical significance of MAO-Inhibitors

A wide range of MAO inhibitors (MAO-Is) have been available for quite some time and their therapeutic effect and value has been tested in a wide variety of disorders including neurodegenerative disorders, ageing and mood disorders like depression (Youdim, 2006; Youdim and Bahkle, 2006; Lopez-Munoz & Alamo 2009; Finberg, 2014). Unfortunately, because of the discovery of the “cheese effect” due to MAO-A inhibition of enzymatic activity in the gut, MAO-I were soon replaced by other types of antidepressant like the commonly prescribed SSRI's. However, there is evidence that there are individual differences in the extent to which the “cheese effect” is observed. For

instance, a study done with MDD patients showed that some individuals were sensitive to the aversive effects of the MAO-I tranylcypromine that were independent of the dose used (McGrath et al., 2006). Surprisingly, in another study with refractory depression in elderly patients (n=16), people responded satisfactory to a 60 mg/day of oral DEP with no apparent aversive side effects (Sunderland et al., 1994). Meanwhile, the discovery of the MAO-B enzyme and the design of MAO-A inhibitors that are reversible led to the reevaluation of the use of these drugs in depression. In a study comparing the effectiveness of imipramine a tricyclic antidepressant (TCA) and the reversible MAO-A moclobemide (MCL) in Indian patients (n=61), both drugs were effective in improving depressive symptoms given by the decrease in scores on the Hamilton Depression Rating Scale (HDRS) and the Montgomery-Asberg Depression Scale (MADRS). Furthermore, patients reported less side effects (eg., dry mouth, constipation, blurred vision) with MCL compared to imipramine (Avasthi et al., 2005). Another study tested whenever or not MCL was effective in treating elderly patients with diagnosis of major depression and or dementia. Results revealed that MCL produced significantly greater improvements in both depressed/demented and depressed group when compared to placebo as measured by the decrease score in the HDRS (Roth et al., 1996). MAO-B also has been used effectively to treat depression, though there have been some controversies in this research. Some investigators have argued that MAO-B inhibitors are void of antidepressant effects (Murphy et al., 1979; Youdim & Finberg, 1983; Finberg, 2014) and that the therapeutic effects seen are due to the loss of binding specificity that happen when using higher doses and as a result both MAO-A and B enzymes are inhibited (Mann et al, 1989). One study found that 5.0 mg/kg of DEP administered orally inhibited 92% of

MAO-B and 5% MAO-A in the brain. However, other studies reported that 5.0 mg/kg administered subcutaneously inhibited 99% MAO-B and 85% MAO-A (Barett et al., 1996b; Feiger et al., 2006; Wecker et al., 2003). Moreover, a recent PET scan study in humans published by Fowler et al. (2015) found that 10.0 mg/kg dose of Zydys DEP (i.e., an orally disintegrating formulation) significantly inhibited 36% of MAO-A activity in the brain. Meanwhile, 2.5 mg/kg, 5.0 mg/kg and 6.0 mg/24h EMSAM (DEP transdermal) was not enough to inhibit significantly MAO-A activity. It is important to note that while very high doses of DEP and some administration routes could potentially inhibit MAO-A enzymatic activity in animal models and in human studies, this does not mean that inhibition of MAO-B is void of antidepressant effects. A case study by Higuchi et al., (2005) found that a dose of 7.5mg of DEP was able to improve the depressive mood and hypobulia in a patient with severe refractory depression. Moreover, EMSAM have shown antidepressant effects at low dose of 6.0 mg after 24 hours of administration (Morgan et al. 2007). Interestingly, another case study by Ashton et al., 2008 found that a high dose of 18mg improved significantly the symptoms of depression without apparent side effects.

MAO-Is also have been used effectively as neuroprotectants in lesions studies. The nonselective MAO-I pargyline (PAR) has shown neuroprotection against the neurotoxin MPTP, by preventing DA (DA) depletion and other metabolites in the striatum in rats and primates (Langston et al., 1984; Bazzu et al., 2013). MAO-B inhibitors like DEP and rasagiline also have been effective in ameliorating some symptoms of Parkinsonism in animal models and in humans (Pelusio, 1993; Parkinson Study Group, 2002; Ebadi et al., 2002; Amit & Youdim; 2004; Waters et al., 2004;

Rascol et al., 2005).

Another concern with the use of MAO-I is the serotonin syndrome. The serotonin syndrome occurs when serotonin-promoting drugs are used in combination with MAO-I which might lead to an excess of serotonin. In turn, this excess can lead to hyperthermia, rigidity, myoclonus and in some cases death (Stembach, 1991) However, serotonin syndrome is extremely rare (Asnis and Henderson, 2014). Thus, while the use of MAO-Is is restricted to some degree, their benefits in treating many disorders including depression and parkinsonism are evident, they are heavily underused and as a result more basic research has to be done. Thus far, there have been no published studies on the effects of MAO inhibitors on effort-related decision making in humans. Understanding the effects of MAO inhibition on effort-related motivational dysfunctions like anergia and fatigue could lead to a deeper understanding of benefits that might have been overlooked in previous clinical research.

1.7 Overview of experiments

The present studies focused on the ability of MAO inhibitors to ameliorate the effort-related impairments induced by the VMAT-2 inhibitor TBZ using the concurrent FR5/chow feeding choice task. Experiment 1 investigated the ability of MCL, a reversible MAO-A inhibitor, to attenuate the effects of TBZ. Although there is substantial evidence supporting MAO-A inhibitor MCL as an effective antidepressant, we hypothesized that due to the high preference of MAO-A enzyme to 5-HT its inhibition will dramatically increase extracellular levels of 5-HT, potentially having negative effects in motivated behavior similar to those seen with SSRI's like fluoxetine (Yohn et al.

2015c). In previous studies done in our laboratory, the serotonin reuptake inhibitor (SSRI) fluoxetine was unable to attenuate TBZ effects on motivation. Furthermore, fluoxetine by itself was enough to dramatically reduce lever pressing without affecting chow consumption (Yohn et al. 2015c). These results are consistent with several clinical studies that indicate the relative ineffectiveness of fluoxetine and other SERT inhibitors for treating effort-related dysfunctions (Katz et al., 2004; Nutt et al., 2007; Fava et al., 2014; Padala et al., 2012; Stenman and Lilja, 2013; Rothschild et al., 2014). Experiment 2 explored the effects of DEP, an irreversible MAO-B inhibitor, in attenuating the effects of TBZ. Based on previous results from Randall et al. (2014) study with DEP using the PROG/chow feeding choice task, we hypothesized that DEP should also be able to shift partially the response allocation induced by TBZ in a less demanding task like the FR5 choice procedure. Experiment 3 looked at the effects of PAR, a relatively nonselective irreversible MAO-I, in recovering normal behavior after injections of TBZ. Based on previous evidence in the use of PAR and other propargylamines as neuroprotectants in Parkinson diseases and lesions studies (Huleatt et al., 2015; Bazzuet al., 2013; Langston, 1984; Heikkila, 1984) it would be reasonable to think that PAR will be able to reverse the effects of TBZ on effort-related choice behavior.

Chapter 2: MAO-I Effect In Effort-Related Decision

2.1 Introduction

The present work was undertaken to characterize the effects of MAO inhibitors on effort-related choice behavior. Three MAO inhibitors with different patterns of selectivity (MCL, DEP, PAR) were assessed for their ability to reverse the effort-related impairments induced by DA depleting agent tetrabenazine (TBZ) in rats tested on the concurrent FR5/chow choice task. The fourth experiment assessed the effect of each drug administered alone on the same task.

2.2 Materials and methods

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=24) weighed 300-350 grams at the beginning of the study and were food-deprived to 85% of their free-feeding body weight for the experiments. 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.

Concurrent FR5/chow-choice procedure:

Behavioral sessions were conducted in operant conditioning chambers (28x23x23 cm³, Med Associates, Georgia, VT, USA) during the light period. Rats were initially trained to lever press on a continuous reinforcement schedule (30 minute sessions, during 5 days) 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 $\geq 1,200$ 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. 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 experimental testing 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.

Pharmacological agents and dose selection

Reversible monoamine oxidase inhibitor A: moclobemide; (4-chloro-N-(2-morpholin-4-ylethyl)benzamide) was obtained from Selleck Chemicals, (Houston, TX, USA) was dissolved in de-ionized water (18.2 megaohm) heated at medium temperature on a hot-plate until it went into solution. De-ionized water was also used as the vehicle control. Doses (2.5, 5.0 and 10.0 mg/kg) were selected based on previous studies (Cryan et al., 2005; Freezer et al., 2005; Eroğlu & Güven, 1988)

Irreversible monoamine oxidase inhibitor B: selegeline (deprenyl) ((R)-(-)-N- α -Dimethyl-N-2-propynylbenzeneethanamine hydrochloride) was obtained from Tocris, (Minneapolis, MN, USA) was dissolved in 0.9% room temperature saline until it went into solution. Saline was also used as the vehicle control. Doses (1.25, 2.5 and 5.0 mg/kg) were selected based on reversal studies (Randall et al., 2014) and unpublished preliminary studies from our laboratory.

Irreversible nonselective monoamine oxidase inhibitor: pargyline;[1] (N-methyl-N-2-propynyl-benzenemethanamine, monohydrochloride) was obtained from Cayman Chemical Company (Ann Arbor, MI, USA) was dissolved in 0.9% room temperature saline until it went into solution. Saline was also used as the vehicle control. Previous studies using mice and rats in vivo have used a wide range of doses that goes as low as 5.0 mg/kg and as high as 256 mg/kg (Bazzu et al., 2010; Blaha et al., 1996; Cryan et al., 2014; Engberg., 1991; Karoum., 1987; Narboux-Nême et al., 2011; Steru et al., 1987) Thus, an initial pilot study of 6.25, 12.5 and 25.0 mg/kg doses was done using rats in the FR5/ chow-choice procedure. Based on these results (not shown), it was decided that a dose progression of 1.56, 3.12 and 6.25mg/kg was a better fit for the study.

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 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 the tetrabenazine solution was 3.5. The saline with 20% DMSO vehicle solution was administered as the vehicle control.

The dose of 0.75mg/kg was used based on previous studies (Nunes et al., 2013; Randall et al, 2014; Yohn et al., 2015a,b,c) and extensive unpublished pilot studies.

Experimental Procedures

For each experiment a different group of rats was used. All rats were trained on the concurrent FR5/chow feeding task as described above, and all experiments employed a within-subject design, in which each rat received all doses or vehicle treatments in their particular experiment in a randomly varied order (acute administration; one treatment per week). Baseline training sessions (i.e; non-drug) were conducted four days per week.

Experiment 1: Ability of the monoamine oxidase A inhibitor moclobemide to diminish the effects of tetrabenazine on the concurrent FR5/chow-choice procedure

Trained rats (n=8) received the following treatment; intraperitoneal injection of tetrabenazine (TBZ) 90 minutes and moclobemide free base (MCL) 60 minutes prior testing: TBZ vehicle plus MCL vehicle, 0.75 mg/kg TBZ plus 2.5 mg/kg MCL, 0.75 mg/kg TBZ plus 5.0 mg/kg MCL, or 0.75 mg/kg TBZ plus 10.0 mg/kg MCL and were tested for 30 minutes on the concurrent FR5/chow-choice procedure. Immediately after the 30 minute session, rats were removed from the chambers, total lever presses were recorded, and chow consumed was calculated.

Experiment 2: Ability of the monoamine oxidase B inhibitor deprenyl to diminish the effects of tetrabenazine on the concurrent FR5/chow-choice procedure

Trained rats (n=9) received the following treatment; intraperitoneal injection of tetrabenazine (TBZ) 90 minutes and deprenyl HCL (DEP) 30 minutes prior testing: TBZ

vehicle plus DEP vehicle, 0.75 mg/kg TBZ plus 1.25 mg/kg DEP, 0.75 mg/kg TBZ plus 2.5 mg/kg DEP, or 0.75 mg/kg TBZ plus 5.0 mg/kg DEP and were tested for 30 minutes on the concurrent FR5/chow-choice procedure. Immediately after the 30 minute session, rats were removed from the chambers, total lever presses were recorded, and chow consumed was calculated.

Experiment 3: Ability of the nonselective monoamine oxidase inhibitor pargyline to diminish the effects of tetrabenazine on the concurrent FR5/chow-choice procedure

Trained rats (n=8) received the following treatment; intraperitoneal injection of tetrabenazine (TBZ) 90 minutes and pargyline HCL (PAR) 30 minutes prior testing: TBZ vehicle plus PAR vehicle, 0.75 mg/kg TBZ plus 1.56 mg/kg PAR, 0.75 mg/kg TBZ plus 3.125 mg/kg PAR, or 0.75 mg/kg TBZ plus 6.25 mg/kg PAR and were tested for 30 minutes on the concurrent FR5/chow-choice procedure. Immediately after the 30 minute session, rats were removed from the chambers, total lever presses were recorded, and chow consumed was calculated.

Experiment 4: Effects of Monoamine oxidase inhibitors; non-selective, A and B on the concurrent FR5/chow-choice procedure

Trained rats (n=8) received the following treatments: intraperitoneal injection of saline 30 min prior to testing, PAR (6.25mg/kg) 30 minutes prior testing, MCL (10mg/kg) 60 minutes prior testing and DEP (2.5mg/kg) 30 minutes prior testing. Animals were tested on the FR5/chow feeding choice task for 30 minutes. Once the session was

over, rats were removed from the chambers, total lever presses were recorded, and chow consumed was calculated.

Statistical Analyses

In experiments 1-3, total number of lever presses and gram quantity of chow intake from the 30 min session were analyzed using repeated measures ANOVA. A computerized statistical program (SPSS 14.0 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).

2.3 Results:

Experiment 1: Ability of moclobemide to diminish the effects of tetrabenazine on the concurrent FR5/chow-choice procedure

In the dose range tested, moclobemide (MCL) failed to produce a reversal of the effects of tetrabenazine (TBZ) on effort-related choice behavior in animals tested on the concurrent FR5/chow-choice procedure. There was an overall significant effect of drug treatment on lever pressing [$F(4,28)=57.25, p<0.01$]. TBZ significantly decreased lever pressing compared to vehicle-vehicle control (planned comparisons, $p<0.01$). Moreover, co-administration of TBZ plus MCL 10.0 mg/kg further decreased lever pressing compared to TBZ plus vehicle (planned comparisons, $p<0.01$). An overall significant effect of drug treatment was also found on chow intake [$F(4,28)=119.80, p<0.01$]. TBZ

significantly increased chow intake (planned comparisons, $p < 0.01$). Furthermore, non-orthogonal planned comparisons revealed that co-administration of TBZ plus MCL 2.5, 5.0, and 10.0 mg/kg ($p < 0.01$) significantly reduced chow intake compared to TBZ plus vehicle.

Experiment 2: Ability of deprenyl to diminish the effects of tetrabenazine on the concurrent FR5/chow-choice procedure

DEP produced a partial reversal of the effects of tetrabenazine (TBZ) on effort-related choice behavior in animals tested on the concurrent FR5/chow-choice procedure. There was an overall significant effect of drug treatment on lever pressing [$F(4,32)=15.31, p < 0.01$]. Planned comparisons showed that TBZ produced a significant reduction on lever pressing compared to vehicle-vehicle control ($p < 0.01$). Moreover, co-administration of TBZ plus 2.5 mg/kg DEP significantly increased lever pressing compared to TBZ plus vehicle (planned comparisons, $p < 0.01$). An overall significant effect of drug treatment was also found on chow intake [$F(4,32)=14.32, p < 0.01$]. TBZ significantly increased chow intake (planned comparisons, $p < 0.01$). Furthermore, non-orthogonal planned comparisons revealed that co-administration of TBZ plus 1.25 mg/kg DEP ($p < 0.05$) and 2.5-5.0 mg/kg ($p < 0.01$) significantly reduced chow intake compared to TBZ plus vehicle. Therefore, co-administration of TBZ and DEP (2.5 mg/kg) significantly increased lever pressing relative to TBZ alone, while chow consumption was significantly reduced at 1.25, 2.5 and 5.0 mg/kg compared to TBZ-vehicle treated animals.

Experiment 3: Ability of pargyline to diminish the effects of tetrabenazine on the concurrent FR5/chow-choice procedure

In the dose range tested, pargyline (PAR) failed to produce a reversal of the effects of tetrabenazine (TBZ) on effort-related choice behavior in animals tested on the concurrent FR5/chow-choice procedure. There was an overall significant effect of drug treatment on lever pressing [$F(4,28)=43.70$, $p<0.01$]. TBZ significantly decreased lever pressing compared to vehicle-vehicle control (planned comparisons, $p<0.01$). However, co-administration of PAR (1.56, 3.125 and 6.25 mg/kg) failed to reverse the effects of TBZ on lever pressing compared to TBZ-vehicle (planned comparisons). An overall significant effect of drug treatment also was found on chow consumption [$F(4,28)=12.22$, $p<0.01$]. TBZ significantly increased chow consumption compared to vehicle-vehicle control (planned comparisons, $p<0.01$). Moreover, co-administration of TBZ plus 6.25mg/kg PAR significantly decreased chow consumption relative to TBZ-vehicle (planned comparisons, $p<0.05$). Thus, co-administration of TBZ and PAR (6.25mg/kg) significantly reduces chow consumption while having no effect on lever pressing compared to TBZ-vehicle.

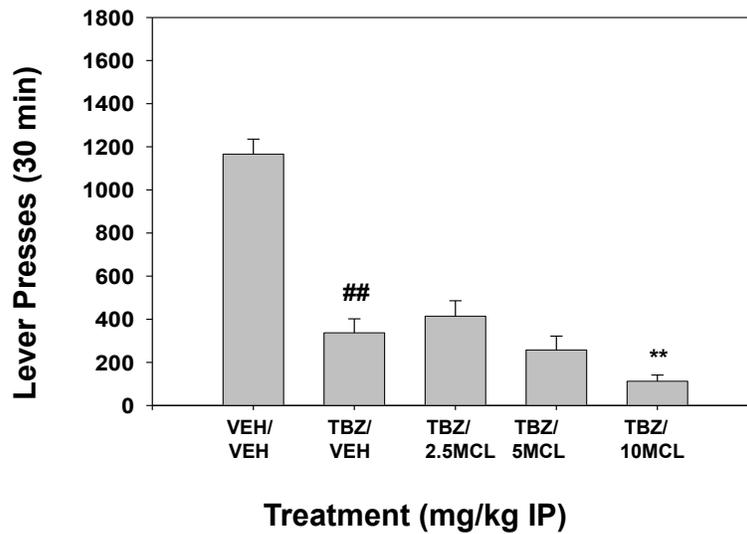
Experiment 4: Effects of Monoamine oxidase inhibitors; non-selective, A and B on the concurrent FR5/chow-choice procedure

There was an overall significant effect of drug treatment on lever pressing [$F(3,21)=25.85$, $p<0.01$]. Post hoc tests revealed that moclobemide (10.0 mg/kg) significantly reduced level pressing when compared to vehicle-saline ($p=0.002$),

($p=0.005$) and DEP ($p=0.007$). However, there was no difference in chow consumption
[$F(3,21)=2.203$ $p = \text{n.s.}$]

TBZ/Moclobemide

A



B

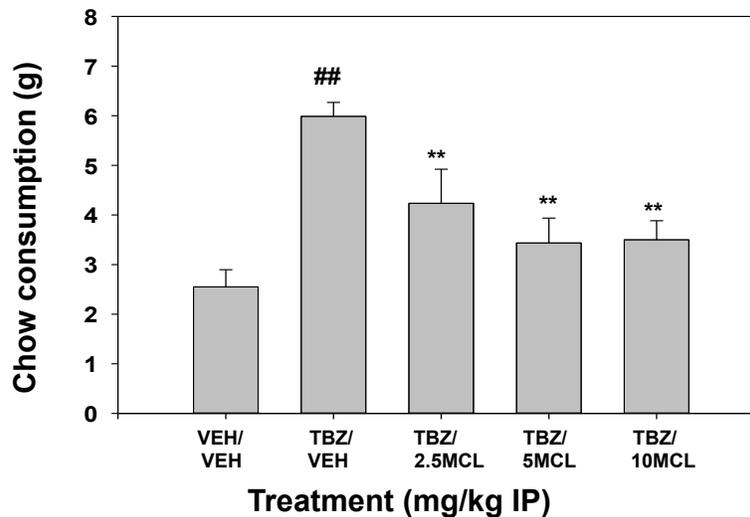


Figure 1: Effects of Monoamine oxidase inhibitor A, moclobemide (MCL) on FR5/chow-choice procedure. On measures of lever pressing, mean (+SEM) total lever presses (A) and chow consumption (B) after 30 minutes of testing. TBZ/VEH significantly decreased lever pressing compared to VEH/VEH. Co-administration of MCL (10 mg/kg) plus TBZ further decreases lever presses compared to TBZ/VEH alone. TBZ/VEH significantly increased chow consumption compared to VEH/VEH. Co-administration of TBZ plus 2.5, 5, and 10mg/kg MCL significantly decreased chow consumption relative to TBZ/VEH.

TBZ/Deprenyl (Selegiline)

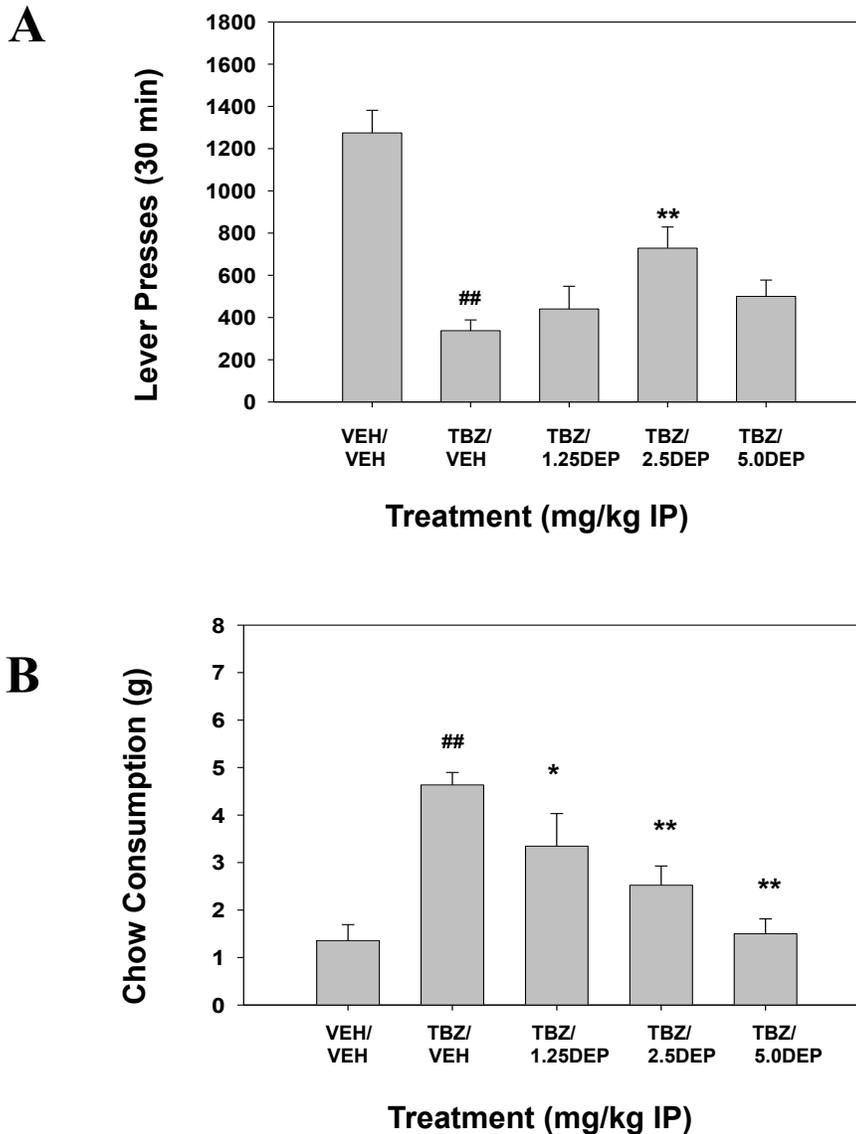


Figure 2: Effects of Monoamine oxidase inhibitor B, deprenyl (selegiline) on FR5/chow-choice procedure. On measures of lever pressing, mean (+SEM) total lever presses (A) and chow consumption (B) after 30 minutes of testing. TBZ/VEH significantly decreased lever pressing compared to VEH/ VEH . Co-administration of TBZ plus 2.5 mg/kg DEP significantly increased lever pressing compared to TBZ plus vehicle. TBZ/VEH significantly increased chow consumption compared to VEH/VEH. Co-administration of TBZ plus 1.25, 2.5 and 5.0 mg/kg DEP significantly decreased chow consumption relative to TBZ/VEH.

TBZ/Pargyline

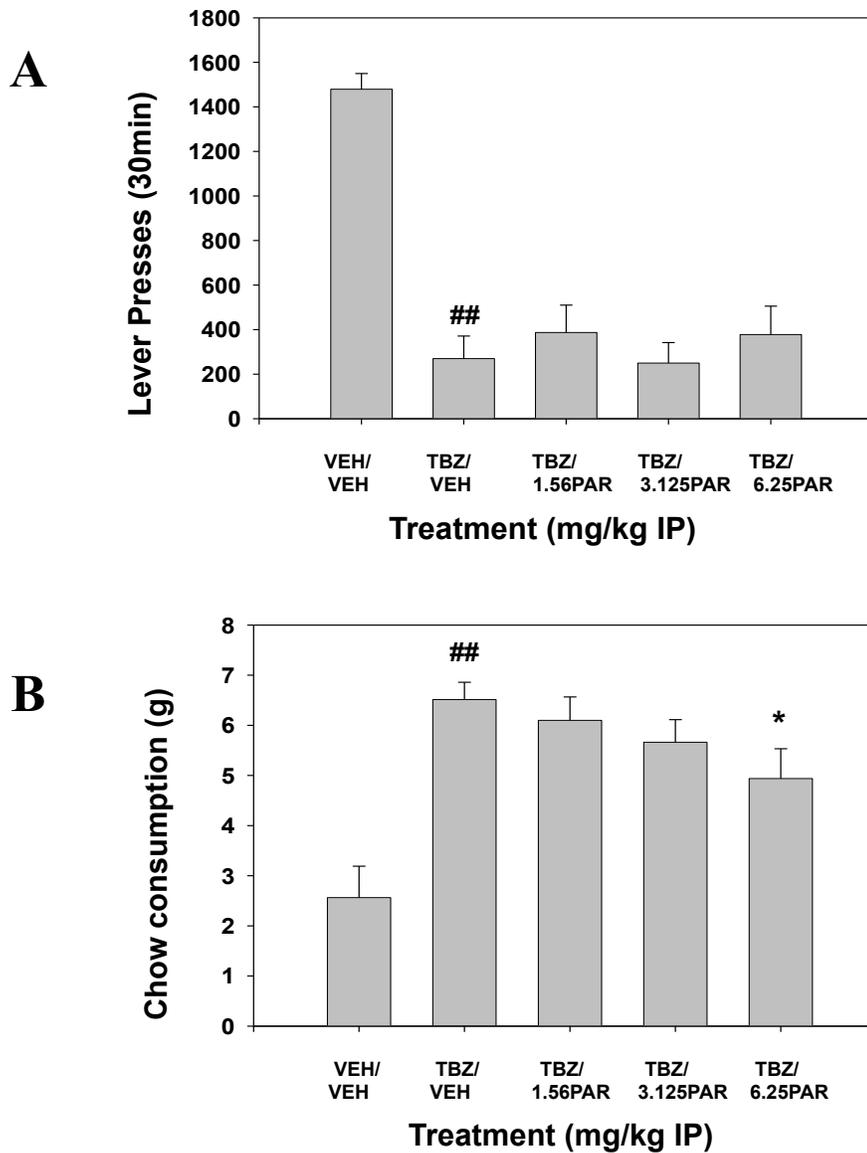
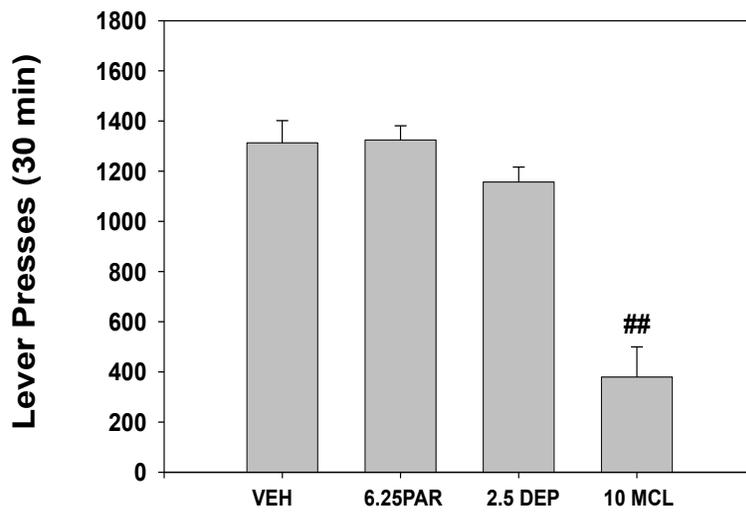


Figure 3: Effects of non-selective Monoamine oxidase inhibitor pargyline on FR5/chow-choice procedure. On measures of lever pressing, mean (+SEM) total lever presses (A) and chow consumption (B) after 30 minutes of testing. TBZ/VEH significantly decreased lever pressing compared to VEH/VEH. Co-administration of PAR (1.56, 3.125 and 6.25mg/kg) plus TBZ failed to reverse the effects of TBZ/VEH on lever pressing. TBZ/VEH significantly increased chow consumption compared to VEH/VEH. Co-administration of TBZ plus 6.25mg/kg PAR significantly decreased chow consumption relative to TBZ/VEH.

Control Experiment

A



B

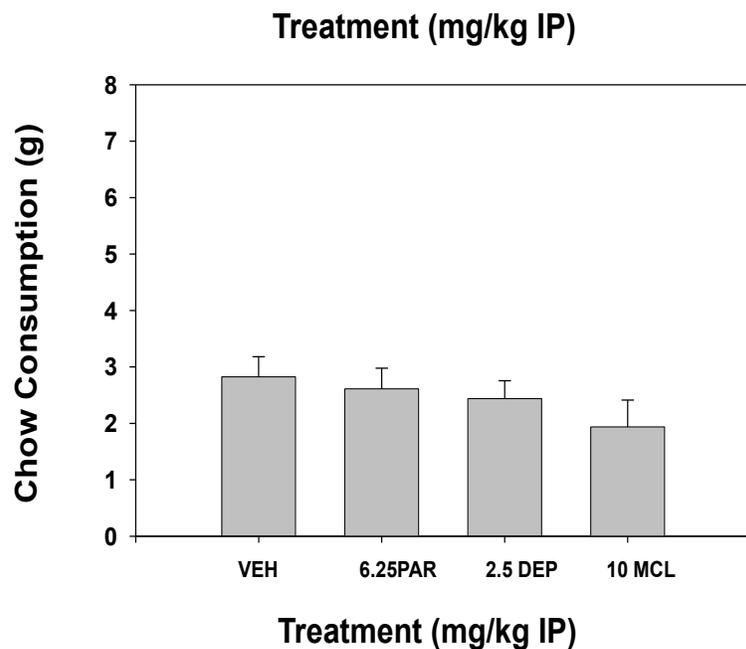


Figure 4: Effects of Monoamine oxidase inhibitors on the concurrent FR5/chow-choice procedure. On measures of lever pressing, mean (+SEM) total lever presses (A) and chow consumption (B) after 30 minutes of testing. MCL (10 mg/kg) significantly reduced lever pressing compared to VEH, PAR6.25mg/kg and 2.5DEP. There was no effect in chow consumption..

2.4 Discussion

The current studies explored the effects of MAO inhibitors using a rat model of effort-related symptoms of depression (i.e., the effects of TBZ on performance of the concurrent fixed ratio 5 (FR5)/chow feeding task). In order to produce effort-related impairments in rats, the VMAT-2 inhibitor and catecholamine depleting agent TBZ was used. The effects of TBZ on effort-related functions has recently been established as a formal model of effort-related motivational symptoms in psychopathology (Nunes et al., 2013; Randall et al., 2014; Yohn et al., 2015a). The use of TBZ as a pharmacological agent to induce effects related to depression in rodents comes in part from the discovery of side effects like fatigue, anergia and general depressive symptoms when TBZ is used to treat Huntington Disease (Frank, 2010; Chen et al., 2012; Frank et al., 2014). Thus, TBZ is a useful drug to alter effort-related choice and in turn model effort-related motivational symptoms of depression in this study. However, is important to emphasize that we are specifically modeling a symptom of depression and other disorders, and not the disorder as a whole. The effort-related dysfunctions seen with TBZ possibly represent a model of motivational symptoms are important for depression, but also can be seen in other disorders such as Parkinson's disease, and Huntington's chorea, and chronic fatigue syndrome. Modeling and studying specific symptoms is consistent with the initiative proposed by NIMH Research Domain Criterion (RDoC), which emphasizes specific psychiatric symptoms and their neurobiology, rather than the traditional diagnostic categories or disorders (Cuthbert and Insel, 2013).

In experiment 1, it was shown that the MAO-A inhibitor maclobemide (MCL) failed to reverse the effects of 0.75mg/kg TBZ on effort-related choice behavior in

animals tested on the concurrent FR5/chow-choice procedure (figure 1). Moreover, TBZ in combination with the highest dose of MCL (10.0 mg/kg) further impaired the rat's performance by reducing level pressing and also reducing chow consumption when compared to TBZ/vehicle. The reduction of chow consumption can be attributed to MCL, since TBZ alone shifted the animal toward the lower effort/lower reward where TBZ plus MCL reduced both lever presses and chow consumption. Furthermore, a control experiment (figure 4) was done to assess the effects of MCL without TBZ to address whenever or not the drug by itself has any positive or adverse effect. The results of this experiment revealed that MCL reduced lever pressing, while chow consumption was unaffected and was comparable to vehicle. Taken together, these results indicate that MCL does not increase exertion of effort in rats assessed by the FR5/chow feeding task. Moreover, MCL combined with TBZ seems to further impair effort-related decision making. A similar pattern was seen with a previous study using fluoxetine, a selective serotonin reuptake inhibitor (SSRI) in the (FR5)/chow feeding task (Yohn et al., 2015c). Although MAO-A inhibitors and SSRI's mechanisms are different, both types of drugs increase extracellular levels of 5-HT, which could potentially lead to downstream effects resulting in effort-related dysfunctions. 5-HT receptors are present within the terminal regions of mesostriatal, mesolimbic and mesocortical DA pathways. Moreover, the VTA is innervated by 5-HT neurons that originate in the dorsal raphe nucleus of the brainstem (Beart and McDonald, 1982). Thus, is not surprising that 5-HT could potentially act as a neuromodulator of DA functions in the VTA. For instance, pharmacological stimulation of the dorsal raphe can evoke excitations or inhibitions of VTA DAergic neurons (Cameron et al., 1997). Moreover, increasing or decreasing 5-HT levels within the synapses in the VTA can

reduce or enhance the discharge rate of these DA neurons (Cameron et al., 1997; Di Mascio et al., 1998; Guiard et al., 2008). In summary, the mesolimbic pathway is one of the most important DA pathways in regards to motivated behavior, and it appears that 5-HT plays a role in modulating DA firing. In the case of MCL, which inhibits the MAO-A enzyme, it is plausible to suggest that an overall increase in 5-HT transmission would lead to impairments in effort-related decision making. Nonetheless, in human studies, it is not clear if MCL affects effort-related behavior in a consistent manner at the dose range typically used. In fact, there are reports indicating that patients with chronic fatigue syndrome treated with MCL seem to benefit from an increase in vigor and overall energy (White and Cleary, 1997; Hickie et al., 2000; Vanderkooy et al., 2002).

In experiment 2, the results shown that the MAO-B inhibitor B DEP (2.5 mg/kg) produced a partial reversal of the effect of TBZ on effort-related choice behavior in animals tested on the concurrent FR5/chow-choice procedure (figure 2). In experiment 4, DEP by itself did not have any effect on effort-related behavior (figure 4). The ability of MAO-B inhibitors such as DEP to improve motivational function is consistent with studies from the clinical literature. Although MAO-B inhibitors were originally developed as antiparkinsonian drugs, recent studies show that selegiline is effective at reducing depressive symptoms in people with major depression (Jang et al. 2013; Sclar et al. 2013). A recently published case study reported that DEP improved depressive symptoms in a treatment-resistant patient at doses that also increased DA transmission as measured by PET imaging (Kitaichi et al. 2013). Krishna et al. (2014) found that administration of MAO-B inhibitors to Parkinson's disease patients reduced apathy symptoms. Smith et al. (2015) showed that rasagiline, an MAO-B inhibitor similar to

DEP, when given in combination with antidepressants to Parkinsonian patients with motivational symptoms, significantly improved fatigue and showed a trend towards reduction in apathy compared to patients that received antidepressants plus placebo. Thus, the ability of DEP to reverse the effort-related effects of TBZ in the present study, and in a previous report (Randall et al. 2014), is consistent with recent clinical reports from both depressed and Parkinsonian patients.

In the present TBZ reversal study, the dose of 2.5 mg/kg DEP was able to partially improve TBZ effects on effort-related behavior by increasing total level presses and reducing chow consumption when compared to TBZ-vehicle. Interestingly neither a lower (1.25 mg/kg) nor a higher dose (5.0 mg/kg) was able to attenuate TBZ effects on level pressing; this indicates that the effect of DEP on TBZ-induced changes in lever pressing followed a narrow inverted-u shaped dose response curve. Perhaps at the lowest dose DEP did not produce effects that were strong enough to be able to produce a reversal, whereas at the highest dose some MAO-A inhibition was occurring and as a result the possible positive effects were overshadowed by adverse effects similar to those seen in the MCL experiment. However, it is important to note that Randall et al. (2014) also showed that the dose of 5.0 mg of DEP was able to rescue motivated behavior in rats tested on the (PROG)/choice feeding task where neither the lowest dose (2.5mg/kg) nor the highest (10.0mg/kg) was able to. One important distinction between the FR5 and the PROG task is that the PROG is more demanding, which could explain why a higher dose of DEP was needed to partially reverse the effects of TBZ when compared to the FR5. It might be possible that higher instrumental demands elicited by the PROG choice task increases the level of endogenous DA being released, and that this could be a factor. For

example, microdialysis studies have shown that different food-related behavioral tasks showed different levels of increase in extracellular DA, and that response requirements could be a factor in determining the magnitude of the increase in DA transmission (Salamone et al. 1994b; Sokolowski et al. 1998; Cousins et al. 1999). Another important consideration is that the selectivity of DEP for MAO-B vs. MAO-A is relative and not absolute. Thus, although a low dose such as 2.5 mg/kg is likely to be producing a relatively selective effect on MAO-B (Magyar 2011), higher doses would probably be producing nonselective effects. Thus, future studies should investigate whenever or not DEP at 2.5, 5.0 and 10.0 mg/kg could affect MAO-A enzymatic activity, and what degree of inhibition is enough to produce adverse effect on effort-related behavior.

In Experiment 3 it was shown that the nonselective MAO-I PAR failed to reverse the aversive effects of TBZ on effort-related behavior. Most behavioral and neuronal studies in rodents effectively uses high doses of PAR that range from 10-256 mg/kg (Langston et al., 1984; Karoum 1987; Steru et al., 1987; Engberg et a., 1991; Blaha et al.,1996; Cryan et al., 2004; Narboux-Nême et al., 2011; Bazzu et al., 2013). Due to our previous findings with some antidepressants studies, in which higher doses adverse effects were found at higher doses (e.g., appetite suppressant effects, motor impairments) we decided to run a pilot study to determine an adequate range of doses. These preliminary findings (results not shown) indicated that doses of 25 and 12.5mg/kg showed adverse effects resembling appetite suppressant effects. Based on these results, in our current study we decided to use 6.25mg/kg as our highest dose. It seems that the range of doses used (i.e.1.56, 3.125 and 6.25mg/kg) were void of effects on TBZ-induced changes in behavior when administered acutely. Moreover, when PAR was administered

at the highest dose by itself, it did not produce any apparent effects as shown in fig 4. It seems that the dose range of PAR tested in the present studies were within the range of doses used in traditional tests of antidepressant activity. Nevertheless, we did not see any reversal effects with PAR in the present dose range. If appetite suppression is a major factor, for future studies we could use the T-Maze paradigm, in which food intake is significantly lower than our operant tasks.

In summary the present studies offer novel information about the motivational effects of a range of monoamine oxidase inhibitors (MAO-I) in effort-related impairments. It was found that not every MAO-I used in these experiments was effective in treating the symptoms of depression induced by TBZ in the FR-5/choice procedure. Moreover, only MAO-B DEP was able to reverse, albeit partially, the performance of rats treated with TBZ, which is consistent with previous work in the PROG/choice task (Randall et al., 2014). Finally the MAO-A inhibitor MCL further impaired the animals when co administered with TBZ. Taking together these results, more studies should be done in order to understand which MAO-inhibitors besides DEP could be useful as a treatment for effort-related dysfunctions like fatigue, anergia and psychomotor slowing, which are seen in depression, Parkinson and Huntington's disease.

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