Wilfrid Laurier University

Scholars Commons @ Laurier

Theses and Dissertations (Comprehensive)

2001

Sensitization to indirect and direct dopamine agonists: Behavioural differences in wheel running

Vanhthong Vilaysinh
Wilfrid Laurier University

Follow this and additional works at: https://scholars.wlu.ca/etd

 Part of the Biological Psychology Commons

Recommended Citation

Vilaysinh, Vanhthong, "Sensitization to indirect and direct dopamine agonists: Behavioural differences in wheel running" (2001). *Theses and Dissertations (Comprehensive)*. 719.
https://scholars.wlu.ca/etd/719

This Thesis is brought to you for free and open access by Scholars Commons @ Laurier. It has been accepted for inclusion in Theses and Dissertations (Comprehensive) by an authorized administrator of Scholars Commons @ Laurier. For more information, please contact scholarscommons@wlu.ca.

INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

ProQuest Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

National Library of Canada
Acquisitions and Bibliographic Services
395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque nationale du Canada
Acquisitions et services bibliographiques
395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

Our file Notre référence

The author has granted a non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of this thesis in microform, paper or electronic formats.

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque nationale du Canada de reproduire, prêter, distribuer ou vendre des copies de cette thèse sous la forme de microfiche/film, de reproduction sur papier ou sur format électronique.

The author retains ownership of the copyright in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

L'auteur conserve la propriété du droit d'auteur qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

0-612-65208-4

Canada

Sensitization to Indirect and Direct Dopamine Agonists:

Behavioural Differences in Wheel Running

By

V. Vilaysinh

Bachelor of Arts (Honours), Wilfrid Laurier University

THESIS

Submitted to the Department of Psychology

in partial fulfilment of the requirements

for the Masters of Arts degree

Wilfrid Laurier University

2001

©V. Vilaysinh

Acknowledgments

I'd like to take this opportunity to thank Dr. Eikelboom for all his support, guidance and patience. Most importantly, for making these past two years enjoyable and enlightening. Also greatly appreciated are the recommendations and support given to me by my committee members Dr. Parker and Dr. Hockley.

For my Mom and Dad, your encouragement and belief that I can achieve whatever goals I set for myself surpasses all others.

I'd also like to acknowledge Vondy, Boun, Cameron, Sunny, and Bou for their support and enthusiasm in my educational pursuits.

A note to great friends, MLN, SK, CC, CH, CL, NP, LA & LP: you have all played an important part in this thesis by keeping me grounded to reality and making sure I have a social life.

Last but not least, thank you David for your help with last minute technical details and just being there for me when I needed someone to lean on.

Abstract

Five experiments examined the effects of repeated exposure to stimulants, largely apomorphine (APO), on wheel running in male Sprague-Dawley rats. In these experiments, minor changes in procedure resulted in profound differences in the effects of APO on wheel running. Experiment 1 compared changes in wheel running after repeated injections of 3.0 mg/kg amphetamine (AMP), 5.0 mg/kg of APO, or vehicle (VEH). AMP resulted in a suppression in wheel running which became more pronounced over trials, while running in APO animals remained similar to the VEH group. Testing with VEH provided support for a conditioned suppression of wheel running in rats previously treated with AMP relative to those treated with VEH. Experiments 2 to 4 examined the effects of repeated injections of a wide range of APO doses on wheel running in two different environments, a wheel rack, and separate wheel cages. Results showed significant quadratic trends in Experiments 2 and 3, suggestive that low APO doses suppress running and higher doses elevate running. However, running in rats repeatedly injected with 1.0 mg/kg APO was either suppressed or elevated, depending on the environment in which they were tested. Experiment 4 concurrently examined the effects of 1.0 mg/kg APO in both environments and found that running on the rack was significantly higher than in the separate cages for the APO animals, but did not differ from VEH treated controls. The effect of noise on APO-induced running in the SEP cages was examined in Experiment 5 but had no effect on the wheel running.

Table of Contents

Sensitization to Indirect and Direct Dopamine Agonists: Behavioural Differences in Wheel Running

The development and expression of sensitization to psychostimulant drugs such as amphetamine (AMP) (Anagnostaras & Robinson, 1996; Langer & Arbilla, 1984; Robinson & Becker, 1986; Segal & Mandell, 1974; Vanderschuren, Schoffelmeer, Mulder, & De Vries, 1999a) and apomorphine (APO) (Gancher, Mayer, & Youngman, 1996; Mattingly, Gotsick, & Marin, 1988a; Mattingly, Gotsick, & Salamanca, 1988b; Voikar *et al.*, 1999) have been well documented. Behavioural sensitization typically refers to a gradual elevation in locomotor activation and emergence of stereotypical behaviour with repeated exposure to a moderate dose of psychostimulant drugs. Graphically, this is represented as a shift to the left of the dose response curve; the same effect being elicited by a smaller drug dose. The gradual increase in locomotion, or sensitization, is thought to play an important role in the addictive properties of these drugs (Robinson & Berridge, 1993; Wise & Bozarth, 1987). Robinson and Berridge (1993) propose that, "the defining characteristics of addiction (craving and relapse) are due directly to drug-induced changes in those functions normally subserved by a neural system that undergoes sensitization-related neuroadaptations" (p. 249). Learning factors and neurochemical changes may both play a role in producing drug sensitization; however, sensitization is the observed change in drug responsiveness and so may be produced by a variety of mechanisms. Most research examining the behavioural effects of a moderate dose of APO (Mattingly *et al.*, 1988b; Moller, Nowak, & Kuschinsky, 1987) and AMP (Bernardi, Scavone, & Frussa-Filho, 1986; Kuczenski, Segal, Weinberger, & Browne, 1982; Segal & Mandell, 1974) has consistently found an initial

elevation in locomotor activity with the first injection of the drug, and then a gradual further elevation in activity and stereotypy with repeated injections.

The mechanisms involved in sensitization are not fully understood; however, much research has provided evidence that the hyperactivity induced by psychomotor stimulants is associated with activation of the postsynaptic dopamine (DA) receptors, which results from an increase in DA or direct agonist concentration in the synaptic cleft (Kalivas & Stewart, 1991; Langer & Arbilla, 1984; Miller, Wickens, & Beninger, 1990; Stewart & Badiani, 1993; Wise & Leeb, 1993). Although APO and AMP are both stimulants, their site of action on the DA system differs. APO is a direct agonist that acts directly on both pre- and post-synaptic DA receptors. At low doses (< 0.2 mg/kg), APO decreases activity in rats (Katsura, Itoh, & Rehfeld, 1984; Mattingly *et al.*, 1988b; Nickolson, 1981; Moller *et al.* 1987; Radhakishun & Van Ree, 1987; Van Ree & Wolterink, 1981). This suppressive effect of APO is thought to be due to the activation of pre-synaptic DA autoreceptors, which inhibits electrical discharge and reduces DA synthesis and release. These autoreceptors are thought to have a higher affinity for DA and APO, and as such are preferentially affected by low doses of APO. At a higher dose (> 0.5 mg/kg), APO elevates activity (Katsura *et al.*, 1984; Mattingly *et al.*, 1988b; Nickolson, 1981). The increase in motor activity seems to be through activation of the post-synaptic receptor, thus mimicking the action of DA. At an even higher dose (> 2 mg/kg), APO produces stereotypy, which is characterized by sniffing, gnawing, licking, and repetitive head movements in animals (Antoniou & Kaafetzopoulos, 1991). AMP on the other hand is an indirect agonist that increases the release of DA from pre-synaptic vesicles and blocks

DA reuptake. AMP elevates locomotor response in a dose-dependent manner, up to very high doses which produce stereotypy (Robinson & Becker, 1986; Russell & Pihl, 1978).

While the site and mechanism of action of these (and other) psychomotor stimulants have become clear, the changes that underlie the sensitization of their effects are not well understood. With repeated administration of both drugs (and other stimulants), the effects produced by the drug become more pronounced. A medium dose will initially produce an elevation in locomotion, and with repeated administration locomotion decreases as the drug response becomes a more pronounced stereotypic behaviour reflective of initially higher doses. With repeated administrations, a gradual increase in locomotion is seen in rats injected with a moderate dose of APO (Mattingly *et al.* 1988b) or AMP (Kuczenski *et al.*, 1982; Segal & Mandell, 1974), which is later replaced by stereotypic behaviour, the same as that seen with an acute injection of a high dose of the drug.

Sensitization results not only from simple exposure to the drug, but also from the interactions between the drug's effects and surrounding circumstances. When a stimulus is presented more than once, there is always a potential of learning, or conditioning. Pavlovian conditioning posits that animals learn to associate a neutral conditioning stimulus with an existing reflex to the extent that the conditioned stimulus will, by itself, elicit a conditioned response. In situations where sensitization is evident, if the conditioned response is similar to the observed drug effect then it may augment the observed drug effect making it stronger or larger over trials (Eikelboom & Stewart, 1982). Since sensitization to drugs occurs over several repeated administrations,

environmental stimuli may play an important role in the expression and induction of sensitization to AMP and APO.

The context in which AMP is administered has profound effects on the magnitude of sensitization. Studies involving AMP administrations have found greater sensitization effects when the drug injections are paired with a unique, novel environment relative to those that were presented in a manner to reduce the environmental associations (Anagnostaras & Robinson, 1996; Badiani & Anagnostaras, 1995). Furthermore, it has been found that after pairings of AMP (the UCS) with an environment (the CS), the CS alone can elicit drug effects (CR) in animals (Stewart & Vezina, 1991). On the other hand, animals that received AMP in their home cage, thus having AMP experience not paired with the CS, and were then studied in the test environment failed to show or express sensitization (Anagnostaras & Robinson, 1996). This context-dependent expression of sensitization is consistent with a Pavlovian conditioning interpretation.

Inconsistent with a simple Pavlovian interpretation, Mattingly and Gotsick (1989) have shown that sensitization to APO develops in the absence of drug associated cues, and therefore did not appear to be context dependent. In their experiment, over nine acquisition trials rats were either administered 5.0 mg/kg subcutaneously (s.c.) of APO before being placed in a photocell arena to test for locomotor activity, or were given the drug 15 minutes after the activity sessions. There was also a group of control rats that were administered only vehicle (VEH) injections. When tested for sensitization by administering the same dose of APO to all rats, both groups of rats that had received APO (both the before and the after group) showed greater activity than controls. Although the association of environmental cues with APO was not necessary in

producing sensitization, some role for Pavlovian conditioning was suggested in that sensitization was greater when the drug was paired with a cue. Also arguing for a more complex explanation of sensitization than simple Pavlovian conditioning, Mattingly, Koch, Osborne, & Gotsick (1997) showed that APO-induced hyperactivity transferred completely from one environment to another. Animals receiving repeated APO in one environment (activity drums) were just as active when tested with APO in a second environment (running wheels) as animals that have always received APO on this second environment. That study, however, did not test all possible control groups. Groups that had received APO during acquisition trials were not tested with VEH and control rats which received VEH during acquisition were not tested with APO. If a VEH test revealed an elevation in activity in both environments in rats in the APO groups, it would suggest that in addition to the drug's direct effects, conditioning may have played a role in the hyperactivity. As this thesis is concerned with wheel running after APO administrations, Mattingly *et al.*'s (1997) research will be discussed later in greater detail.

Another important issue that affects the magnitude of sensitization is the interval between drug injections. Sensitization effects have been found to be greater when the intervals between drug administrations are larger (Castro, Abreu, Calzadilla, & Rodriguez, 1985; Kolta, Shreve, de Souza, & Uretsky, 1985; Nelson & Ellison, 1978; Post, 1980; Vanderschuren, *et al.*, 1999b). Also important is the interval before testing, for instance, Vanderschuren *et al.* (1999b) found that after a single injection of 5.0 mg/kg AMP, a second injection of the same dose of AMP three days later resulted in marginal sensitization. However, sensitization effects were more evident when the second injection was one week later, and even greater when it was three weeks later. It would

therefore be important to consider not only dose, but also intervals between drug administrations and between acquisition and test trials when comparing sensitization effects.

Researchers often refer to the sensitized response to a drug in terms of locomotor behaviour, without specifically identifying the type of activity performed by the animal. Many apparati have been used as a measure of locomotion, such as activity drums, open fields and running wheels. It would be appropriate to look at some of the differences between these activities, as it would be naïve to assume that they all measure the same type of locomotion. For example, when comparing activity in running wheels with other apparati, positive correlations are sometimes observed, however, often they are low (Anderson, 1937). Because researchers are not very specific when referring to locomotion, and as wheel running is the focus of this thesis, it will be specifically referred to as wheel running, or simply running. All other forms of activity will be referred to as locomotion or activity.

When the effects of stimulants on wheel running are explored, the findings appear inconsistent. In one study, APO over trials induced an elevation in running (Mattingly *et al.* 1997), whereas in a second study, over trials AMP caused a suppression in running (Serwatkiewicz, Limebeer, & Eikelboom, 2000). In Mattingly *et al.*'s (1997) study, male Wistar rats were administered eight injections of 5.0 mg/kg APO or VEH spaced 72 hours apart. There was a 15-minute delay before they were placed in the running wheels or an open field activity drum for half an hour, which were kept in a dark testing room. Initially APO had no effect on wheel running but gradually over the eight injections the running increased until by the end of the experiment they were running more than three

times the amount of VEH rats. A post training activity test was assessed 72 hours after the last training session. When given APO at test, animals with APO experience showed an elevation in running, but so did the group that had received APO in the open field; this is evidence of cross-sensitization with APO.

Contrary to Mattingly *et al.* (1997), Serwatkiewicz *et al.* (2000) did not find an elevation in wheel running with AMP--they found a suppression in running. In their study all testing was conducted in the light. Male Sprague-Dawley rats were randomly assigned to one of three groups: AMP/SAL, SAL/AMP, and SAL/SAL. On the first wheel day, group AMP/SAL received an injection of 2.0 mg/kg AMP 20 minutes prior to being placed in the wheels for one hour. The following day they received an injection of saline in their home cage. Group SAL/AMP were treated identical to group AMP/SAL except they were injected with saline on the wheel day and AMP in their home cage. The control condition, group SAL/SAL received saline on both days. This procedure was repeated for a total of five acquisition trials. Running in group AMP/SAL decreased over trials while running in group SAL/AMP did not differ from controls. All animals were tested in a counterbalanced order 72 hours after the last acquisition trial with 2.0 mg/kg AMP and saline. Results indicated that group SAL/AMP did not differ from SAL/SAL controls when tested with AMP but both groups ran more than group AMP/SAL. Even though the animals in SAL/AMP and AMP/SAL had identical drug histories, only those animals that were administered AMP associated with the running wheel showed sensitization. No significant results were found with the saline test, indicating that there was no evidence of conditioning in either group. A subsequent experiment revealed that

AMP over a wide range of doses (1.0, 2.0, and 5.0 mg/kg) suppressed wheel running in a dose-dependent manner.

The effects of AMP and APO on wheel running are interesting because they are both stimulants that are expected to increase activity in a dose-dependent manner within a dose range that does not elicit stereotypy. However, this was not the case for wheel running after AMP administrations in the present research. The two studies just discussed indicate that there may be important differences between psychomotor stimulants, and there may be many factors that influence the expression of sensitization. The present research aims to provide a better understanding of how AMP and APO affect wheel running and how these effects change with repeated drug administration.

The elevation in wheel running with repeated APO administration (Mattingly *et al.*, 1997) and suppression with AMP (Serwatkiewicz *et al.*, 2000) may have been simply due to the drugs' effects, however, there is always the possibility that because these two studies were performed in different labs, the differences may have been due to variation in procedures. For instance, there were some differences in spacing of injections between Mattingly *et al.* (1997) and Serwatkiewicz *et al.*'s (2000) studies. The time differences in the between drug administrations, however, would only be able to explain differences in magnitude of sensitized responses and not the opposite direction of responses that the two wheel running studies found. Thus, the difference in injection schedules between the two studies is not believed to have played a critical role in producing the opposite direction of the response to wheel running.

Other procedural differences were examined and were found not to explain the differences in wheel running (Eikelboom, 1999). The wheels in Serwatkiewicz *et al.*'s

(2000) study had side cages attached, whereas Mattingly *et al.*'s (1997) wheels did not have side cages, forcing the rats to remain in the wheels during testing. Also, in Mattingly *et al.*'s study, quarter wheel turns were measured as opposed to full turns measured in Serwatkiewicz *et al.*'s study. Both these equipment differences might have led to differences in the behaviours being measured, for example quarter turns could have measured rocking motions. However, when rats were tested with and without side cages, with both full and quarter wheel turns being measured, AMP consistently suppressed running (Limebeer, 1998). Another procedural difference that was examined was the light/dark conditions. Mattingly *et al.* tested their animals in the dark, but in the day time, and Serwatkiewicz *et al.* tested their animals in the light. Serwatkiewicz (1999) found no difference between animals tested in the light or the dark; AMP produced an equivalent suppression in both conditions. Thus, this left the difference between the two drugs, AMP and APO, to be explored.

The original intent of the following experiments was to replicate the procedures of both Mattingly *et al.* (1997) and Serwatkiewicz *et al.* (2000) as much as possible. However, due to unexpected results and equipment limitations, several changes in procedure were made from one experiment to the next. First, injection intervals between acquisition trials and test varied slightly from one experiment to the next. In all experiments, injections during acquisition were spaced between 48 and 72 hours apart and the delay before testing was between seven and ten days. Mattingly *et al.* (1988a) found no difference in mean activity counts of rats injected with 5.0 mg/kg APO using a one- versus seven-day interval between injections. Furthermore, sensitization to APO was maintained for at least 18 days following the last injection. Finally it has been

suggested that a time delay is necessary for the induction of sensitization (Castro *et al.*, 1985). Thus, the minor differences in the time between drug injections across the experiments are not believed to significantly influence wheel running behaviour.

The wheel running apparatus also varied from one experiment to the next due to equipment availability at the time of the experiments. The apparatus used in the first, third, and fourth experiments was a rack that consisted of 12 wheels, three rows of four wheels, and the type used in the second, fourth, and fifth experiments were four individual wheels that were separated from each other. This variation in apparatus was not expected to affect the sensitization to AMP and APO since several equipment differences were examined in a previous experiment and found not to affect the sensitization to AMP (Limebeer, 1998). However, as the results of each experiment were analyzed, it appeared that the changes in equipment did have a significant effect on the wheel running behaviour of rats treated with APO. Other minor variations in procedure were also made and the specific changes will be explained in greater detail at the beginning of each experiment.

Experiment 1

The first experiment aimed to replicate previous findings, that sensitization to APO increases wheel running, whereas sensitization to AMP decreases wheel running. Since all rats were tested under identical conditions, procedural differences were eliminated in this first experiment. The intent was to have eight acquisition trials using the same APO dose as in Mattingly *et al.*'s (1997) study, and the middle dose of AMP used in the study by Serwatkiewicz *et al.* (2000). However, due to unexpectedly profound stereotypy exhibited by the rats that received APO, the acquisition trials were reduced to four and at

test, the doses of APO and AMP were reduced by half for ethical and health concerns of the rats. The design of this experiment included testing all rats with VEH to find evidence for conditioning. All rats were also tested with APO and AMP as research has shown evidence of cross-sensitization of APO and AMP (Laudrup & Wallace, 1999). However, due to the unexpectedly different effects that APO and AMP had on running, the analysis for cross-sensitization was not performed. Instead, it was more appropriate to make comparisons between the VEH group rats with the drug group rats on the VEH test and the appropriate drug test.

Method

Subjects

Twenty-four male Sprague-Dawley rats (Charles River Canada) that weighed between 329 and 407g on the day of the first injection were housed individually in standard shoebox cages (51 x 28 x 22cm). These animals had been used in a previous experiment involving the effects of single and pair housing on food and water intake (Lopak, 2000). They had ad-lib access to rat chow pellets and tap water for the duration of the experiment except during testing in the wheel apparatus. The colony room was maintained at 21-22°C. The lights were kept on a 12:12 light/dark cycle with the experimental procedure being conducted during the light portion of the cycle.

Apparatus

Twelve running wheels (11 cm wide, 33 cm in diameter) on a single rack were kept in the animals' colony room. All of the wheels had resting cages attached (25 x 17 x 20 cm) to which the animals had free access during the wheel running part of the experiment. Each wheel had one magnet aligned with a reed switch, which recorded one count for

each full revolution of the wheel. Counts were recorded by the Dataquest III system (Mini-Mitter Co.) in 5-second bins and were summed for the full hour. Animals could see and hear each other in the wheels.

Drugs

Apomorphine hydrochloride (APO; 5.0 mg/ml) was dissolved fresh every day in a VEH consisting of 1% ascorbic acid. D-amphetamine sulfate, (AMP; 3.0 mg/ml), was dissolved in a VEH consisting of physiological saline. VEH injections were either ascorbic acid or physiological saline. All drugs were injected at a volume of 1.0 ml/kg.

Procedure

After the rats finished the pair housing experiment, they were habituated in the colony room for two weeks before this procedure. During this time they were weighed every day during the light part of the cycle. The procedure of this experiment followed that used by Serwatkiewicz *et al.* (2000). Each animal received injections of either AMP intraperitoneally (i.p.), APO s.c. or VEH, half i.p. and half s.c. Due to the number of wheels available, animals were tested in two replicates of 12. At the beginning of the experiment the animals were randomly assigned (counterbalanced for their previous experience) to one of three groups: GVEH, GAMP, and GAPO, based on the drug injected. On each acquisition day, all animals were weighed, and given the appropriate injection of VEH, AMP or APO and returned to their home cage. Twenty minutes later they were placed in the wheel cages for one hour. Then they were removed and returned to their home cages. A seven-day interval followed before sensitization tests for this experiment. On days 15, 17, 19, animals were given a VEH test (TVEH), a 1.5 mg/kg AMP test (TAMP) and a 2.5 mg/kg APO test (TAPO) in a counterbalanced manner.

Results

The effect of drug on mean number of wheel turns over four acquisition trials is shown in Figure 1. A 3 (GROUP; GAMP, GAPO and GVEH) x 4 (TRIAL) mixed analysis of variance (ANOVA) revealed significant main effects of TRIAL, F (3, 63) = 8.79, $p < 0.01$, GROUP, F (2, 21) = 7.26, $p < 0.01$, and a TRIAL x GROUP interaction, F (6, 63) = 6.27, $p < 0.01$. (In this thesis for all repeated measures test performed, reported values are also significant with a Greenhouse-Geisser sphericity correction factor).

Post-hoc tests were performed to determine how the groups differed. Tukey's HSD multiple comparisons revealed that the groups did not differ on trial 1. On trial 2, GAMP rats ran significantly less than GVEH rats, $p < 0.05$, while on trials 3 and 4, rats in GAMP ran significantly less than animals in both GVEH and GAPO, $p < 0.05$. No differences for any trials were found between rats in GAPO and GVEH. In comparison to the initial injection, GAMP rats ran less with each drug treatment. GAPO and GVEH animals increased their running over treatments in an equivalent manner.

The effects of TVEH, TAMP, and TAPO tests on the three groups of rats are shown in Figure 2. A 3 (GROUP) x 3 (TEST) mixed ANOVA revealed only a significant GROUP x TEST interaction, F (4, 42) = 3.53, $p < 0.05$. To assess the effects of the specific tests, three one-way ANOVA's were conducted (one for each test). Significant TVEH, F (2, 21) = 5.57, $p < 0.05$, TAMP, F (2, 21) = 4.72, $p < 0.05$, and TAPO, F (2, 21) = 3.99, $p < 0.05$ differences in wheel running were found.

As differences between the two drugs and VEH are the important contrasts, the focus will first be on the difference between the GVEH and GAMP rats on the TVEH and TAMP tests. Tukey's HSD multiple comparisons revealed that GAMP rats ran

significantly less than GVEH animals, on both the TVEH and TAMP tests, $p < 0.05$. These results suggest that prior exposure to AMP has an effect on running after both VEH and AMP injections. These effects are consistent with a sensitization explanation--that repeated AMP administration suppresses running more than the initial AMP injection. Further, the finding that GAMP rats (relative to GVEH rats) suppressed running in the TVEH test indicates that cues, such as environmental stimuli, handling, and injection, may have become associated with the drug's effects. These results suggest that AMP injections may induce a conditioned suppression of running in addition to its direct drug effects.

Similar comparisons between GVEH and GAPO animals on the TVEH and TAPO tests revealed a different profile. GAPO rats ran more than GVEH rats in the TAPO test, an effect that approached significance, $p = 0.07$. This difference in APO effect is supportive of a sensitization of APO induced running. When tested with TVEH, running in GAPO rats was not significantly different from GVEH rats and in fact GAPO rats' average running was lower than that of animals in GVEH. Thus, there was no evidence for conditioning factors in explaining why rats with prior APO experience ran more in response to an APO injection than drug naïve rats.

Discussion

The results of the first experiment indicate that more research would be necessary to better understand how stimulants affect wheel running. Since the running suppression with AMP was replicated, further experimentation with AMP and wheel running was not carried out in this thesis. Instead, lower doses of APO were explored because a dose of 5.0 mg/kg produced stereotypy that may have affected the rats' running. Several

possibilities that may have produced the differences in running are discussed for the first experiment, however they are only suggestions and are not explored in this thesis.

The first experiment confirmed Serwatkiewicz *et al.*'s (2000) finding. Repeated AMP administration suppressed wheel running, with the suppression becoming more pronounced over trials. The suppression in wheel running is an important finding because previous literature has found that repeated AMP treatment elevated locomotor activity in other types of apparati such as open fields and activity drums (Bernardi *et al.*, 1986; Kuczenski *et al.*, 1982; Segal & Mandell, 1974). In comparison, previous research on AMP and wheel running sometimes reported an elevation in running, (Evans & Vaccarino, 1986) while other studies found a running suppression (Geary, Fudge, & Le Sauter, 1992). It was suggested by Serwatkiewicz *et al.* (2000) that studies which reported a running suppression used animals that had no or very limited wheel access. Conversely, those that found an elevation in running involved animals that had extensive exposure to a running wheel. In other work using rats that were either naïve to the running wheel or had 24-hour wheel access for 24 days it was revealed that with a 3.0 mg/kg AMP administration, wheel-naïve rats ran significantly less than VEH injected controls while rats that had previous exposure to the wheel ran considerably more than VEH injected controls (Vilaysinh & Eikelboom, 2000). The amount of exposure to the running wheel may thus be an important factor in determining whether AMP will produce a running suppression or elevation.

The effects of repeated APO administration on wheel running were different from those of AMP. With repeated 5.0 mg/kg APO administration, there was no difference in the number of wheel turns compared with the control group rats. In comparison,

Mattingly *et al.* (1997) found an elevation in running with this dose of APO using eight acquisition trials. Since Mattingly *et al.* used Wistar rats and this study used Sprague-Dawley rats, it is possible that test strain differences are responsible for the varying sensitivity of APO on wheel running. Research has found that different strains of rats respond differently with AMP (George, Porrino, Ritz, & Goldberg, 1991; Leith & Kuczenski, 1982) and APO (Essman, Luedtke, PcGonigle, & Lucki, 1995) administrations. The Sprague-Dawley rats used in the present research seem to be more sensitive to a high dose of APO compared to the Wistar rats used in Mattingly *et al.*'s study. In their study, they had eight acquisition trials using a 5.0 mg/kg APO dose, but did not report any stereotypy that may have interfered with wheel running. It is possible that additional acquisition trials in this experiment could have elevated running, however, health concerns for the animals prevented further acquisition trials using this high dose. Thus, further studies using a lower APO doses in this preparation with Sprague-Dawley rats will be necessary.

It is also possible that the effects of APO might change in a complex manner with dose. As discussed earlier, APO acts on both the DA autoreceptors and post-synaptic receptors depending on the dose administered. Lower doses might result in an AMP-like wheel running suppression or might result in an elevation of running. Clearly from this first study, at these doses, repeated AMP and APO administration have different effects on wheel running behaviour and this difference in effect was not due to procedural differences.

Experiment 2

Although the number of wheel turns in rats administered 5.0 mg/kg APO did not differ from VEH rats, the pattern of running may not be the same. It appeared that 5.0 mg/kg APO was a high dose that produced stereotyped behaviour which may have prevented the running elevation reported by Mattingly *et al.* (1997). It is possible that smaller doses of APO, that do not produce stereotypy, may have a stronger elevating effect on running. Since a range of APO doses has not been tested, it is not clear if the differences in APO and AMP's effects on wheel running are dose specific. As the 5.0 mg/kg dose seemed large in terms of the behaviours it elicited, a range of lower doses was tested in this second experiment.

In this second experiment, several procedural changes were made from the first experiment. The number of acquisition trials was increased from four to five since the magnitude of sensitization gets larger with each trial. The 20-minute delay before the rats were placed in the wheels was eliminated due to the time course difference of AMP and APO. Vanderschuren *et al.* (1999a) found that AMP's locomotor effects are greatest around 120 minutes after the injection, whereas Mattingly *et al.* (1988b) showed significant increases in activity over approximately 45 minutes after APO administration. Therefore in this experiment that used only APO, there was no delay before rats were placed in the wheels, and only 45 minutes of wheel running was measured.

There was also a change in the apparatus used. In the first experiment, 12 wheels were aligned on a single rack and kept in the colony room. This second experiment used four wheels that were separated from each other and kept in a testing room different from the colony room. This change was made due to the unavailability of wheels on the rack

at the time of the experiment. Since wheel differences were examined and found not to influence running (Limebeer, 1998), it was believed that the difference in apparatus would not influence APO's effects on the animals' running.

The design of this experiment included testing with 0.0, 1.0, and 2.5 mg/kg APO. These doses were chosen in order to include the lowest (0.0 mg/kg) and the highest dose (1.0 mg/kg) of APO administered during acquisition trials. To be able to make comparisons with Experiment 1, 2.5 mg/kg APO was also included at testing.

Method

Subjects

Twenty-four male Sprague-Dawley rats (Charles River Canada) that weighed between 363 and 466 g on the first day of injection served as subjects. These rats were previously involved in a study looking at the effects of pair-housing on feeding and had experienced periods of individual and pair housing (Lopak, 2000). For this experiment, they were individually housed and had ad-lib access to food and water.

Apparatus

Four individual running wheels (11 cm wide x 33 cm in diameter) were kept in a quiet room separate from the animals' colony room. All of the wheels had resting cages (25 x 30 x 25 cm) attached to which the animals had free access during the wheel part of the experiment. Cages and wheels were separate from each other and placed on a table around the room preventing rats from visual contact. Each wheel had one magnet aligned with a reed switch, which recorded one count for each full revolution of the wheel. Counts were recorded by the Vital View system in 5-second bins and were summed for the full session.

Drugs

Aliquots of APO (0.1, 0.3 and 1.0 mg/ml) were prepared every testing day in a VEH consisting of 1% ascorbic acid. VEH injection was 1% ascorbic acid. All drugs were injected s.c. at a volume of 1.0 ml/kg.

Procedure

After completing the pair-housing experiment, all animals were individually housed and given seven days of daily weighing before the start of the present experiment. At the beginning of the experiment, rats were randomly assigned to one of four groups (GVEH, G0.1, G0.3, or G1.0) based on the dose of APO injected. Due to the number of wheels available, animals were tested in six replications of four with each dose tested in each replication. On acquisition days, groups of four animals were transported from the colony room to the test room. They were injected s.c. with the appropriate dose of APO and then placed in the wheel cages for 45 minutes. This procedure was carried out at least 48 hours apart, on days 1, 3, 6, 8, and 10. On the days that they were not tested, rats were simply weighed. Ten days after the last acquisition trial, on days 20, 22, and 24, they were tested with VEH, 1.0, and 2.5 mg/kg APO (TVEH, T1.0, and T2.5) in a counterbalanced manner.

Results

Figure 3 shows the effects of low doses of APO administrations on mean number of wheel turns over five acquisition trials. A 4 (GROUP; GVEH, G0.1, G0.3, and G1.0) x 5 (TRIAL) mixed ANOVA revealed significant main effects of TRIAL, $F(4, 80) = 6.72$, $p < 0.01$, GROUP $F(3, 20) = 6.77$, $p < 0.01$, and a significant TRIAL x GROUP

interaction, F (12, 80) = 2.51, $p < 0.01$. Subsequent tests explored the effects of APO dose on running for each acquisition trial.

The relationship between the dose of a drug and the response it elicits is typically depicted and interpreted in terms of a dose-response curve. Since this experiment used a range of APO doses, it is possible to explore the dose-response relationship. The effects of dose of APO on the pattern of running in rats in this experiment were assessed by performing separate trend analyses for each acquisition trial. There was a significant linear contrast for all trials, with the lowest F value in trial 1, F (1, 20) = 9.08, $p < 0.01$, and no higher order trends. This result suggests that as the dose of APO increases from 0.0 mg/kg to 1.0 mg/kg, there is also a corresponding increase in the running suppression.

Figure 4 shows the effects of TVEH, T1.0, and T2.5 APO tests on mean number of wheel turns. A 4 (GROUP) x 3 (TEST) mixed ANOVA revealed only a significant main effect of TEST, F (2, 40) = 16.19, $p < 0.01$. Average running was lower when rats were tested with 1.0 mg/kg and 2.5 mg/kg APO than when tested with VEH. To assess the effect of the tests, three one-way ANOVA's were conducted (one for each test). Only the TVEH test was significant, F (3, 20) = 3.29, $p < 0.05$. Trend analysis was performed for TVEH test, and a significant linear contrast was found, F (1, 20) = 8.95, $p < 0.01$. This indicates that as the previous exposure to APO increased from 0 to 1.0 mg/kg running was increasingly suppressed in the TVEH condition. This finding is consistent with a dose-dependent conditioned suppression explanation, with the greatest suppression seen in G1.0 rats.

Discussion

This experiment found that APO at doses between 0.1 and 1.0 mg/kg produced a dose-dependent suppression in running, represented by the significant linear trend during acquisition. This finding was unexpected and was not completely consistent with previous literature exploring these doses of APO and their effects on activity. To review, at low doses (< 0.2 mg/kg), APO decreased activity in rats (Katsura *et al.*, 1984; Mattingly *et al.*, 1988b; Nickolson, 1981; Radhakishun & Van Ree, 1987; Nowak & Kuschinsky, 1987; Van Ree & Wolterink, 1981) and at higher doses (> 0.5 mg/kg), APO elevated activity (Katsura *et al.*, 1984; Nickolson, 1981) and elevated running (Mattingly *et al.*, 1988b). Evidence has suggested that the inhibitory effect of low APO dose was due to autoreceptor stimulation and the excitatory effect of high APO dose was due to postsynaptic receptor stimulation (Katsura *et al.*, 1984; Nickolson, 1981). Therefore, it would have been expected that at low doses there may be a running suppression, and a dose of 1.0 mg/kg APO should stimulate the DA postsynaptic receptor and elevate running, which was not found. It should be noted that these results are consistent with AMP effects seen previously in this lab (Serwatkiewicz *et al.*, 2000), where AMP also suppressed running in a dose dependent manner.

There are some studies reporting a suppression in locomotion with high doses of APO, but they also found elevations in stereotyped behaviour (Segal & Mandell, 1974). There was a negative correlation between locomotion and stereotypy--higher stereotyped behaviour resulted in lower locomotion. Stereotypy may be an explanation for the suppression in running seen with 1.0 mg/kg, as engaging in stereotypic behaviour may interfere with running in the wheel. Evidence from the first two experiments however,

does not provide strong support for this explanation. For example, in Experiment 1, APO at a dose of 5.0 mg/kg did not suppress nor elevate running although stereotypy was present. Since higher APO doses result in higher stereotyped behaviour, a greater suppression in running with 5.0 mg/kg than with 1.0 mg/kg would have been expected. Therefore, it is unlikely that stereotypy was the main contributing factor in the wheel running suppression with a 1.0 mg/kg APO dose.

As there seems to be a suppressive trend in running in drug response from 0.1 to 1.0 mg/kg and also a difference in running from 1.0 to 5.0 mg/kg of APO, a wider range of drug doses was tested in the third experiment.

Experiment 3

The results from the first and second experiments suggest that APO dose plays an important role in the drug's affect on wheel running. At doses used in Experiment 2, (0.1 to 1.0 mg/kg), APO had a dose-dependent suppressive effect on running. At a high dose used in Experiment 1 (5.0 mg/kg), running was neither suppressed nor elevated, although the animals did exhibit severe stereotyped behaviours that may have prevented an elevation in their running. There were also differences between these two experiments in response to TVEH test injections. In Experiment 2 there was a suppression in running seen in rats previously exposed to APO when tested with VEH. This suppression varied with prior APO dose, becoming larger as the dose increased. In contrast, in Experiment 1 where 5.0 mg/kg had no effect on the amount of running there was no evidence for any conditioned effect. Given the complex actions of APO on DA receptors and now the complex effects of APO on wheel running, it seemed prudent to explore a larger dose range of APO in this experiment.

Several changes from Experiment 2 were made in this experiment. First, instead of the separate wheels that were used in the second experiment, the wheels on the rack were used again and kept in the animals' colony room for this experiment. The animals were pair-housed through-out the experiment, for convenience and space limitation in the colony room as opposed to individually housed as in Experiment 1. This change was believed to not have any effect on the results since all rats were tested individually in the wheels.

Method

Subjects

Forty-eight male Sprague-Dawley rats (Charles River Canada) that weighed between 200 and 250g on the first day of injection served as subjects. They were naïve to experimentation and were pair-housed throughout the entire experiment.

Apparatus

The wheels used in this experiment were the same as those of Experiment 1.

Drugs

Aliquots of APO (0.03, 0.1, 0.3, 1.0 and 3.0 mg/ml) were prepared every testing day in a VEH consisting of 1% ascorbic acid. VEH injection was ascorbic acid.

Procedure

The animals were habituated in the colony room for two weeks before the experimental procedure. During this time they were weighed daily. At the beginning of the experiment the animals were randomly assigned to one of six groups (GVEH, G0.03, G0.1, G0.3, G1.0 or G3.0) based on the APO dose injected. Animals were tested in groups of 12 in the colony room. On acquisition days, they were injected s.c. with the

appropriate dose of APO and then placed in the wheel cages for 45 minutes. On the days that they were not tested, they were simply weighed. This procedure was carried out for days 1, 3, 6, 8, and 10. On days 20, 22, and 24, ten days after the last acquisition trial, they were tested with TVEH, T1.0, and T2.5 APO in a counterbalanced manner. After four acquisition trials, one of the G3.0 rats exhibited stereotypic behaviour that was similar to that discussed in Experiment 1, and therefore did not receive a fifth acquisition trial. All rats did however, receive all tests.

Results

Figure 5 shows the effect of a range of APO doses on mean number of wheel turns over five acquisition trials. A 6 (GROUP: GVEH, G0.03, G0.10, G0.30, G1.00, and G3.00) x 5 (TRIAL) mixed ANOVA revealed significant main effects of TRIAL, $\underline{F}$ (4, 164) = 21.319, $\underline{p} < 0.01$, GROUP, $\underline{F}$ (5, 41) = 2.86, $\underline{p} < 0.05$, and a significant TRIAL x GROUP interaction, $\underline{F}$ (20, 164) = 3.52, $\underline{p} < 0.01$.

Following Experiment 2, to assess whether there was a dose-response relationship, separate trend analyses were performed for each acquisition trial. The groups did not differ on the first acquisition trial, $\underline{F} < 1.0$. For trials 2 to 5 there was always a significant linear trend, with the smallest F value in trial 3, $\underline{F}$ (1, 42) = 5.09, $\underline{p} < 0.05$. On trials 2 and 3 the quadratic trend approached significance, $\underline{F}$ (1, 42) = 3.874, $\underline{p} = 0.06$, and $\underline{F}$ (1, 42) = 3.87, $\underline{p} = 0.06$, respectively. On trials 4 and 5 the quadratic trend was significant, $\underline{F}$ (1, 42) = 6.51, $\underline{p} < 0.05$, and $\underline{F}$ (1, 41) = 4.57, $\underline{p} < 0.05$, respectively. The significant linear and quadratic trends suggest that the graphic representation of the dose-response curve for the dose range of APO tested in this study is curvilinear.

Figure 6 shows the effect of TVEH, T1.0 and T2.5 APO tests on mean number of wheel turns. A 6 (GROUP) x 3 (TEST) mixed ANOVA revealed a significant main effect of GROUP, F (5, 42) = 2.48, $p < 0.05$, and a significant GROUP x TEST interaction, F (10, 84) = 3.59, $p < 0.01$. The effects of the tests were assessed using three one-way ANOVA's (one for each test). No significant group difference effect was found for TVEH, suggesting that in this experiment prior drug history did not significantly influence running. There was a significant effect of GROUP in the T1.0 test, F (5, 47) = 3.06, $p < 0.05$, and a significant GROUP effect in the T2.5 test, F (5, 47) = 2.97, $p < 0.05$.

Trend analyses were performed for T1.0 and T2.5 tests. There was a significant linear trend for T1.0, F (1, 42) = 10.42, $p < 0.01$, and a quadratic trend that approached significance, F (1, 42) = 3.22, $p = 0.08$. Testing with T2.5 revealed both a significant linear, F (1, 42) = 6.48, $p < 0.05$, and quadratic trend, F (1, 42) = 5.48, $p < 0.05$. The significant quadratic trend suggests that rats treated with low APO doses run less and those treated with higher doses run more, compared to control VEH animals receiving APO for the "first" time. These test results seem consistent with the effects of APO seen during acquisition trials in this experiment. On the first acquisition trial APO at all doses had little effect and during test when GVEH rats received APO it also appeared to have minimal effects. For the groups that received repeated APO administration, the effect of T2.5 test seemed to potentiate the effects seen during acquisition.

Discussion

Interestingly, this third experiment testing a larger range of APO dose failed to find the suppression in running seen with 1.0 mg/kg APO in Experiment 2. In fact this dose and the 3.0 mg/kg dose of APO produced elevations in running. In the second

experiment, rats were transported to a testing room, whereas in this third experiment they remained in the colony room. Fraioli, Crombag, Badiani, & Robinson (1999) reported that sensitization to the locomotor increasing effects of AMP were very sensitive to the exact procedure used in their induction. Only when rats were transported to a novel environment, and not when AMP was administered in their home cage was sensitization evident. In their study, rats were administered seven intravenous (i.v.) daily infusions of either saline or 0.375 mg/kg AMP in two different environments. The HOME groups received the infusions in their home cage whereas the NOVEL groups received the infusions in a novel environment. Seven days following their last saline or AMP treatment, all rats were given a challenge infusion of 0.375 mg/kg AMP, using the procedure used to induce sensitization. With the first injection, there was no difference in locomotor activity between HOME and NOVEL groups of rats administered AMP and those administered saline. In the HOME groups, rats that received repeated AMP treatments showed greater locomotor activity than those that received saline, however, this small locomotor effect did not change with repeated administration. In addition, this group also failed to show sensitization to the challenge infusion of AMP. So in the home cage, the locomotor effects of AMP were relatively minor. On the other hand, locomotor activity in rats treated with AMP in a novel environment became progressively larger with each infusion and sensitization was evident when they were given the AMP challenge. This suggests that the nature of the environment in which the rats receive the drug (HOME vs NOVEL) may profoundly the development of sensitization.

The fourth experiment examined APO effects on wheel running of rats tested in the colony room (as in Experiment 2), and rats transported to a novel testing room (as in Experiment 3).

Since minor changes in procedure that were originally believed to not have a significant effect on wheel running, did in fact seem to have an effect, the fourth experiment replicated Experiment 2 and 3 as much as possible.

Experiment 4

Experiment 4 aimed to clarify the discrepant findings between Experiments 2 and 3 with 1.0 mg/kg APO. This experiment specifically tested 0.0 and 1.0 mg/kg APO repeating the procedures of Experiments 2 and 3.

Method

Subjects

Thirty-six male Sprague-Dawley rats that weighed between 292 and 360 g on the first day of injection served as subjects. They were naïve to experimentation and were individually housed through out the experiment.

Apparatus

Four separate wheels (the same as in Experiment 2) were located in a testing room, different from the animals' colony room. Twelve running wheels on a single rack (the same as in Experiment 3) were located in the colony room.

Drugs

Aliquots of APO (1.0 mg/ml) were prepared every testing day in a VEH consisting of 1% ascorbic acid. VEH injection was ascorbic 1% acid. All drugs were injected s.c. at a volume of 1.0 ml/kg.

Procedure

Rats were randomly assigned to one of four conditions: the first two groups were treated the same as those in Experiment 3, using separate wheel cages (SAPO, n = 8 and SVEH, n = 8), the third and fourth groups were treated the same as those in Experiment 2, using the wheel rack (RAPO, n = 10 and RVEH, n = 10). Rats tested in the separate cages were tested in four replicates of four rats. Animals tested in the wheel rack were tested in two replicates of ten rats. On each acquisition day, SAPO and SVEH rats were transported from the colony room to the test room. Then they were injected with the appropriate drug and placed into the separate wheels. Their running was measured for 45 minutes and then they were transported back to their colony room. For animals in groups RAPO and RVEH, they were injected with the appropriate drug and then placed in the wheel cages on each acquisition day. Their wheel running was measured for 45 minutes and then they were returned to their home cages. This procedure was carried out for days 1, 3, 7, 9, and 11. On the days they were not given the injections, they were simply weighed. There was an eight day delay before they were tested with TVEH, T1.0, and T2.5 in a counterbalanced manner on days 19, 21, and 23. One of the rats in the RAPO group exhibited severe stereotypy and bleeding from the digits and was not tested with T2.5 test.

Results

Figure 7 shows the effect of 1.0 mg/kg APO on wheel running of rats tested in the wheel rack and separate cages over five acquisition trials. To assess the effect of APO in the different testing environment on wheel running, a 5 (TRIAL) x 2 (DRUG: APO and VEH) x 2 (PLACE: RACK and SEPARATE) mixed ANOVA was conducted. There

were significant main effects of TRIAL, F (4, 128) = 7.85, $p < 0.01$, DRUG, F (1, 32) = 9.65, $p < 0.01$, and the main effect of PLACE approached significance, F (1, 32) = 3.54, $p = 0.07$. There was also a significant TRIAL x PLACE interaction, F (4, 128) = 3.29, $p < 0.05$, a PLACE x DRUG interaction that approached significance, F (1, 32) = 3.82, $p = 0.06$, and a significant TRIAL x PLACE x DRUG triple interaction, F (4, 128) = 3.11, $p < 0.05$. Five separate 2 (DRUG) x 2 (PLACE) ANOVAs were conducted (one for each trial) and several significant results were found. The main effect of PLACE was significant on trials 3, 4, and 5, with the smallest F value in trial 4, F (3, 32) = 4.28, $p < 0.05$. The main effect of DRUG was significant for trials 1, 2, 4, and 5, with the smallest F value in trial 5, F (1, 32) = 4.68, $p < 0.05$, and approached significance on trial 3, F (1, 32) = 3.53, $p = 0.07$. The DRUG x PLACE interaction was significant for trials 4 and 5, F (1, 32) = 5.02, $p < 0.05$, and F (1, 32) = 5.86, $p < 0.05$, respectively.

To determine how the place and dose interacted, simple main effects comparing APO to VEH in each environment were analyzed. Significant differences in the drug effect in the two testing environments were found. When rats were tested on the rack, groups RAPO and RVEH differed significantly only on trial 1, F (1, 32) = 4.95, $p < 0.05$. This finding indicates that rats administered APO suppressed their running compared to those administered VEH in the wheel rack only on the first trial. However, with additional APO injections RAPO animals did not differ in running from the RVEH rats. A different profile existed for those rats tested in the separate cages. Rats in group SAPO ran significantly less than rats in group SVEH on trials 2, 3, 4, and 5, with the lowest F value in trial 2, F (1, 32) = 4.94, $p < 0.05$.

Comparisons between the two groups of rats receiving APO (one in each environment) revealed that running differed on trials 3, 4 and 5, lowest F value on trial 3, $F(1, 32) = 7.54$, $p < 0.05$. On these trials, rats administered APO in the rack (group RAPO) ran significantly more than rats administered APO in the testing room (group SAPO). This difference in running between the APO animals tested in the wheel rack and the separate cages could be due to the variation in environmental setting or mechanics of the wheels, and therefore might not accurately reflect the drug's effects. However, comparisons of control rats' running in the two environments failed to support any of these assumptions. There were no differences in running for the animals receiving VEH in either environment, $F < 1$ on all trials. Since the control animals ran the same amount in both environments, it suggests that the differences in environment and/or wheel apparatus did not prevent or facilitate running in control rats.

The effects of TVEH, T1.0 and T2.5 APO tests on wheel running in the two environments are shown in Figure 8. A 2 (DRUG) x 2 (PLACE) x 3 (TEST) mixed ANOVA revealed a significant main effect of PLACE, $F(1, 31) = 4.66$, $p < 0.05$, a significant DRUG x PLACE interaction, $F(1, 31) = 4.65$, $p < 0.05$, a DRUG x TEST interaction, $F(2, 62) = 4.03$, $p < 0.05$ and a significant DRUG x PLACE x TEST triple interaction, $F(2, 62) = 3.43$, $p < 0.05$. To assess the effect of the tests on running, three separate 2 (DRUG) x 2 (PLACE) ANOVAs were conducted (one for each test). There was a significant main effect of DRUG for the TVEH test, $F(1, 32) = 7.38$, $p < 0.05$. Animals that had a history of APO ran less than rats with no APO experience when tested with VEH suggestive of a conditioned suppression of running.

For test T1.0, the main effect of PLACE, F (1, 32) = 7.15, $p < 0.05$, and of DRUG was significant, F (1, 32) = 4.05, $p = 0.05$. The DRUG x PLACE interaction was also significant for the T1.0 test, F (1, 32) = 7.38, $p < 0.05$. No significant results were found for the T2.5 test, however, the DRUG x GROUP interaction approached significance, F (1, 32) = 3.86, $p = 0.06$.

To fully examine the DRUG x GROUP interaction, simple main effects were analyzed. For rats tested on the rack, significant simple main effects of tests TVEH and T1.0 were found, F (1, 32) = 6.37, $p < 0.05$, and F (1, 32) = 12.57, $p < 0.01$, respectively. The simple main effect of test T2.5 approached significance, F (1, 32) = 3.54, $p = 0.07$. In the rack condition, RAPO rats that were administered TVEH at test suppressed their running compared to RVEH rats. However, when administered T1.0 and T2.5 at test, RAPO rats ran more than RVEH rats. For rats tested in the separate cages, there were no significant simple main effects, indicating that both SAPO rats and SVEH rats ran equally on all tests.

Discussion

The question that this experiment aimed to answer was whether procedural differences had an effect on wheel running of rats administered 1.0 mg/kg APO. The results for the acquisition trials indicate that rats administered APO and tested in the wheel racks ran significantly more than those tested in the separate cages. The suppression in running of rats transported to the testing room and placed in the separate cages was found both in this experiment and in Experiment 2. However, repeated 1.0 mg/kg APO administration seems to have a different effect on rats tested in the colony room using the wheels on a single rack. In both Experiment 3 and this experiment, APO

did not suppress running and in fact in Experiment 3 this dose elevated running relative to the VEH control group. The equivalent running of rats treated with VEH in the two environments in this experiment and in the comparing VEH group rats in Experiments 2 and 3, rules out the possibility that environment and/or apparatus differences was responsible for the APO group differences. Running in the two environments were different only when rats were repeatedly injected with 1.0 mg/kg APO. This suggests that the effects of APO at this dose are significantly influenced by environmental factors.

From informal observation, in the wheel racks running in one cage would create a noisy environment for all the rats that were tested at that time. The noise could potentially have acted as a stimulus triggering running in the other rats. The separate wheel cages, on the other hand, were distinctly separated from each other and running in one cage did not create as much noise. The speculation that environmental noise was important in the effects of repeated 1.0 mg/kg APO administration on wheel running was tested in Experiment 5.

Experiment 5

Evidence suggests that environmental stimuli have profound effects on the activity of rats treated with stimulants, and also rats that have been food deprived. Research by Davis (1988) examining the effects of APO and AMP on acoustic startle found that startle was greater in rats after an injection of 3.0 mg/kg APO or 4.0 mg/kg AMP. Also, Hall (1956) found that minimal changes in environmental stimulation can affect a food-deprived rat's activity. For example, for food deprived rats, an increase or change in environmental stimuli resulted in an increase in wheel running. It has been suggested that deprivation does not necessarily increase activity, but increases reactivity to external

stimuli that is measured as running in the wheel (Campbell & Sheffield, 1953). It is possible that exposure to drugs also increases reactivity to external stimuli. Therefore, increasing environmental stimuli should affect wheel running in rats administered a drug more so than those not given any drug.

There was a distinct difference in the amount of environmental stimuli rats were exposed to in the above experiments. The running suppression was always observed with repeated 1.0 mg/kg APO in rats tested in the separate wheel cages, but not in the wheel rack. Since the wheels in the rack produced more noise compared to the separate cages, it is possible that APO rats were more reactive to the noise in the rack. The fifth experiment tested all animals in the separate cages, manipulating the amount of noise present during testing.

Method

Subjects

Sixteen male Sprague-Dawley rats (Charles River Canada) that weighed between 295 and 314 g on the first day of injection served as subjects. These rats were previously involved in a study looking at the effects of pair-housing on feeding and had experienced periods of individual and pair housing (Lopak, 2000). For this experiment they were individually housed and had ad-lib access to food and water.

Apparatus

The wheels used were the same as Experiment 2.

Drugs

APO (1.0 mg/ml) was dissolved every testing day in a VEH consisting of 1% ascorbic acid.

Procedure

After being housed individually animals were given seven days of daily weighing before the start of the experiment. At the beginning of the experiment, rats were randomly assigned to one of two groups (NOISY and QUIET) based on the environmental manipulation. The rats were tested in four replicates of four in a counterbalanced manner. Rats in the NOISY group were injected with APO and placed in the wheel cages for 45 minutes with a radio playing in the background for the entire duration. Rats in the QUIET group were treated the same except the environment was quiet. This procedure was repeated for days 1, 3, 5, 8, and 10.

Results

Figure 9 shows the mean running in APO-treated rats that were tested in a noisy versus quiet environment over five acquisition trials. The results were analyzed using a 2 (GROUP) x 5 (TRIAL) repeated measures ANOVA. No significant results were found, indicating that over the five trials, group NOISY did not differ from group QUIET.

Discussion

Manipulation of noise in this experiment was unsuccessful in explaining the running differences with repeated administration of 1.0 mg/kg APO. The choice of noise was perhaps not an ideal environmental manipulation. Since the radio played continuously for the duration of the wheel sessions for rats in the NOISY group, they may have habituated to the sound of the radio and therefore this noise might not have affected their running. Another important environmental manipulation that was not explored in this thesis is the difference in testing rooms in Experiments 2 and 3. Evidence suggests that animals differ in their response to drug administrations when injections are given in the

home versus a novel environment (Fraioli *et al*, 1999). Perhaps rats that were physically moved from their colony room to the test room experienced a stronger, or at least a different, drug-environment association than those that were housed and tested in the colony room. These and other speculations of environmental influences of APO-induced wheel running remain to be tested in future studies.

General Discussion

The experiments in this thesis indicate that the effects of repeated AMP and APO administration on wheel running are affected by dose, number of drug injections, and the administration environments. How these factors combine to result in the running observed is not clear. The procedures employed in Experiments 1 to 4 consistently involved two phases, acquisition and testing. The findings of the acquisition trials across all experiments will be reviewed first, then the findings of the tests, and finally research on how drugs and wheel running relate to other areas of research will be discussed.

When the effects of APO doses on rats' running during the acquisition trials of Experiments 1 to 4 were compared, several interesting patterns emerged. First, in Experiment 2, a significant linear contrast suggested that as the dose of APO increased from 0.0 to 1.0 mg/kg, there was also a corresponding decrease in running. In Experiment 3, the significant quadratic trend suggested that the dose-response curve for APO on wheel running is curvilinear. Evidence from Experiments 1 to 4 suggest that the dose response curve may be depicted as a U-shape, with low APO doses producing a suppression in running and higher doses an elevation. However, the inconsistent findings with 1.0 mg/kg APO on wheel running adds complexity to this simple interpretation.

A 1.0 mg/kg dose of APO either elevated or suppressed wheel running during acquisition trials in different experiments. In Experiment 2, rats injected with 1.0 mg/kg APO ran very little (< 5 wheel turns on all acquisition trials), whereas in Experiment 3, they ran considerably more than VEH treated rats (> 300 wheel turns by the fifth acquisition trial). When the procedures of Experiments 2 and 3 were replicated in Experiment 4 with repeated 1.0 mg/kg APO administration, rats' running was again dependent on the environment that they were tested in. Consistent with Experiment 2, results from Experiment 4 revealed that APO rats tested in the separate wheel cages suppressed their running compared to running in the other groups. For the APO rats tested on the rack in Experiment 4, running increased in the same manner as VEH rats. The important finding was that APO rats' running on the rack was significantly higher than APO rats' running in the separate cages. VEH rats ran the same amount in both the rack and separate cages, indicating that differences in environment and procedure did not affect running in non-APO treated rats, suggesting some type of drug-environment interaction. In Experiment 5, one hypothesis for this environmental difference, environmental noise, was investigated, but failed to explain the difference.

Experiment 1 comparing AMP and APO suggests an extra level of complexity. Both drugs are stimulants, AMP being an indirect agonist, meanwhile APO acts directly on the DA receptor. However, in this experiment running on the rack was not suppressed after a high dose of APO. AMP in Experiment 1 and Serwatkiewicz *et al.* (2000) consistently suppressed wheel running on the rack. Thus the same environment has different effects on running in response to the two stimulants. While the environment influences how higher doses of APO affect running, the pattern seen with AMP is consistently

suppressed, but AMP in the separate cages has not been tested. Several studies contrasting the effects of AMP and APO have found that they produce changes in behaviour that are dose dependent and distinguishable from each other (Fray *et al.*, 1980; Laudrup & Wallace, 1999). It would be beneficial to test a wider range of stimulants and examine how environmental stimuli influence running.

For Experiments 2 to 4, animals were tested with TVEH, T1.0, and T2.5 APO after the acquisition trials. As acquisition trials in all these experiments included 1.0 mg/kg APO group of rats, it is possible to look for test commonalties over these experiments. While there were differences in the APO-induced running during acquisition, there seems to be a consistent pattern in the TVEH tests when all rats received a VEH injection. First, the average running in APO rats tested with TVEH was always lower than VEH control rats. During acquisition trials, G1.0 rats in Experiment 2 and SAPO rats in Experiment 4 ran less than the appropriate VEH control rats. The APO group suppression seen with the TVEH tests in these two experiments provided evidence of conditioning. On the other hand, RAPO rats in Experiment 4 did not show a suppression in running during acquisition trials. In this condition and in Experiment 3 animals receiving 1.0 mg/kg APO actually ran as much as or more than the GVEH rats. Thus the suppression of APO rats relative to VEH rats seen on TVEH test does not seem to be linked to the observed drug effects during acquisition on wheel running. However the fact that running in APO animals is suppressed on TVEH tests suggest that the unconditioned effect of APO on wheel running might actually be higher than the observed running after APO. How this conditioned suppression interacts with the environmental factors influencing APO's effects on wheel running is not clear at this point.

Evidence for conditioning with AMP injections was just as unclear as that with APO. In the first experiment, AMP treated rats tested with VEH showed a conditioned suppression of wheel running, relative to VEH injected rats. A similar conditioned suppression, however, was not evident in Serwatkiewicz *et al.*'s (2000) study. When AMP rats in their study were tested with saline, running did not differ from saline injected controls. Rats with AMP wheel pairing (group AMP/SAL) showed a suppression in running compared to the other two groups (SAL/SAL and SAL/AMP). Pairing the drug with the wheel was an important factor in sensitizing the AMP suppression of running. Serwatkiewicz *et al. 's* rats that were administered AMP in their home cage and saline before wheel access, thus having the same AMP and wheel experience as those that were administered AMP before wheel access and saline in their home cage, ran equivalently to controls. This finding suggests that although the conditioned suppression was not found in saline tests, the drug-environment association is still an important variable influencing the degree of AMP-induced suppression in wheel running.

The sensitization of APO on wheel running were evident in Experiments 1 to 4 (with RAPO rats). In Experiments 1, 3, and RAPO in Experiment 4, where APO did not suppress running relative to VEH rats, APO animals showed elevated running relative to VEH rats when they were all tested with T1.0 and T2.5 APO. In addition, those rats that ran less than VEH rats during acquisition trials (Experiments 2, 3, and SAPO in Experiment 4) continued to run very little when tested with T1.0 and T2.5 APO. This argues strongly that the elevation in running seen in some of the APO groups over acquisition trials (Experiments 1, 3, and RAPO in Experiment 4) is a true sensitization as

the effects of the test injection of APO were larger in APO experienced rats than in VEH treated rats. The experiments where APO induced a suppression during acquisition are more difficult to interpret in the T1.0 and T2.5 tests as there may be a floor effect and so differences in running between VEH and APO treated rats may not be evident.

The results from the experiments in this thesis and previous research indicate that although the dose and number of injections influence the animals' response to AMP or APO administrations, environmental factors play a key role in how the animals will respond to the drug. Different doses of AMP have been found to increase locomotor behaviour in dose-dependent manner (Antoniou & Kafetzopoulos, 1991). However, with wheel running, in rats naïve to the wheel, there is a consistent dose-dependent suppression in running (Serwatkiewicz *et al.*, 2000). Consistent with this finding, Experiment 1 in this thesis found a suppression in running with a 3.0 mg/kg AMP dose. Responding to APO administrations has also been found to be dose-dependent, with lower doses suppressing and higher doses elevating locomotion (Mattingly *et al.*, 1988b; Nickolson, 1981). This thesis also confirmed that APO at low doses suppresses wheel running while at higher doses of APO running is not suppressed and in certain circumstances may be elevated.

Since repeated injections are necessary to observe and measure sensitization, the number of injections also influences the animals' response to the drug. For example, Damianopoulos and Carey (1993) found that the first injection of 2.0 mg/kg APO produced hypolocomotion in rats, but that by the fourth injection hyperlocomotion was observed in comparison to the control group. They also found that five out of the 18 rats that received the APO injections continued to suppress their locomotive behaviour for all

four trials suggesting some individual differences in response to APO. This is an important finding for the present research because it suggests that at 2.0 mg/kg, APO can produce both a suppression and an elevation in locomotion with repeated injections. In comparison to this thesis, a 1.0 mg/kg dose of APO also showed both an elevation and a suppression in running. It is possible that in Damianopoulos and Carey's (1993) study and in this thesis, that additional injections, more than the four or five administered, may increase locomotion and wheel running; however, this was not tested.

When 1.0 mg/kg APO was investigated in this thesis, the environment in which the rats received the injections proved to be significant in determining whether wheel running would be elevated or suppressed. Comparison of the procedures used by Mattingly et al. (1997) and this thesis may provide important insight into the differences in wheel running behaviour. Mattingly et al. used two running wheels that were kept in separate sound-attenuated experimental cubicles. In comparison to the running wheels used in this thesis, Mattingly et al's procedure had more in common with the separate cages condition than the rack condition. Thus, it would be expected that the running in Mattingly et al.'s animals would be more similar to the rats tested in the separate cages. However, the elevation in running in Mattingly et al.'s animals was more similar to the rats that were tested in the rack. The results from Mattingly et al.'s study and this thesis indicate that although running seems to be affected by environment, the exact manipulation(s) that determines whether running is increased or decreased is not known.

The importance of environment in sensitization to stimulants is shown in other studies. For instance, Fraioli *et al.* (1999) found that sensitization to AMP is environment sensitive: rats that were transported to a novel environment showed

sensitization to AMP but those that received the drug in their home cage did not. In comparison to the present thesis, differences were found in wheel running behaviour of rats that were administered APO in the colony room and those that were transported to a testing room. This interaction between environment and APO-induced wheel running should be studied in future research.

The effects of repeated APO and AMP administration on wheel running investigated in this thesis provides evidence that the dose of the drug, type of drug, and the circumstances surrounding drug administration are critical to rats' wheel running behaviour. The importance of research involving wheel running is two-fold; first, it is distinguishably different from other forms of locomotor behaviour (Sherwin, 1998) and second, wheel running involves properties that are also reported to be important in drug addiction (Werme, Thoren, Olson, & Brene, 1999). Research involving the effects of drugs on locomotor behaviour has utilized many different types of apparati to measure locomotion but few have utilized the running wheel. Previous research involving the effects of stimulants on wheel running, and the present thesis studying the effects of AMP and APO on wheel running have found inconsistent results. Depending on the drug dose, wheel experience of the animals, and type of testing environment, stimulants can produce varied results on wheel running behaviour. With other forms of locomotor behaviour, stimulants (at doses that act on the post-synaptic DA receptor) have consistently produced an elevation in activity in a dose-dependent manner. The low correlation between the wheel and other apparati used to measure locomotion are not trivial. Not only has running in a wheel been found to be much greater than running on a flat treadmill (Collier & Hirsch, 1971) and faster than on a planar runway (Hadded *et al.*,

1994), research has also shown that wheel running is reinforcing and appetitive (Belke & Heyman, 1994; Iverson, 1993; Sherwin, 1998)—properties which are also important in drug addiction. Recently, Werme *et al.* (1999) reported a genetic link between drug-taking behaviour and wheel running. Current research looking at limited and unlimited access to a running wheel found striking parallels to that of drug self-administration (Lattanzio, 2000). The motivational properties of drug taking may be similar to that of wheel running, therefore, future research should recognize the potential of wheels in the study of drug addiction.

References

Anagnostaras, S. G. & Robinson, T. E. (1996). Sensitization to the psychomotor stimulant effects of amphetamine: Modulation by associative learning. Behavioral Neuroscience, 110, 1397-1414.

Anderson, E. E. (1937). Interrelationship of drives in the male albino rat: I. Intercorrelatations of measures of drives. Journal of Comparative Psychology, 24, 73-118.

Antoniou, K., & Kafetzopoulos, E., (1991). A comparative study of the behavioural effects of d-amphetamine and apomorphine in the rat. Pharmacology Biochemistry and Behaviour, 39, 61-70.

Badiani, A. & Anagnostaras, S. G. (1995). The development of sensitization to the psychomotor stimulant effects of amphetamine is enhanced in a novel environment. Psychopharmacology, 117, 443-452.

Belke, T. W. & Heyman, G. M. (1994). A matching law analysis of the reinforcing efficacy of wheel running in rats. Animal Learning and Behavior, 22, 267-274.

Bernardi, M. M., Scavone, C., & Frussa-Filho, R. (1986). Differential effects of single and long-term amphetamine and apomorphine administrations on locomotor acitivity of rats. General Pharmacology, 17, 465-468.

Castro, Abreu, P., Calzadilla, C. H., & Rodriguez, M. (1985). Increased or decreased locomotor response in rats following repeated administration of apomorphine depends on dosage interval. Psychopharmacology, 85, 333-339.

Collier, G. & Hirsch, E. (1971). Reinforcing properties of spontaneous activity in the rat. Journal of Comparative and Physiological Psychology, 77, 155-160.

Davis, M. (1988). Apomorphine, d-amphetamine, strychnine and yohimbine do not alter prepulse inhibition of the acoustic startle reflex. Psychopharmacology, 95, 151-156.

Damianopoulos, E. N. & Carey, R. J. (1993). Apomorphine sensitization effects: evidence for environmentally contingent behavioral reorganization processes. Pharmacology, Biochemistry, and Behavior, 45, 655-663.

Eikelboom, R. (1999). [Procedural differences affecting amphetamine administrations on wheel running]. Personal communication.

Eikelboom, R. & Stewart, J. (1982). Conditioning of drug-induced physiological responses. Psychological Review, 89, 507-528.

Essman, W.D., Luedtke, R. R., PcGonigle, P., & Lucki, I. (1995). Variations in the behavioural responses to apomorphine in different strains of rats. Behavioural Pharmacology, 6, 4-15.

Evans, K. R. & Vaccarino, F. J. (1986). Intra-nucleus accumbens amphetamine: dose-dependent effects on food intake. Pharmacology, Biochemistry, and Behavior, 25, 1149-1151.

Fraioli, S, Crombag, H. S., Badiani, A., & Robinson, T. E. (1999). Susceptibility to amphetamine-induced locomotor sensitization is modulated by environmental stimuli. Neuropsychopharmacology, 20, 533-541.

Fray, P. J., Sahakian, B. J., Robbins, T. W., Koob, G. F., & Iverson, S. D. (1980). An obersavational method for quantifying the bahvioural effects of dopamine agonists:

contrasting effects on d-amphetamine and apomorphine. Psychopharmacology, 69, 253-259.

Gancher, S., Mayer, A., & Youngman, S. (1996). Changes in apomorphine pharmacodynamics following repeated treatment in 6-hydroxydopamine-lesioned rats. Brain Research, 729, 190-196.

Geary, N., Fudge, J., & Le Sauter, J. (1992). Scheduled running wheel activity indexes the specificity of pharmacological anorexia. Behavioral and neural biology, 58, 1-7.

George, F. R., Porrino, L. J., Ritz, M. C., & Goldberg, S. R. (1991). Inbred rat strain comparisons indicate different sites of action for cocaine and amphetamine locomotor stimulant effects. Psychopharmacology, 104, 457-462.

Hadded, N. G., Szalda-Petree, A., Karkowski, A., Foss, R. L. & Berger, L. H. (1994). Wheel-running in discrete trial and operant paradigms under various effort requirement. Physiology and Behavior, 56, 487-493.

Iverson, I. H. (1993). Techniques for establishing schedules with wheel running as reinforcement in rats. Journal of the Experimental Analysis of Behavior, 60, 219-238.

Kalivas, P. W. & Stewart, J. (1991). Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Research Review, 16, 223-244.

Katsura, G., Itoh, S., & Rehfeld, J. F. (1984). Effects of cholcystokinin on apomorphine-induced changes of motility in rats. Neuropharmacology, 23, 731-734.

Kolta, M. G., Shreve, P., De Souza, V., Uretsky, N. J. (1985). Time course of the development of the enhanced behavioral and biochemical responses to amphetamine after pretreatment with amphetamine. Neuropharmacology, 24, 823-829.

Kuczenski, R., Segal, D. S., Weinberger, S. B., & Browne, R. G. (1982). Evidence that a behavioural augmentation following repeated amphetamine administration does not involve peripheral mechanisms. Pharmacology Biochemistry, and Behavior, 17, 547-553.

Langer, S.Z. & Arbilla, S. (1984). The amphetamine paradox in dopaminergic neurotransmission. Trends in Biochemical Sciences, 9, 387-390.

Lattanzio, S. (2000, November). Ad-lib and two-hour daily wheel access: effects on feeding and running. Poster session presented at the annual meeting of the Society for Neuroscience, New Orleans, LA.

Laudrup, P. & Wallace, L. J. (1999). Sensitization elicited by directly and indirectly acting dopaminergic agonists: comparison using neural network analysis. Psychopharmacology, 141, 169-174.

Leith, N. J. & Kuczenski, R. (1982). Two dissociable components of behavioural sensitization following repeated amphetamine administration. Psychopharmacology, 76, 310-315.

Limebeer, (1998). Wheel running sensitization: an artifact? Unpublished honours thesis, Wilfrid Laurier University, Ontario, Canada.

Lopak, V. (2000). Environmental manipulation affecting feeding. Unpublished manuscript, Wilfrid Laurier University, Waterloo, Ontario, Canada.

Mattingly, B. A. & Gotsick, J. E. (1989). Conditioning and experiential factors affecting the development of behavioural sensitization to apomorphine. Behavioral Neuroscience, 103, 1311-1317.

Mattingly, B. A., Gotsick, J. E., & Marin, C. (1988a). Locomotor activity and stereotypy in rats following repeated apomorphine treatments at 1-, 3-, or 7-day intervals. Pharmacology, Biochemistry, and Behaviour, 31, 871-875.

Mattingly, B. A., Gotsick, J. E., & Salamanca (1988b). Latent sensitization to apomorphine following repeated low doses. Behavioral Neuroscience, 102, 553-558.

Mattingly, B. A., Koch, C., Osborne, F. H., & Gotsick, J. E. (1997). Stimulus and response factors affecting the development of behavioral sensitization to apomorphine. Psychopharmacology, 130, 109-116.

Miller, R., Wickens, J. R., & Beninger, R. J. (1990). Dopamine D-1 and D-2 receptors in relation to reward and performance: a case for the D-1 receptor as a primary site of therapeutic action of neuroleptic drugs. Progress in Neurobiology, 34, 143-183.

Moller, H. G., Nowak, K., & Kuschinsky, K. (1987). Studies on interactions between conditioned and unconditioned behavioural responses to apomorphine in rats. Naunyn-Schmiedeberg's Arch Pharmacology, 335, 673-679.

Nelson, L. R. & Ellison, G. (1978). Enhanced stereotipies after repeated injections but not continuous amphetamines. Neuropharmacology, 17, 1081-1084.

Nickolson, V. J. (1981). Detailed analysis of the effects of apomorphine and d-amphetamine on spontaneous locomotor behaviour of rats as measured in a tv-based, automated open-field system. European Journal of Pharmacology, 72, 45-56.

Nowak, K., & Kuschinsky, K. (1987). Conditioning of behavioural effects produced by an intermediate dose of apomorphine: hypokinesia, ptosis and stereotypies. Naunyn-Schmiedeberg's Arch Pharmacology, 336, 262-266.

Post, R. M. (1980). Intermittent versus continuous stimulation: Effect of time interval on the development of sensitization or tolerance. Life Sciences, 26, 1275-1282.

Radhakishun, R. S. & Van Ree, J. M. (1987). The hypomotility elicited by small doses of apomorphine seems exclusively mediated by dopaminergic systems in the nucleus accembens. European Journal of Pharmacology, 136, 41-47.

Robinson, T. E. & Becker, J. B. (1986). Enduring changes in brain and behavior produced by choronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. Brain Research Reviews, 11, 157-198.

Robinson, T. E. & Berridge, K. C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Research Reviews, 18, 247-291.

Russell, R. L., & Pihl, R. O. (1978). The effect of dose, novelty, and exploration on amphetamine-produced stereotyped behavior. Psychopharmacology, 60, 93-100.

Segal, D. S. & Mandell, A. J. (1974). Long-term administration of d-amphetamine: Progressive augmentation of motor activity and stereotypy. Pharmacology Biochemistry and Behavior, 2, 249-255.

Serwatkiewicz, C. (1999). Amphetamine induced wheel running suppression: a dose effect? Unpublished Honours Thesis, Wilfrid Laurier University, Ontario, Canada.

Serwatkiewicz, C., Limebeer, C., & Eikelboom, R. (2000). Sensitization of amphetamine induced wheel running suppression: dose and context factors. Psychopharmacology, 151, 219-225.

Sherwin, C. M. (1998). Voluntary wheel running: a review and novel interpretation. Animal Behaviour, 56, 11-27.

Stewart, J. & Badiani, A. (1993). Tolerance and sensitization to the behavioural effects of drugs. Behavioural Pharmacology, 4, 289-312.

Stewart, J. & Vezina, P. (1991). Extinction procedures abolish conditioned stimulus control but spare sensitized responding to amphetamine. Behavioral Pharmacology, 2, 65-71.

Vanderschuren, L. J. M. J., Schoffelmeer, A. N. M., Mulder, A. H., & De Vries, T. J. (1999a). Dopaminergic mechanisms mediating the long-term expression of locomotor sensitization following pre-exposure to morphine or amphetamine. Psychopharmacology, 143, 244-253.

Vanderschuren, L. J. M. J., Schmidt, E. D., De Vries, T. J., Van Moorsel, C. A. P., Tilders, F. J. H., & Schoffelmeer, A. N. M. (1999b). A single exposure to amphetamine is sufficient to induce long-term behavioural, neuroendocrine, and neurochemical sensitization. The Journal of Neuroscience, 19, 9579-9586.

Van Ree, J. M. & Wolterink, G. (1981). Injection of low doses of apomorphine into the nucleus accumbens of rats reduces locomotor activity. European Journal of Pharmacology, 72, 107-111.

Vilaysinh, V. & Eikelboom, R. (2000, November). Stimulants and Wheel Running in Rats. Poster session presented at the annual meeting of the Society for Neuroscience, New Orleans, LA.

Voikar, V., Soosaar, A., Volke, V., Koks, S., Bourin, M., Mannisto, P. T., & Vasar, E. (1999). Apomorphine-induced behavioural sensitization in rats: individual

differences, role of dopamine and NMDA receptors. European Neuropsychopharmacology, 9, 507-514.

Werme, M., Thoren, P., Olson, L., & Brene, S. (1999). Addiction-prone Lewis but not Fischer rats develop compulsive running that coincides with down regulation of nerve growth factor inducible-b and neuron-derived orphan receptor 1. The Journal of Neuroscience, 19, 6169-6174.

Wise, R. A. & Bozarth, M. A. (1987). A psychomotor stimulant theory of addiction. Psychological Review, 94, 1-24.

Wise, R. A. & Leeb, K. (1993). Psychomotor-stimulant sensitization: a unitary phenomenon? Behavioural Pharmacology, 4, 339-349.

Figure Captions

Figure 1. One hour mean (± SEM) number of wheel turns of rats injected with VEH, 3.0 mg/kg AMP, or 5.0 mg/kg APO over four acquisition trials.

Figure 2. One hour mean (± SEM) number of wheel turns of rats tested with VEH, 1.5 mg/kg AMP and 2.5 mg/kg APO.

Figure 3. Forty-five minute mean (± SEM) number of wheel turns of rats injected with VEH, 0.1, 0.3, and 1.0 mg/kg APO over five acquisition trials.

Figure 4. Forty-five minute mean (± SEM) number of wheel turns of rats tested with VEH, 1.0, and 2.5 mg/kg APO (bars are in ascending acquisition APO dose order).

Figure 5. Forty-five minute mean (± SEM) number of wheel turns of rats injected with VEH, 0.03, 0.10, 1.00, and 3.00 mg/kg APO over five acquisition trials.

Figure 6. Forty-five minute mean (± SEM) number of wheel turns of rats tested with VEH, 1.0 and 2.5 mg/kg APO (bars are in ascending acquisition APO dose order).

Figure 7. Forty-five minute mean (± SEM) number of wheel turns of rats injected with VEH and 1.0 mg/kg APO either in their colony room (RVEH and RAPO) or in the testing room (SVEH and SAPO).

Figure 8. Forty-five minute mean (± SEM) number of wheel turns of rats tested with VEH, 1.0, and 2.5 mg/kg APO either in their colony room (RVEH and RAPO), or in the testing room (SVEH and SAPO).

Figure 9. Forty-five minute mean (± SEM) number of wheel turns of rats injected with 1.0 mg/kg APO in the testing room with the radio on (NOISY), or off (QUIET).

Figure 1

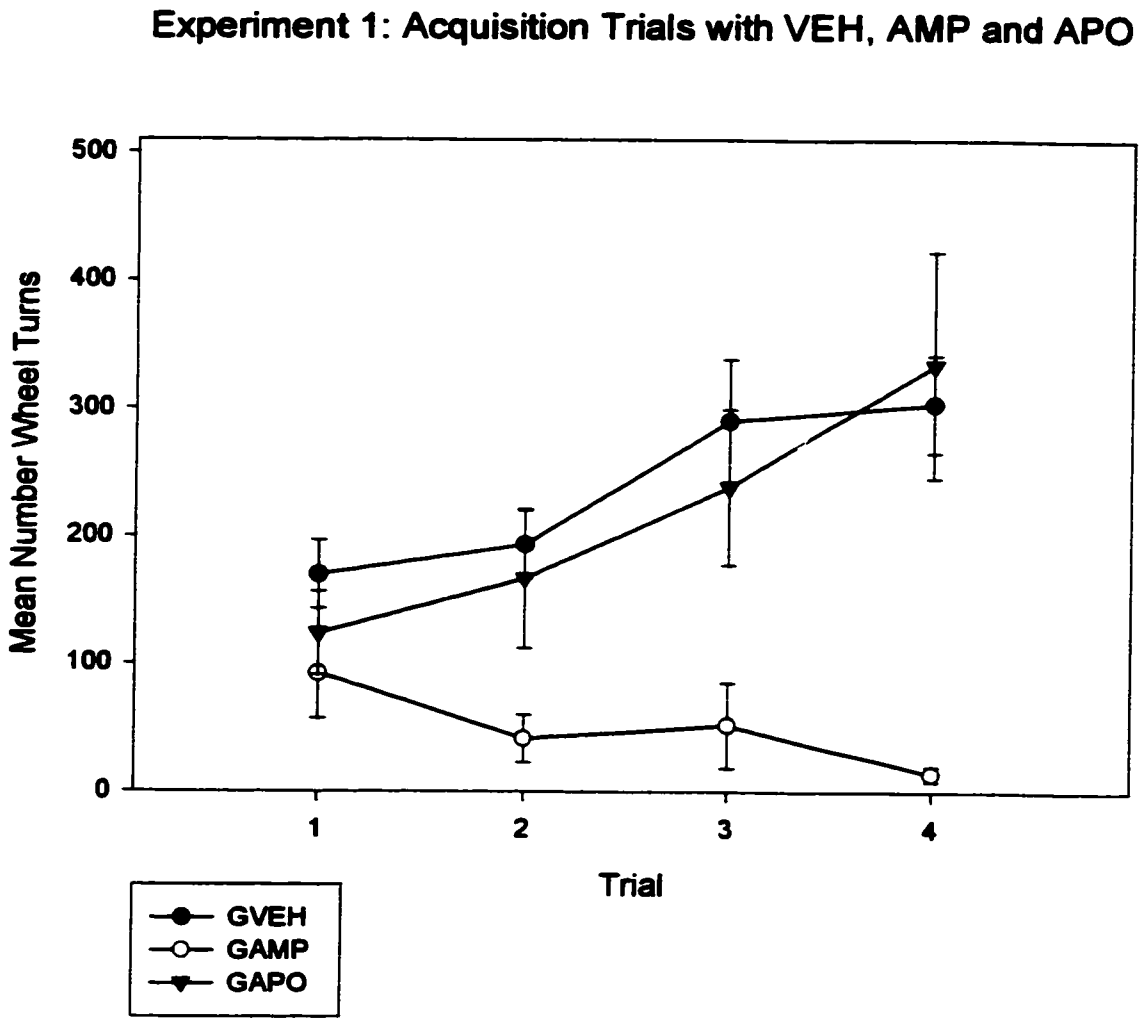

Experiment 1: Acquisition Trials with VEH, AMP and APO
Mean Number Wheel Turns
500
400
300
200
100
0
1
2
3
4
Trial
GVEH
GAMP
GAPO

Figure 2

Experiment 1: Testing with VEH, 1.5 mg/ kg AMP and 2.5 mg/kg APO

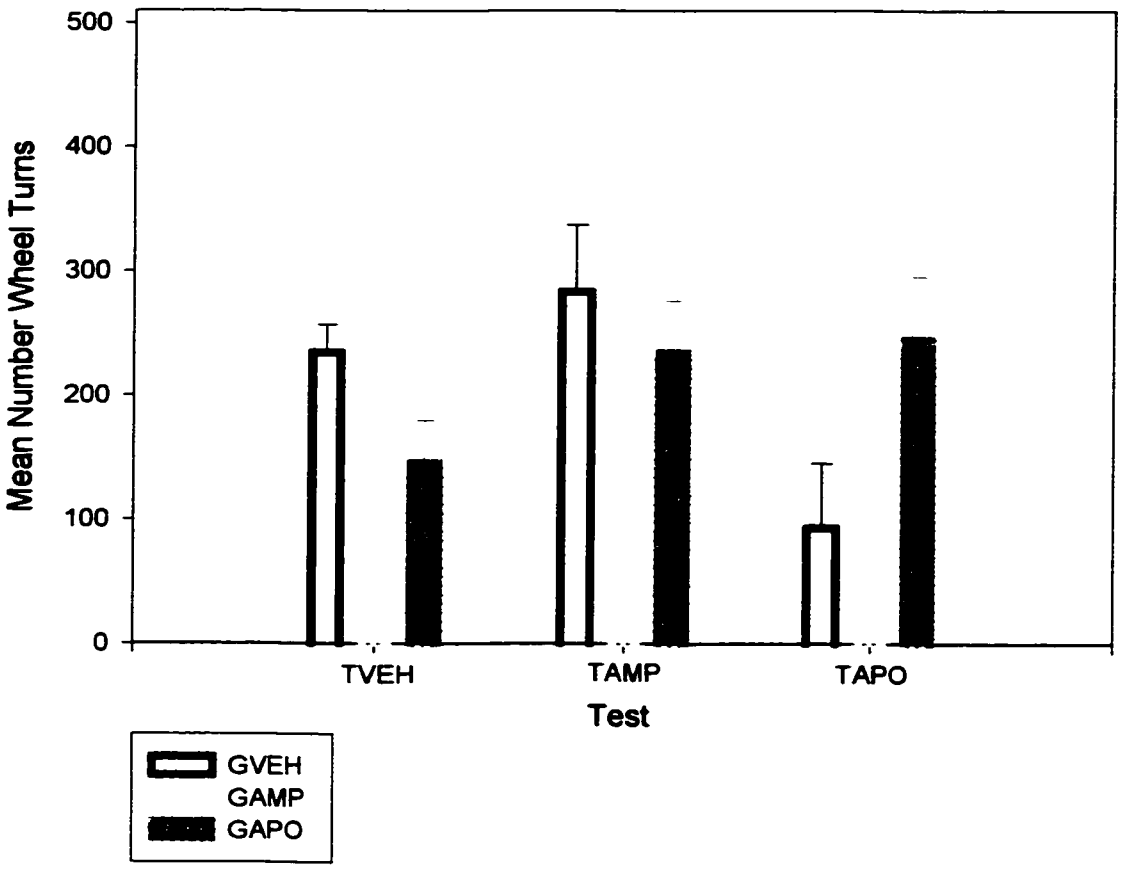


Figure 3

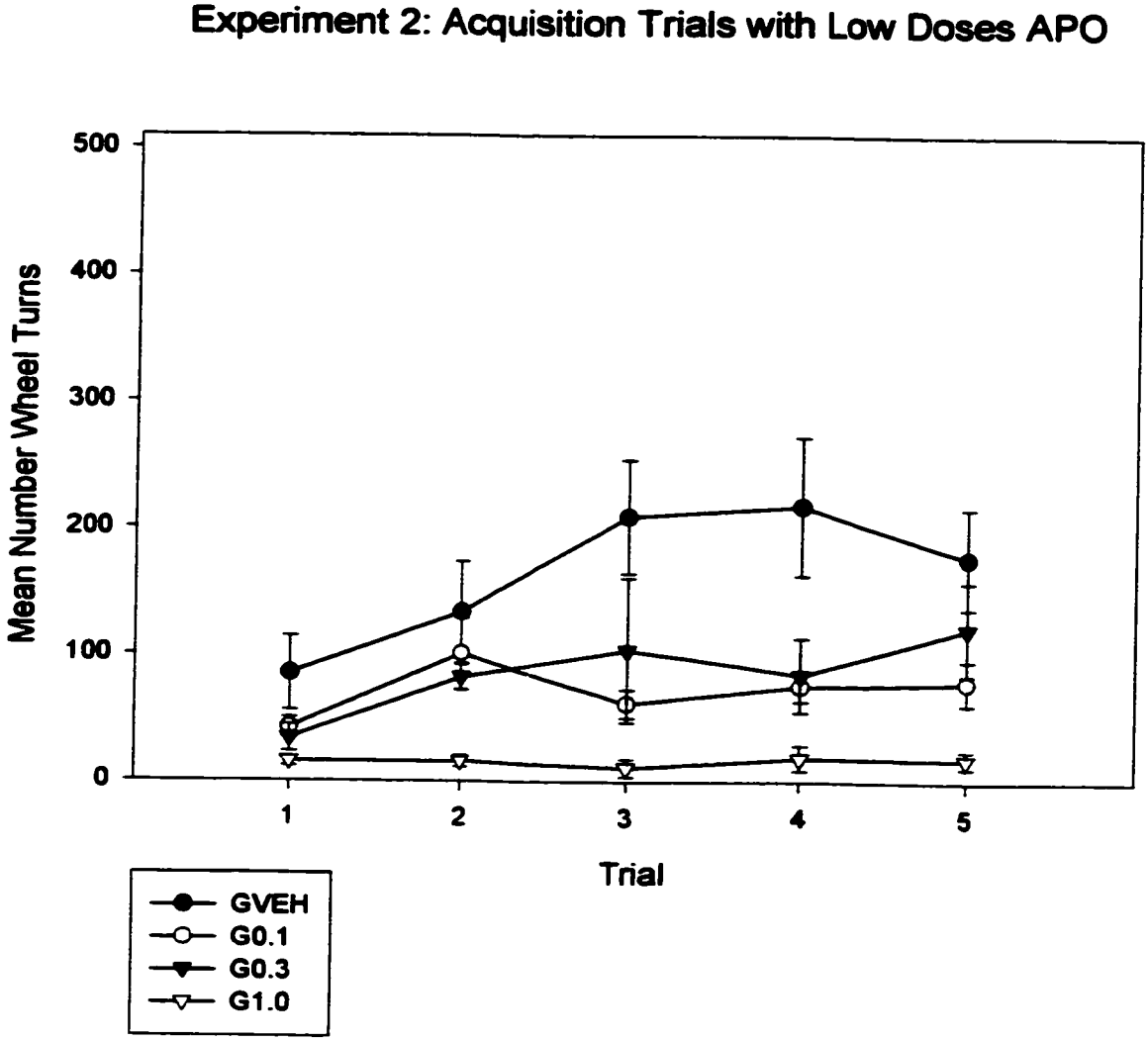

Experiment 2: Acquisition Trials with Low Doses APO
Mean Number Wheel Turns
500
400
300
200
100
0
1
2
3
4
5
Trial
GVEH
G0.1
G0.3
G1.0

Figure 4

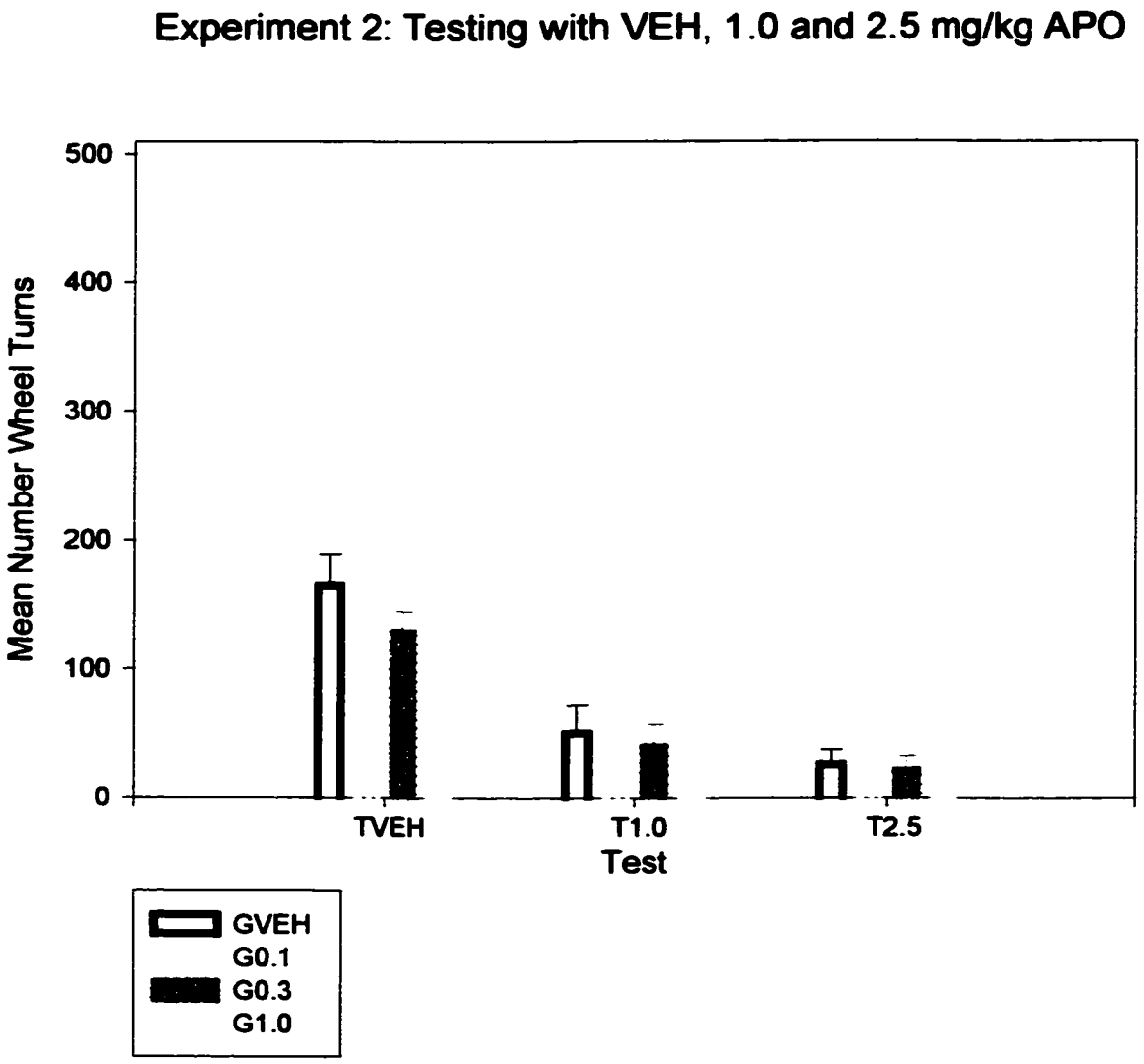

Experiment 2: Testing with VEH, 1.0 and 2.5 mg/kg APO
Mean Number Wheel Turns
500
400
300
200
100
0
TVEH
T1.0
T2.5
Test
GVEH
G0.1
G0.3
G1.0

Figure 5

Experiment 3: Acquisition Trials with Larger Range of APO Dose:

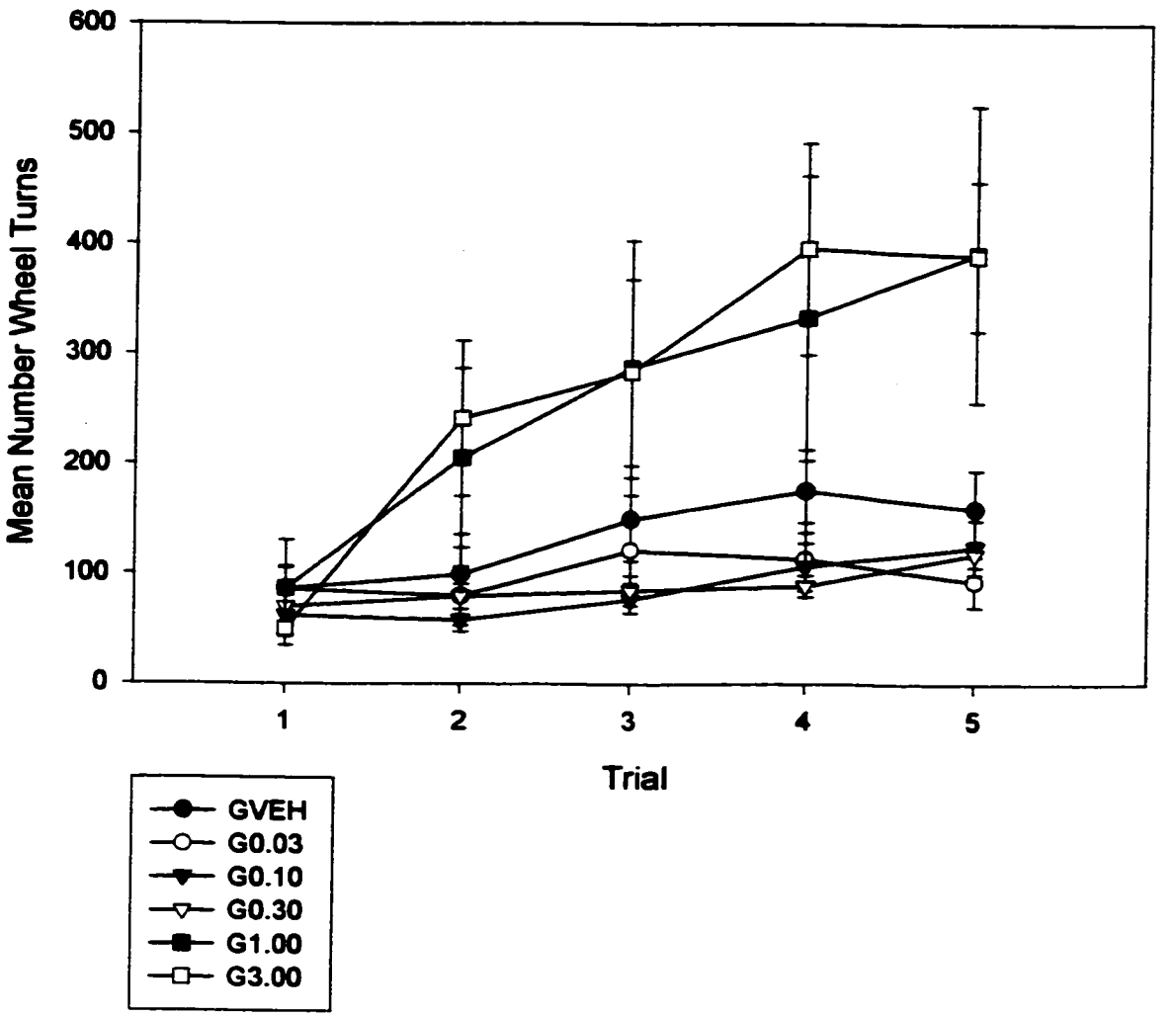


Figure 6

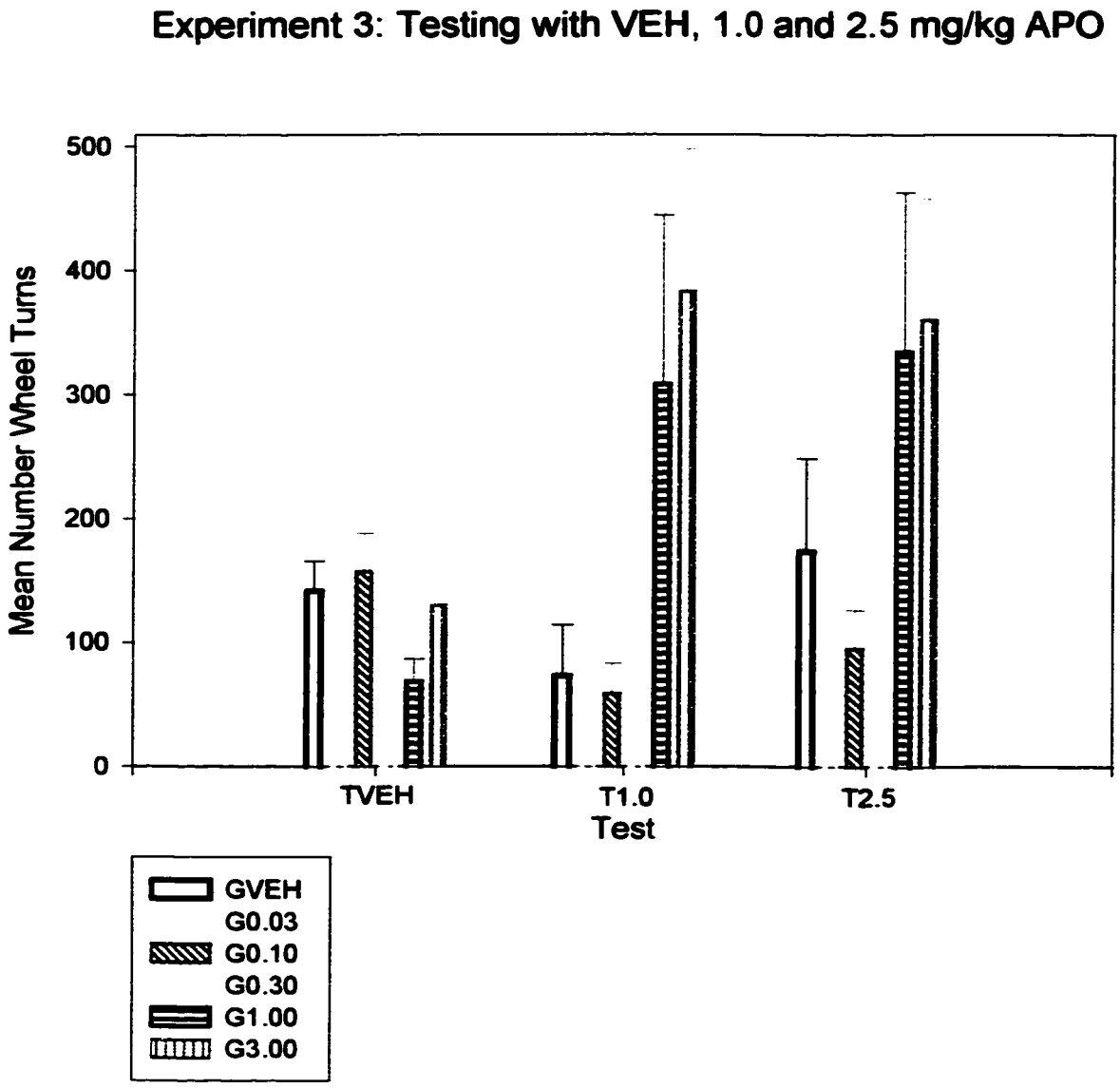

Experiment 3: Testing with VEH, 1.0 and 2.5 mg/kg APO
Mean Number Wheel Turns
500
400
300
200
100
0
TVEH
T1.0
T2.5
Test
GVEH
G0.03
G0.10
G0.30
G1.00
G3.00

Figure 7

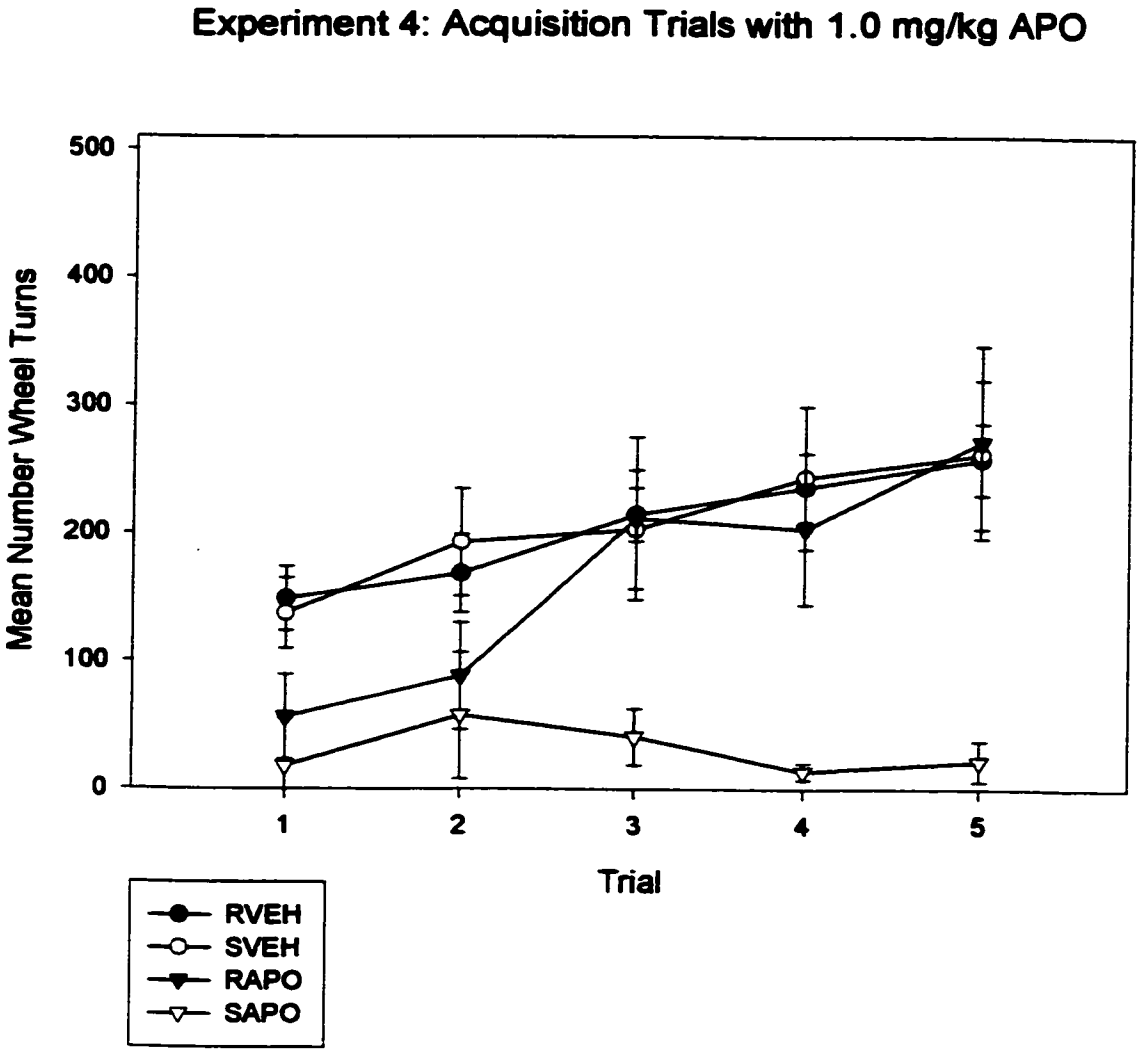

Experiment 4: Acquisition Trials with 1.0 mg/kg APO
Mean Number Wheel Turns
500
400
300
200
100
0
1
2
3
4
5
Trial
RVEH
SVEH
RAPO
SAPO

Figure 8

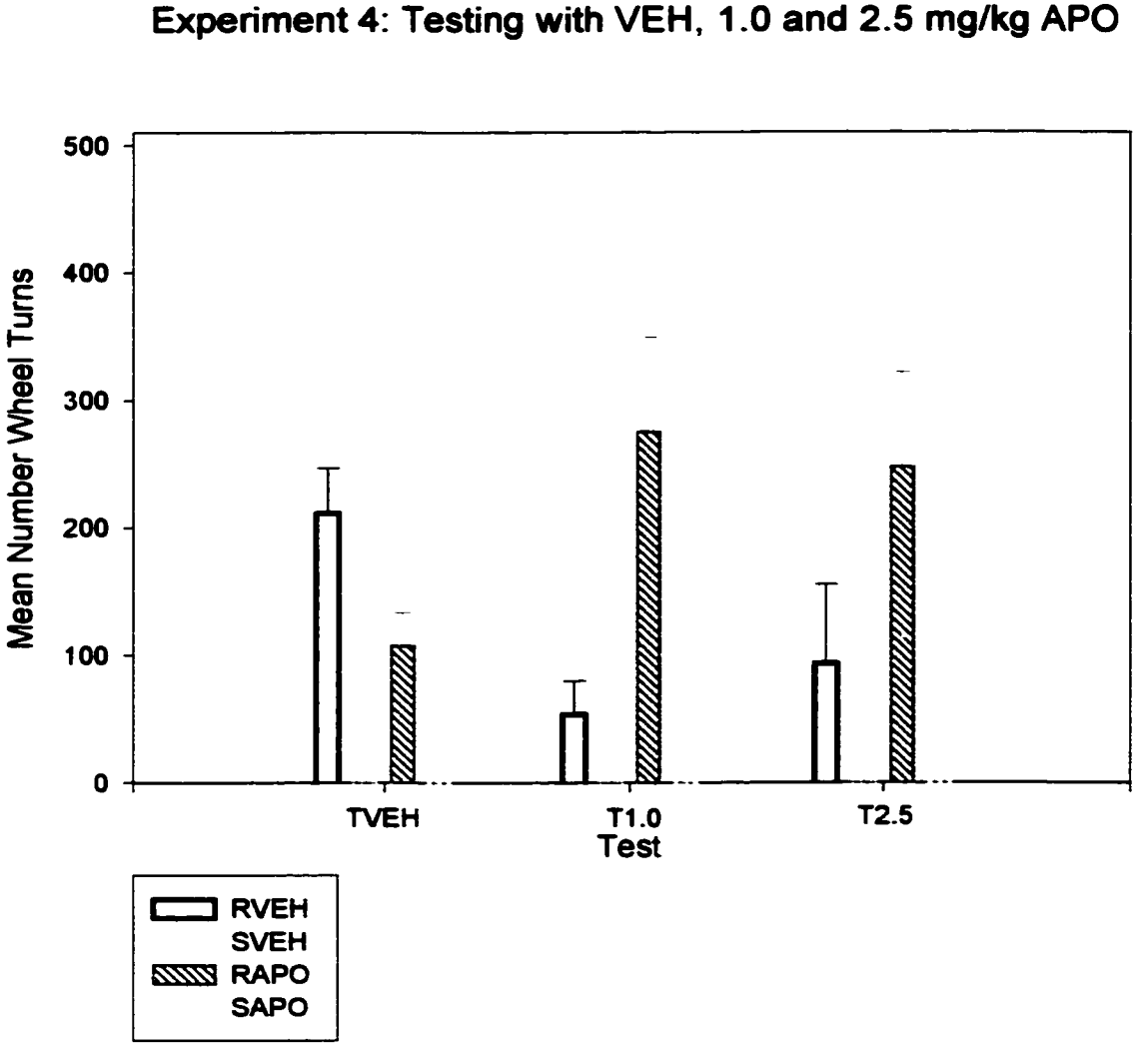
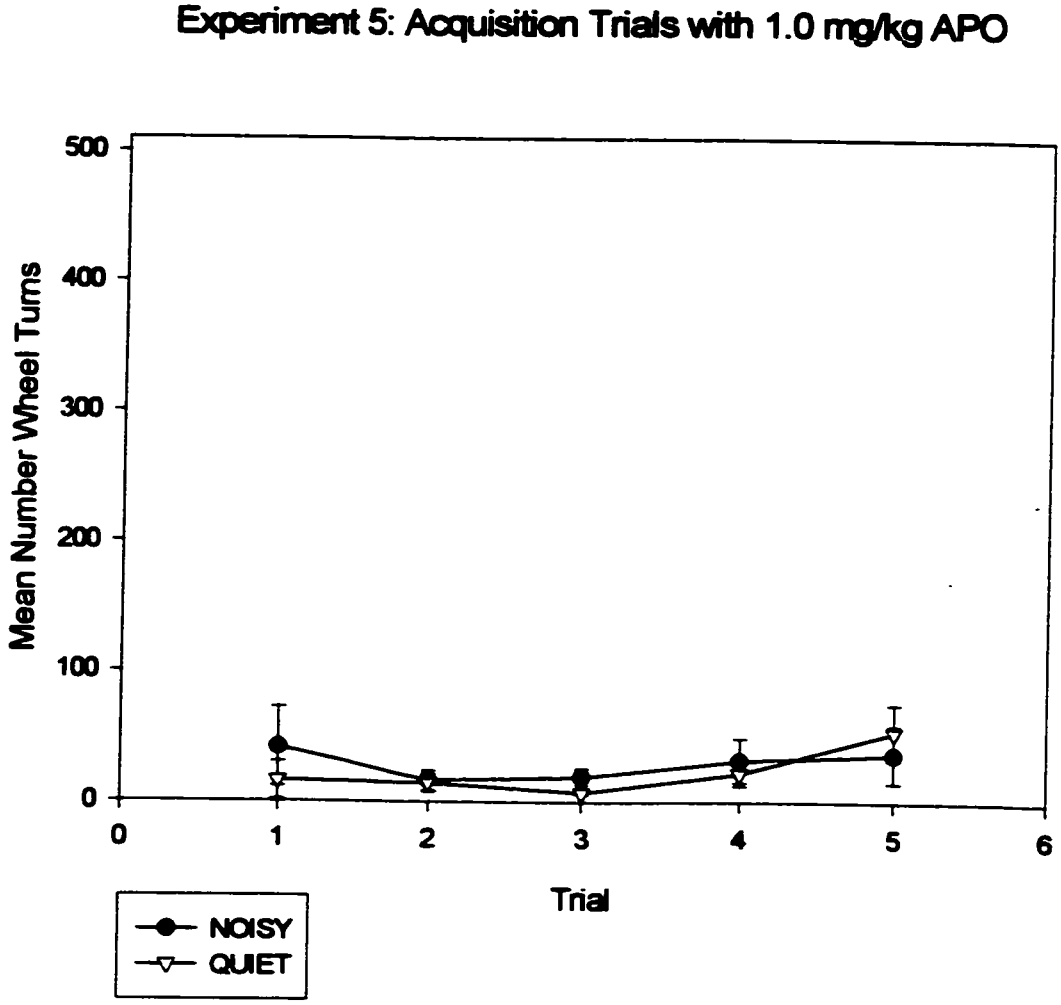

Experiment 4: Testing with VEH, 1.0 and 2.5 mg/kg APO
Mean Number Wheel Turns
500
400
300
200
100
0
TVEH
T1.0
T2.5
Test
RVEH
SVEH
RAPO
SAPO

Figure 9


Experiment 5: Acquisition Trials with 1.0 mg/kg APO
Mean Number Wheel Turns
500
400
300
200
100
0
0
1
2
3
4
5
6
Trial
NOISY
QUIET