The Characteristics of Methylphenidate on Animal Behavior

Nachum Dafny
Department of Neurobiology and Anatomy, The University of Texas Medical School at Houston

Abstract
Although methylphenidate has been used for decades as a leading treatment for behavioral disorders such as attention deficit hyperactivity disorder (ADHD). Recently it has been used as a cognitive enhancer and for recreation. The mechanism underlying its actions is still unrevealed. Enhancement of mental function by prescription psychostimulants that promise to improve mental performance, attention, memory, planning, etc., is now wide spread. Moreover, in the last two decades stimulants such as MPD have been prescribed to very young children and adults for treating behavioral disorders such as ADHD. This study aims to provide a short review of methylphenidate’s effect on the animal’s behavior.

Keywords: Psychostimulant; Ritalin; Behavior; Sensitization; Circadian rhythm; Cognitive enhancer

Introduction
Psychostimulant medication such as amphetamine was used to treat attention deficit hyperactive disorder (ADHD) patients from 1930’s until it was found it elicits dependency. The psychostimulants methylphenidate (MPD) has since become the drug of choice to treat ADHD patients [1]. MPD is a CNS stimulant that closely relates to the structure of dextroamphetamine [2], a derivative of amphetamine. The neuropharmacological profile of MPD is also similar to that of cocaine [2]. The drug was first synthesized in 1944 and used initially as an analeptic for several types of barbiturate-induced coma. It was later used as a drug to improve memory in elderly patients. Since then, its usage has been extended to improve the alertness in children and adults with emotional, behavioral, and learning difficulties [1]. MPD is highly effective in treating ADHD [3] and useful in providing relief from intractable pain in narcolepsy and chronic fatigue.

Several articles reported that people deserve the right to boost their brains with psychoactive pills, like those prescribed for Attention Deficit Hyperactivity Disorder (ADHD), narcolepsy and memory-impaired older folks. Students of all ages are already taking MPD (Ritalin), to help them study and perform in exam better. Some students contend that: by using psychostimulants for studying can also be used to fight depression, anxiety, attention deficit hyperactivity disorder (ADHD). Recently it has been used as a cognitive enhancer and for recreation. The mechanism underlying its actions is still unrevealed. Enhancement of mental function by prescription psychostimulants that promise to improve mental performance, attention, memory, planning, etc., is now wide spread. Moreover, in the last two decades stimulants such as MPD have been prescribed to very young children and adults for treating behavioral disorders such as ADHD. This study aims to provide a short review of methylphenidate’s effect on the animal’s behavior.

Keywords: Psychostimulant; Ritalin; Behavior; Sensitization; Circadian rhythm; Cognitive enhancer

Introduction
Psychostimulant medication such as amphetamine was used to treat attention deficit hyperactive disorder (ADHD) patients from 1930’s until it was found it elicits dependency. The psychostimulants methylphenidate (MPD) has since become the drug of choice to treat ADHD patients [1]. MPD is a CNS stimulant that closely relates to the structure of dextroamphetamine [2], a derivative of amphetamine. The neuropharmacological profile of MPD is also similar to that of cocaine [2]. The drug was first synthesized in 1944 and used initially as an analeptic for several types of barbiturate-induced coma. It was later used as a drug to improve memory in elderly patients. Since then, its usage has been extended to improve the alertness in children and adults with emotional, behavioral, and learning difficulties [1]. MPD is highly effective in treating ADHD [3] and useful in providing relief from intractable pain in narcolepsy and chronic fatigue.

Several articles reported that people deserve the right to boost their brains with psychoactive pills, like those prescribed for Attention Deficit Hyperactivity Disorder (ADHD), narcolepsy and memory-impaired older folks. Students of all ages are already taking MPD (Ritalin), to help them study and perform in exam better. Some students contend that: by using psychostimulants for studying can also be used to fight depression, anxiety, attention deficit hyperactivity disorder (ADHD). Recently it has been used as a cognitive enhancer and for recreation. The mechanism underlying its actions is still unrevealed. Enhancement of mental function by prescription psychostimulants that promise to improve mental performance, attention, memory, planning, etc., is now wide spread. Moreover, in the last two decades stimulants such as MPD have been prescribed to very young children and adults for treating behavioral disorders such as ADHD. This study aims to provide a short review of methylphenidate’s effect on the animal’s behavior.
Methylphenidate has been abused for both ‘cognitive enhancement’ and recreational purposes to get ‘high’ in addition to improve attention and control misbehavior, increase wakefulness and task focusing. Their euphoric effects usually occur when they are crushed and snorted or injected.

Animal assay to study the behavioral effect of Psychostimulant

One of the most used assays to study animal behavior is the open field assay (Figure 1). Open field assays were introduced more than 80 years ago, it resembles a natural behavioral pattern and is one of the most widely used methods in animal behavioral research. Its popularity stems from the simplicity of the apparatus and of clearly defined behaviors. Certain measurable motor behaviors are sensitive to a wide range of drugs and experimental manipulations and are sufficiently reliable under standardized conditions to give repeatable measures on an enormous range of independent variable. Simplicity, reproducibility (Figure 2), ease of quantification, and wide applicability are the prime determinant of its popularity. Open-field locomotor behaviors represent the interaction of the subject with the experimental situation. Most investigators study the effects of psychostimulants in open-field testing whether repetitive (chronic) drug exposure elicits behavioral tolerance or sensitization [6,7]. Since drug liability is defined mainly on the basis of the subject behavioral expression to chronic drug exposure such as behavioral withdrawal, sensitization or tolerance. Behavioral expressions after psychostimulants administration develop gradually and progressively during the course of repeated exposure of psychostimulants, and this expression can persist for long periods of time after its discontinuation [8]. Thus, withdrawal, sensitization and tolerance are considered a form of drug induced neuronal plasticity and are used as an experimental model and as a marker for drugs effects, and for its liability of abuse. Behavioral tolerance is defined by the following criterion: repetitive exposure with the same dose of MPD will become less effective to elicit its initial effects. Behavioral sensitization is defined as reverse tolerance i.e., repetitive exposure with the same MPD dose will elicit a significant increase in its behavioral effects compared to that elicited by the initial (acute) dose (Figure 3).

Behavioral sensitization and/or tolerance are considered a long lasting neuroplasticity elicited following repetitive psychostimulant exposure. It has been suggested that behavioral tolerance and sensitization represent an enduring alteration of drug response and have been used as an experimental model of drug craving [9]. It was reported that the same repetitive dose of MPD in some animals elicited behavioral sensitization and in others behavioral tolerance. Moreover, the neuronal recording from central nervous system (CNS) structures belonging to the brain motive/reward circuit recorded from animals expressing behavioral sensitization to chronic MPD exposure responded to MPD in significantly different ways compared to those animals expressing behavioral tolerance to chronic MPD exposure [10-12]. Since chronic MPD use can elicit either behavioral sensitization or tolerance, psychostimulant therapy given to adolescents and young adults may increase the risk for Substance Use Disorder [10], 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.

Repetitive (chronic) treatment with psychostimulants to children, such as MPD and amphetamine, can modulate the neurodevelopmental processes critically. It has been reported that drugs such as MPD modulate the circadian rhythm as a result of molecular alteration of clock genes [14]. The alteration of the circadian activity behavior alters the body’s homeostasis. There is some concern about children with ADHD who are going through these neurodevelopmental processes while being treated with MPD for extended periods of time.

What is the best animal model to study the effect of methylphenidate

Key questions are which animal and which strain should be used to study the physiological properties of MPD? Obviously, the most appropriate animal model is the one that best mimics ADHD in
Citation: Dafny N (2015) The Characteristics of Methylphenidate on Animal Behavior. Pharm Anal Acta 6: 404. doi:10.4172/21532435.1000404

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 adult and adult rats, respectively (Table 1).

The response to psychostimulants varies with age in humans and other animals [9]. 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 [17]. 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 MPD in the young, which could cause some undesired behavioral disorders. 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. Whereas 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 [18]. Rats exposed to MPD during the period equivalent to human adolescence display behavioral changes that endure into adulthood. This suggests that MPD has a neurobiological effect in adolescents that modulates the ‘normal’ development to adulthood [15,9].

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 [18]. Adolescent rats of both sexes show sensitization to locomotor activating effects of cocaine, whereas different locomotor sensitization profiles were found in adult rats [18]. 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 [18].

Gender differences in the effects of methylphenidate

Biomedical investigations have been conducted almost exclusively with male subjects. The reason for excluding females as subjects in research is that they have greater biological complexity than males due to their reproductive cyclicity [19,20]. It has only recently become evident that the gonadal steroid hormones have multiple functions due to their reproductive cyclicity [19,20]. It has only recently become evident that the gonadal steroid hormones have multiple functions [20]. The institute of Medicine concluded that “…the understanding of sex differences in health and illnesses merits serious scientific inquiry in all aspects of biomedical and health-related research”. Furthermore, sex-related differences are often controversial and not documented.

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 (Figure 4). 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 [15]; reared in social isolation; have been exposed to environmental pollutants; have undergone neonatal anoxia, hippocampal x-irradiation in infancy, or selective neurotoxic lesion of DA, NE, etc. neurons; and genetically mutant mice. 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 [16]. 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 [16]. Therefore, the SHR strain is used most often in ADHD/methylphenidate studies.

| Figure 2: The figure summarizes (N=8) the effect of acute and chronic effect of 2.5 mg/kg methylphenidate (MPD) on Horizontal activity, Total Distance Traveling, and number of stereotypic movement. The black circle sums the activity/10 min after the initial (acute) MPD injections, the white circle sums the activity at experimental day 11 after six daily MPD exposure and 3 washout days. The histogram in the upper right corner depicts the total change from two baseline days activity (set arbitrarily at 0) and six daily MPD exposure, 5 days of washout and MPD rechallenge at day 14. The numbers indicate the experimental days. * indicates significant (p<0.05) from the initial effect of MPD. The figure shows that repetitive (chronic) MPD elicited behavioral sensitization. |
Differences in the response to cocaine, amphetamine and MPH in response to repetitive exposure (Figure 5) may be due to sex differences in drug pharmacokinetics, particularly drug metabolism. The neural systems mediating the behavioral response to psychomotor stimulants are sexually dimorphic and the gonadal hormones postulated to have important implications for gender differences in the acute and chronic responses to psychostimulants and in the susceptibility of addiction to these drugs. There are also remarkable gender differences in the behavioral expression of ADHD patients. For example, ADHD is more often diagnosed in males than in females and is 2-to-9 fold more prevalent in males. Females with ADHD may be more severely affected than males [21] as female ADHD subjects tend to have a higher genetic loading for the disorder. Anderson and Teicher (2001) hypothesized that there is an extensive overproductive of DA receptors in the male striatum and NAc during pre-pubertal development, which may help to explain why males are more often afflicted with ADHD because dopaminergic activity increases in these regions can produce hyperactivity and stereotypical behavior. Sex differences in ADHD may also be attributed to sex differences in DA receptor density. Striatal D2 receptor density in males increases 144% ± 26% between 25 to 40 days, while females D2 receptor density increases only 31% ± 7%. The rise in males’ striatal DA receptors parallels early development of ADHD motor systems [17].

In general, females were more sensitive than males to cocaine. The development of behavioral sensitization to cocaine was 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 female and males, and suggests that sex based research is an important variable to be considered in studying mechanisms and treatment and will provide more effective prevention and treatment strategies. It was reported that adult female rats are more seriously addicted to psychostimulants and express a more rapid and robust behavioral response to acute cocaine and amphetamine. Also, they usually display a greater and more rapid behavioral sensitivity to chronic exposure to these drugs compared to their male counterparts [22,23]. This sexual dimorphism was only observed in adult rats, suggesting that gonadal hormones secreted in adulthood might modulate the responsiveness to psychostimulants.

Acknowledgement

Acknowledgements I would like to thank Mallinckrodt Inc. for their gift of methylphenidate, and Dr. P.B. Yang, and C.M. Claussen for manuscript preparation. Supported in part by NIH DA R01 027222.

References

1. Godfrey J (2009) Safety of therapeutically methylphenidate in adults: a systematic review of the evidence. J Psychopharmacol 23: 194-205.
2. Gatley SJ, Volkow ND, Gifford AN, Fowler JS, Dewey, SL (1999) Dopamine-transporter occupancy after intravenous doses of cocaine and methylphenidate. J Am Acad Child Adolesc Psychiatry 37: 1242-1243.
3. Challiman TD, Lipsky JJ (2000) Methylphenidate: its pharmacology and uses. Mayo Clin 75: 711-721.
4. Kuczynski R, Segal DS (1997) Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. J Neurochem 68: 2032-2037.
5. Gerasimov MD, Franceschi, M, Volkow ND, Gifford A, Gatley SJ (2000) Comparison between intraperitoneal and oral methylphenidate administration: A microdialysis and locomotor activity study. J Pharmacol Exp Ther 296: 51-57.
6. Gaytan O, al-Rahim S, Swann A, Dafny N (1997) Sensitization to locomotor effects of methylphenidate in the rat. Life Sci 61: 101-107.
7. Yang PB, Amini B, Swann AC, Dafny N (2003) Strain differences in the behavioral responses of male rats to chronically administered methylphenidate. Brain Res 971: 139-152.
8. Askenasy EP, Taber KH, Yang PB, Dafny N (2007) Methylphenidate (Ritalin): Behavioral Studies in the Rat. Intern. J Neurosci 117: 1-38.
9. Dafny N, Yang PB (2006) The role of age, genotype, sex, and route of acute and chronic administration of methylphenidate: A review of its locomotor effects. Brain Res Bul 66: 393-405.
10. Claussen CM, Chong SL, Dafny N (2014) Nucleus accumbens neuronal activity correlates to the animals behavioral response to acute and chronic methylphenidate. Physiol Behav 129: 85-94.
11. Jones Z, Dafny N (2014) Acute and chronic dose-response effect of methylphenidate on ventral tegmental area neurons correlated with animal behavior. J Neural Transm 121: 327-345.
12. Tang B, Dafny N (2013) Behavioral and dorsal raphe neuronal activity following acute and chronic methylphenidate in freely behaving rats. Brain Res Bull 88: 53-63.
13. Van Emmerik-van Oortmerssen K, van de GInd G, van den Brink W, Smit F, Cruenelle CL (2013) Prevalence of attention-deficit/hyperactivity disorder in substance use order patients: a meta-analysis and meta-regression analysis. Drug Alcohol Depend 122: 11-29.
14. Alghaim MF, Yang PB, Wilcox VT, Burau KD, Swann AC (2009) Prolonged methylphenidate treatment alters the behavioral diurnal activity pattern of adult male Sprague-Dawley rats. Pharmacol Biochem Behav 92: 93-99.
15. Barron E, Yang PB, Swann AC, Dafny N (2009) Adolescent and adult male spontaneous hyperactive rats (SHR) respond differently to acute and chronic methylphenidate (Ritalin). Int J Neurosci 119: 40-58.
16. Sagvolden T, Lamm MC, Taljaard JJ (2000) Methylphenidate affects striatal dopamine differently in an animal model for attention-deficit/hyperactivity disorder—the spontaneously hypertensive rat. Brain Res Bull 53: 187-192.
17. Andersen SL, Teicher MH (2000) Sex differences in dopamine receptors and their relevance to ADHD. Neurosci Biobehav Rev 24: 137-141.
18. Laviola G, Wood RD, Kuhn C, Francis R, Spear CR (1995) Cocaine sensitization in periadolescent and adult rats. The J of Pharmacol and Exp Therap 275: 345-351.
19. Kelly SJ, Ostrowski NL, Wilson MA (1999) Gender differences in brain and behavior 64: 655-664.
20. McEwen BS, Alves SE, Boltch K, Weiland NG (1998) Clinically relevant basic science study of gender differences and sex hormone effects. Psychopharmac Bull 34: 251-259.
21. Biederman J, Faraone SV, Spencer T, Wilens T, Nick E (1994) Gender differences in a sample of adults with attention deficit hyperactivity disorder Psychiatry Res 53: 13-29.
22. Van Harran E, Meyer M (1991) Sex differences in locomotor activity after acute and chronic cocaine administration. Pharmacol Biochem Behav 39: 923-927.
23. Volkow ND, Wang GJ, Fowler JS, Fischma, M, Foltin R (1999) Methylphenidate and cocaine have a similar in vivo potency to block dopamine transporters in the human brain. Life Sci 65: 7-12.