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Review

The effect of brain augmenting drug Ritalin on animal behavior

Nachum Dafny

Department of Neurobiology and Anatomy, The University of Texas Medical School at Houston, 6431 Fannin Street, Houston, TX 77030, USA.

ABSTRACT

Methylphenidate (MPD) known as Ritalin is one of the most common pharmacological drugs used in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). It is also gaining popularity as a cognitive enhancer and for recreational purposes. Treatment of ADHD with psychostimulants lasts for a prolonged period of time and can evoke adverse effects such as schizophrenia, withdrawal, sensitization, tolerance and conditioned place preference. Drug dependence is experimentally determined at least in part by its capacity to elicit withdrawal, tolerance or sensitization. This article aims to provide a short review on the effects of MPD on animal behavior.

KEYWORDS: psychostimulant, Ritalin, behavior, sensitization, circadian rhythm, cognitive enhancer

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1. Introduction

Recently, several newspapers reported that healthy people deserve the right to boost their brains with psychoactive pills, like those prescribed for Attention Deficit Disorder (ADD), Attention Deficit Hyperactivity Disorder (ADHD), narcolepsy and memory-impaired older folks. College students are already taking methylphenidate (Ritalin), mainly before exams, to help them study better. Some students contend that "We should welcome new methods of improving our brain function and doing it with pills is no more morally objectionable than healthy eating or getting a good night's sleep" [1]. But what do we know about this psychoactive drug?

Psychoactive drug use dates back to prehistoric times; there is archaeological evidence for their use dating back to several thousand years. A psychoactive drug acts on the central nervous system (CNS) to modulate consciousness, perception, mood and behavior. These drugs were used therapeutically as medication or for ritual and spiritual purposes as well as recreationally to alter one's mood and to get 'high'. Because psychoactive drugs elicit changes in consciousness and mood, the user feels alert, joyful, pleasant and euphoria. Many psychoactive drugs are used and abused despite the risks and negative consequences such as dependence. Methylphenidate belongs to this family of psychoactive drugs. The most commonly

prescribed medication for ADHD patients include amphetamine (e.g. Adderall, a mixture of amphetamine salts), methylphenidate (e.g. Concerta, a formulation that releases the drug over longer period of time, and Ritalin, which is short-acting and generally less potent than amphetamine).

Methylphenidate hydrochloride is one of the most commonly prescribed psychostimulants for the treatment of children and adults with ADHD, a developmental disorder that affects as much as 5-15% of school-aged children in the United States [2]. This disorder is characterized by a persistent pattern of inattention and/or hyperactivity and impulsivity that is displayed more frequently and is more severe than that typically observed in individuals at a comparable level of development.

Methylphenidate is a CNS stimulant that, as a piperidine derivative, is closely related to the phenethylamine, *d*-amphetamine (dextroamphetamine), a stereoisomer of amphetamine. The structure and neuropharmacological profile of methylphenidate is also similar to that of cocaine [3, 4]. The drug was first synthesized in 1944 and was used initially as an analeptic for reversal of barbiturate-induced coma. It was patented in 1954 by the Ciba Pharmaceutical Company and prescribed as a treatment for depression, chronic fatigue, narcolepsy and other ailments. It was later used to improve memory in elderly patients.

From the 1960s, it has been used to treat children with ADHD. Moreover, its use has been extended to improve alertness, attention and cognition in children and adults with emotional, behavioral, and learning difficulties, or with minimal brain dysfunction (MBD), as well as in 'normal' subjects. Methylphenidate is highly effective in treating ADHD and may also be useful in providing relief from intractable pain, in narcolepsy, chronic fatigue, and as a cognitive enhancer.

2. Pharmacokinetics and pharmacodynamics

When methylphenidate is given orally, it is absorbed from the intestinal tract and has a half-life of about 1 h in plasma. Methylphenidate is metabolized *via* de-esterification to ritalinic acid and released into the urine within 48 h [5]. Following systemic injection in rodents, it reaches a peak level at about 8 to 20 min post-injection [6], which is similar to systemic cocaine and amphetamine administration in humans [3].

The therapeutic effects of methylphenidate in treatment of ADHD have been attributed to an increase in the efflux of catecholamine neurotransmitters [6]. This arises from methylphenidate's blockade of neuronal reuptake of catecholamines, which increases their extracellular concentration [7]. Methylphenidate and amphetamine bind to the dopamine transporter (DAT) with an affinity similar to that of cocaine [8]. Like cocaine, methylphenidate is an indirect catecholamine (CA) agonist. It does not bind to catecholaminergic receptors directly but rather facilitates catecholaminergic transmission indirectly [3-4]. This action has also been linked to its reinforcing properties [3, 4, 9].

Methylphenidate and cocaine are similar in terms of their actions on the DAT [3]. The relationship between drug doses (i.e., molar concentration of the drug in the plasma) and percentage occupancy of DAT is identical for cocaine and methylphenidate in rodents and humans [10]. The dose and route of administration are important because the behavioral and neurochemical responses to the drug depend on the rate at which the drug reaches peak concentrations in the brain [7].

Peak plasma concentrations (Tmax) of methylphenidate following intravenous (i.v.), intraperitoneal (i.p.), and oral administration were 8-20 min, 15-28 min, and 60-90 min, respectively [11]. Similar peak concentrations were obtained following i.v., i.p. and/or oral administration of amphetamine or cocaine [11]. A short Tmax (i.v., 8-20 min) is one of the main factors in eliciting adverse effects such as euphoria, tolerance and sensitization. Like amphetamine and cocaine, methylphenidate rapidly penetrates the brain, with free passage across the blood brain barrier, but differs from amphetamine and cocaine in that its rate of clearance from the brain is much slower. Brain concentrations of methylphenidate exceed that of plasma since the psychostimulant is binding to DAT.

Stimulants have been abused for both 'cognitive and performance enhancement' and recreational purposes to get 'high'. For the former, they suppress appetite and facilitate weight loss, increase wakefulness focus, attention and enhance cognition. Their euphoric

effects usually occur when they are crushed and snorted or injected. Intravenous (i.v.) or intranasal administration of methylphenidate has a higher mortality rate than that of cocaine or amphetamine.

Methylphenidate has moderate effects on the peripheral circulatory system. In rats, its administration in low doses (2.0 to 5.0 mg/kg i.p.) stimulates locomotor activity (Fig. 1) and, following its repeated administration, elicits behavioral sensitization (Fig. 2). At higher doses (10.0 mg/kg i.p.) this drug stimulates stereotypical behavior and tolerance [5, 12].

The efficacy of methylphenidate in treatment for ADHD is clear. The treatment lasts for a prolonged period of time. During adolescent years, crucial neurodevelopment occurs with the production and elimination of numerous neuronal synaptic connections, i.e., synaptic pruning. Chronic treatment with psychostimulants, such as methylphenidate and amphetamine, can modulate the neurodevelopmental processes critically. It has been reported that drugs such as methylphenidate modulate the circadian rhythm as a result of molecular alteration of clock genes [13, 14, 15]. The alteration of the circadian activity behavior (Figs. 3 and 4) alters the body's homeostasis. There is some concern about children with ADHD who are going through these neurodevelopmental processes while being treated with methylphenidate for extended periods of time.

Additional concerns are that psychostimulant therapy given to adolescents and young adults may increase the risk for substance use disorder [16], while other reports suggest that psychostimulant treatment in adolescents with ADHD protects them from later substance use disorder. These contradictory reports call for basic in-depth studies to resolve this critical issue. Animal models using behavior and neuronal recordings following acute and chronic methylphenidate treatment can be helpful in this respect.

3. Animal models used to study the effect of methylphenidate

Key questions are, which animal and which strain should be used to study the physiological properties of methylphenidate? Obviously, the most appropriate animal model is the one that best mimics ADHD in humans and is able to predict aspects of ADHD behavior. There are differences between different animal strains in their susceptibility to psychostimulants and their chronic effects, such as tolerance or sensitization. Repeated administration of psychostimulants results in the initiation and intensification of biochemical and neurobiological activities that lead to addiction with behavioral tolerance or sensitization. Behavioral tolerance or sensitization refers to a phenomena whereby the repeated administration of the drug produces either attenuation (tolerance) or a progressive augmentation (sensitization) of the animal's behavioral response to a repetitive drug challenge [5, 12, 16, 17].

Since no biological marker for ADHD has yet been identified, diagnosis of ADHD is presently based on behavioral symptoms alone. Many suggested animal models of ADHD exist. These include rats that are outbred from a general colony, reared in social isolation, have been exposed to environmental pollutants, have undergone neonatal anoxia, have undergone hippocampal x-irradiation in infancy, genetically mutant mice, or animals that had selective lesion in specific brain areas induced by local injection of neurotoxins [5]. There are also inbred strains, including Naples high/low excitability and Spontaneously Hypertensive Rat (SHR) strain, the latter of which was bred from progenitor Wistar Kyoto (WKY) rats [5, 18]. The SHR is hyperactive with a variety of behavioral characteristics that are comparable to the behavior of children with ADHD, including motor and cognitive impulsiveness, impaired attention, and hyperactivity [18]. Therefore, the SHR strain is used most often in ADHD/methylphenidate studies.

4. Behavioral changes after long-term treatment with methylphenidate

Drug tolerance, sensitization and withdrawal develop after repeated use of psychostimulants and are used as an experimental marker to indicate a drugs ability to elicit dependence (addiction). Several reviews suggest that behavioral tolerance and sensitization in animals represent an enduring alteration of drug response and serve as a model for drug craving [5, 12, 16].

4.1. Behavioral tolerance

Behavior tolerance to psychostimulants is expressed as the need to increase drug dose in order to maintain or reinstate the original drug effect. It is suggested

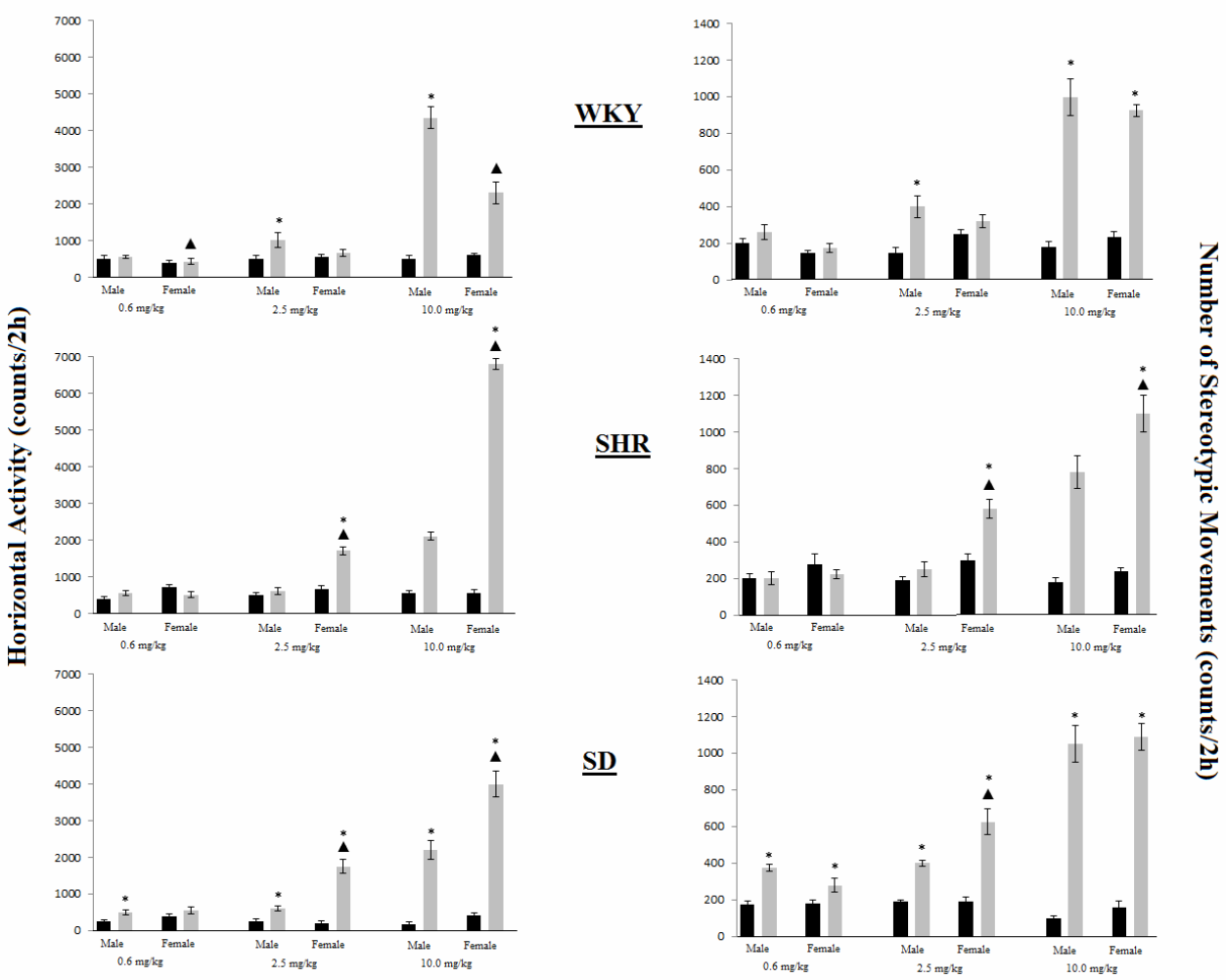

Fig. 1. Acute effects of methylphenidate on female and male WKY, SHR and SD rats.
The figure summarizes the relationship between drug dose (0.6, 2.5 and 10.0 mg/kg) and response following a single i.p. injection of methylphenidate on horizontal locomotor activity (figure, left side) and stereotypic activity (figure, right side) of female and male WKY, SHR and SD rats using the open field assay. Each group (N = 8) was given saline on experimental day 1 and methylphenidate on experimental day 2. Methylphenidate (0.6 mg/kg i.p.) failed to elicit any changes in the horizontal locomotor activity of female and male WKY and SHR groups, while this low dose of methylphenidate increased the horizontal activity of male SD rats (Fig. 1 – left column). A higher dose (2.5 mg/kg i.p.) increased (* $P < 0.05$) only the horizontal activity of male WKY and SD rats and female SHR and SD rats (Fig. 1 – middle column), compared with the saline control group. Female SHR and SD exhibited a (▲ $P < 0.05$) greater increase in activity, compared to their male counterparts. The highest methylphenidate dose (10.0 mg/kg i.p.) induced a robust increase in locomotor activity when compared to baseline. *criterion of statistical significance ($P < 0.05$) when comparing the sexes of each rat strain on experimental and control day: i.e., Experimental day 2 (grey bar) and Experimental day 1 (black bar). ▲ indicates significant ($P < 0.05$) difference.

that the development of tolerance to a substance can contribute to drug dependence.

4.2. Behavioral sensitization

Intermittent use of psychostimulants results in the intensification of the behavioral response to the drug, a phenomenon known as behavioral sensitization [5, 19, 20, 21]. Behavioral sensitization describes the progressive and enduring augmentation of behavioral responses to psychostimulants that develop during their repeated administration. It persists for long periods of time and it is thought to be the

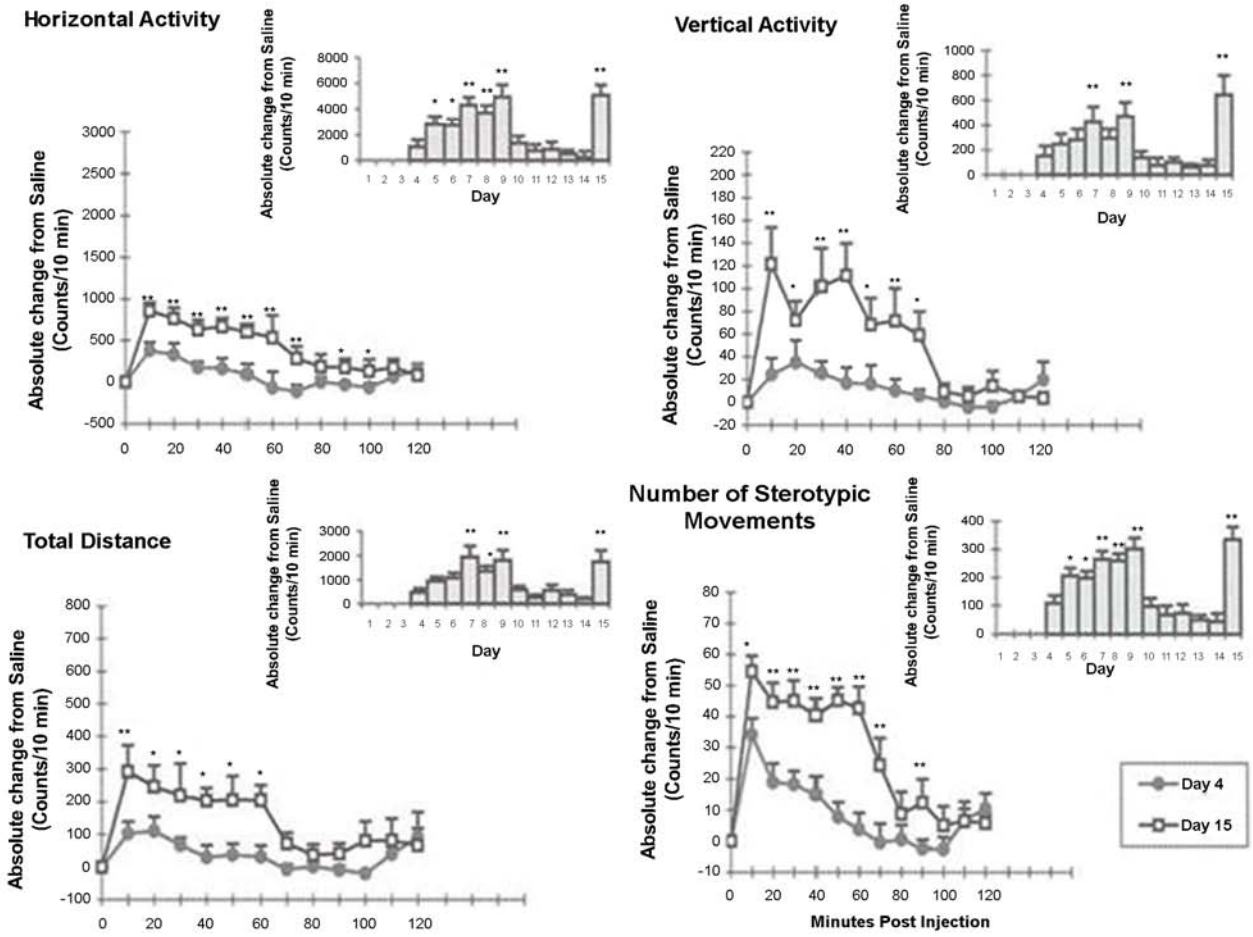

Fig. 2. This figure illustrates behavioral sensitization. The filled circles of the temporal graph show the time course for the effect of the initial (acute) treatment with methylphenidate (2.5 mg/kg i.p.) in drug-naïve animals. The baseline activity was subtracted to show difference from baseline. The open squares indicate the activity on experimental day 15, after single-daily injections of methylphenidate (2.5 mg/kg i.p.) for 6 consecutive days, followed by 5 days of washout and rechallenge with methylphenidate (2.5 mg/kg i.p.) at experimental day 15. The embedded histograms in the upper right corner of each temporal graph are the summation of the activity under the temporal graph at all the experimental days. Each group consist of N = 8 rats. *criterion of statistical significance ($P < 0.05$). **criterion of statistical significance ($P < 0.01$). The first three days are the baseline activity set arbitrarily at 0.

early manifestation of neuronal plasticity associated with drug dependence (addiction) and abuse [9, 20, 21]. Behavioral sensitization, which is used to study disorders such as drug dependence, bipolar disorder, memory and learning disorders, exhibits two distinct temporal domains; the induction and expression phases. The induction phase is the transient sequence of cellular and molecular events precipitated by psychostimulants, which lead to enduring changes in neuronal function that underlie behavioral augmentation. Induction of behavioral sensitization to psychostimulants occurs in the midbrain ventral tegmental area (VTA), while the brain site participating in the behavioral expression following repetitive use of the drug is the nucleus accumbens (NAc). The neuronal network(s) contributing to the long-term expression of behavioral sensitization incorporate several other interconnected mesolimbic nuclei and the prefrontal cortex (PFC), which are known as the ‘motive circuit’.

4.3. Behavioral dependence

Behavioral dependence can be divided into two types. These are psychological dependence, by which the

user feels compelled to take the drug, (i.e. positive reinforcement) despite negative consequences, and physical dependence by which the user must use the drug to prevent and avoid the unpleasant withdrawal symptoms (i.e. negative reinforcement) [9, 16, 22]. The drug self-administration task provides evidence that the positively reinforcing effects of a drug are responsible, at least in part, for the acquisition and maintenance of drug-taking behavior.

Animal self-administration of drugs is one of the experimental cues demonstrating that the drug elicits reward. Only a few studies have investigated whether animals self-administer methylphenidate [12]; they reported that methylphenidate indeed elicited this behavior. They concluded that the reinforcing effects of methylphenidate were similar to amphetamine and cocaine. Methylphenidate also induced conditioned place preference following repetitive use of the drug [12]. Both these findings suggest that methylphenidate has reinforcing properties.

4.4. Behavioral withdrawal

Behavioral withdrawal syndrome follows abrupt discontinuation of the drug and results in characteristic signs and symptoms such as hyperactivity (Fig. 4) and agitation. To escape the withdrawal symptoms, the subject continues to consume the drug. Recently, it was reported that chronic treatment of methylphenidate elicits withdrawal behaviors [13, 14, 23, 24, 25].

5. Age-dependent effects of methylphenidate

The ontogeny of the brain/behavior relationship during the period between preadolescence, adolescence and attained sexual maturity needs more attention. Based on many reports, the following age classification can be derived: from postnatal day 21 (P-21) to P-30, P-31 to P-39, P-40 to P-50, P-60 to P-75 and P-76 and above the rats are considered as juveniles, periadolescents, adolescents, young adults and adult rats, respectively (Table 1).

The response to psychostimulants varies with age in humans and other animals [5]. During normal development, overproduction of synaptic connections and receptors occurs, which is followed by their pruning or competitive elimination. The marked overproduction and elimination of synapses and receptors during adolescence may serve as a permissive factor for a number of behavioral/ psychiatric disorders, including ADHD [26]. Between 5 and 15 years of age in humans, DA synaptic density in the frontal cortex decreases by approximately 40%. This phenomenon can be modified by chronic methylphenidate exposure in the young, which could cause some undesired behavioral disorders.

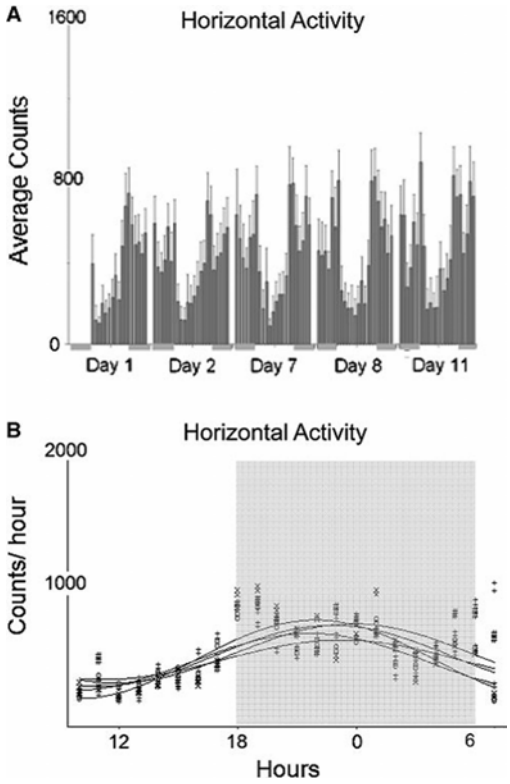

Fig. 3. Horizontal activity counts and Cosine Curve Statistical Analysis graph of control group prior to saline or MPD injection.
Most of the studies investigating drug effects on animal behavior record several minutes post injection. Fig. 3A and B show results of experiments testing the hypothesis that prolonged drug treatment causes molecular damage of the genes that regulate the circadian activity pattern of locomotor activity. The figure shows the 24-h histogram of horizontal locomotor activity (HA) of control animals (N = 8) of experimental days 1, 2, 7, 8, and 11 (Fig. 3A). Fig. 3B shows the superimposed analysis curves using the Cosine Curve Statistical Analysis test examine the activity pattern over 24 h (Fig. 3B). The figure shows that the activity pattern of experimental days 1, 2, 7, 8 and 11 fit the cosine curve, indicating identical activity patterns during these experimental days. The shaded part summarizes the 12-h dark night phase of the recording.

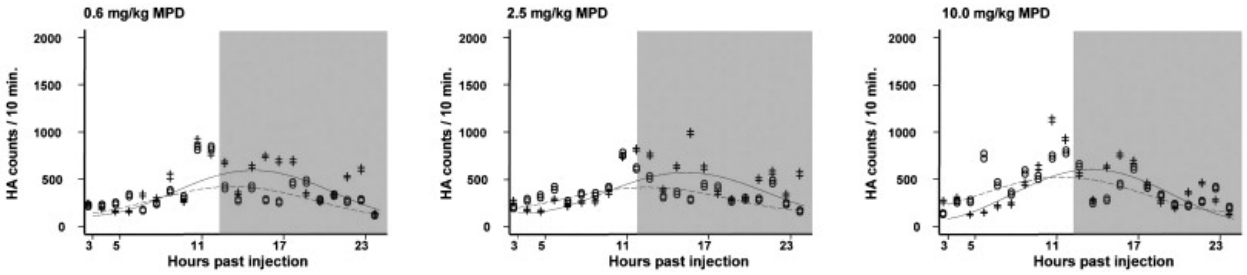

Fig. 4. Washout phase of all MPD treated groups (Day1 vs. Day 8).
The figure shows the superimposed (N = 8) analysis curves of experimental day 1 *versus* day 8 using the Cosine Curve Statistical Analysis (CCSA) test examining the activity pattern of the baseline (experimental day 1 and experimental day 8). The figure compares the activity after saline administration on experimental day 1 with activity obtained on the first washout day after six consecutive once-daily injections at 07:00 with methylphenidate. The figures show that six once-daily treatments of 0.6, 2.5 or 10.0 mg/kg i.p. methylphenidate alters significantly ($P < 0.05$) the activity pattern of 24-h horizontal activity (HA). The data using the CCSA test that shows significant change in 24-h pattern activity further suggest that six days of methylphenidate elicits withdrawal behavior i.e., long term effects on animal homeostasis.

Table 1. Stages of development of the postnatal rat.

Juvenile	Periadolescent	Adolescent	Young adult	Adult
P-21 to P-30	P-31 to P-39	P-40 to P-50	P-60 to P-75	P- > 75

The time-course and nature of this phenomenon parallels the ADHD time-course as a result of alteration or over-production and regressive synaptic elimination described above.

Adolescent and adult rats are affected differently by catecholaminergic agonists. Adolescent rats exhibit an attenuated behavioral response compared to adult rats, while adult rats exhibit a greater behavioral response to psychostimulants compared to adolescent rats [27]. Rats exposed to methylphenidate during the period equivalent to human adolescence display behavioral changes that endure into adulthood. This suggests that methylphenidate has a neurobiological effect in adolescents that modulates the 'normal' development to adulthood [5, 28].

Studies of amphetamine and cocaine sensitization in developing animals have yielded conflicting results, depending upon the age at the time of testing, the intervals between the repetitive drug treatment, and the challenge dose [27]. Adolescent rats of both sexes show sensitization to locomotor activating effects of cocaine, whereas different locomotor sensitization profiles were found in adult rats [27]. However, others have reported that younger animals treated chronically with psychostimulants rarely exhibit sensitization and that, even when sensitization occurs, it persists for a shorter period of time. When the effects of chronic cocaine were compared in adolescent and adult rats the former showed alterations in psychopharmacological sensitivity. These apparently did not rely on age-specific decreases in brain drug availability but rather appeared to be related to alterations in CNS sensitivity [27].

6. Gender differences in the effects of methylphenidate

There are remarkable gender differences in the behavioral expression of ADHD patients [26]. For example, ADHD is 2 to 9 fold more prevalent in males than females. Females with ADHD may be more severely affected than males, possibly because female ADHD subjects tend to have a higher genetic loading for the disorder. It was hypothesized that there is extensive overproduction of DA receptors in the male striatum and NAc during pre-pubertal development [5]. This could help to explain why males are often afflicted with ADHD because an increase in dopaminergic activity in these regions can produce hyperactivity and stereotypical behavior.

Gender differences in ADHD may also be attributed to differences in DA receptor density. Striatal D_2 receptor density in male rats increases 144% ± 26% between 35-40 days of age, while females' D_2 receptor density increases only 31 ± 7%. The rise in males' striatal DA receptors parallels early development of ADHD motor symptoms [5].

Gender-dependent differences in the response to cocaine and amphetamine have also been reported. These could be due to differences in drug pharmacokinetics, particularly their metabolism. The neural systems mediating the behavioral response to psychomotor stimulants are sexually dimorphic and are modulated by genes as well as pituitary and gonadal hormones. For example, estrogen enhances the acute behavioral and neurochemical responses to dopamine, amphetamine and cocaine in female rats. The effects of gonadal hormones are postulated to have important implications for gender differences in the acute and chronic drug responses and in the susceptibility of addiction to psychomotor stimulants.

In general, females (humans and rodents) are more sensitive than males to cocaine and amphetamine [5]. The development of behavioral sensitization to cocaine is also a function of sex-specific alterations in sensitivity to psychostimulants. In addition, accumulating evidence indicates that the antecedents, consequences, and mechanisms of drug abuse and addiction are different in females and males. It was reported that adult female rats are more severely addicted to psychostimulants and express a more rapid behavioral sensitivity to chronic exposure of these drugs compared to their male counterparts. This sexual dimorphism was only observed in adult rats, suggesting that gonadal hormones secreted in adulthood might modulate the responsiveness to psychostimulants [5]. Such findings suggest that gender is an important variable to be considered in studying mechanisms and treatment; the study of sex differences in psychostimulant therapy will provide more effective prevention and treatment strategies.

7. Conclusion

Prescription drugs have killed thousands of people every year [29]. This attrition has prompted drug enforcement officials to declare that prescription drug abuse represents a "substantial threat". Methylphenidate, a prescribed drug used mainly for treatment of ADHD, is used also for cognitive enhancement and recreation. However, care is warranted because methylphenidate has structural and pharmacological similarities to amphetamines and cocaine. Animal research shows that the property and vulnerability of using methylphenidate is the same as for amphetamines and cocaine. Based on the data available there are reasons to suspect that methylphenidate has a significant potential to become a drug of abuse.

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9. Conflict of interest statement

There are no conflicts of interest in the material presented in this monograph.

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