

Methylphenidate Elicits Long Term Sex Difference Effects

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ABSTRACT

ADHD is commonly treated with the psychostimulant methylphenidate (MPD). The use of MPD as a recreational drug and cognitive enhancer has expanded among regular people across a range of age groups. Because MPD and cocaine and amphetamines have such similar pharmacological profiles, there is worry that MPD may lead to addiction and dependence. The goal of this study was to ascertain whether and for how long MPD use as a child has an impact on adult female and male normal participants. A computerised monitoring system was used to record behavioural activity both before and after acute and chronic MPD exposure. The locomotors of five distinct behavioural expressions were noted. On experimental day 1 (ED1 BL), Baseline (BL) activity was obtained in all groups, followed by 3 to 37 washout days and an MPD re-challenge at ED 11, ED 27, ED 36, or ED 42, followed by six daily Saline or MPD injections. Each of the MPD dosage groups at ED 11, ED 27, ED 36, or ED 42 produced a rechallenge response that resulted in behavioural sensitization in some animals and behavioural tolerance in other animals. All five types of behavioural manifestations showed gender disparities. According to the observations, each of the five behavioural expressions under investigation is controlled by a different neural circuitry, and MPD's effects are prolonged when it is administered for six days.

INTRODUCTION

Nowadays, Ritalin, also known as methylphenidate (MPD), is a medication used to treat ADHD [1-3]. MPD is a stimulant with effects that are comparable to those of cocaine and methamphetamine [4]. Owing to its chemical makeup, there has been substantial debate regarding whether MPD is currently an addictive substance or has the capacity to do so. One of the most frequently recommended medications for kids with behavioural disorders is MPD. In some parts of the United States, its use among school-age children has increased by 15%, while in metropolitan regions of Europe, it has increased from 3% to 6%. Adult MPD usage frequently persists [2,5,6]. Also, the prevalence of its use as a cognition enhancer has increased both its legal and criminal use among adults in their professional and college years [7]. This is especially troubling because earlier meta-analyses have shown that chronic behavioural changes and SUD are more likely with later initiation at or after the adolescent stage, even though MPD initiation during childhood appears to mitigate or even lower the risks of Substance Abuse Disorder (SUD) [8-10]. According to estimates, MPD users have a lifetime prevalence of cocaine use that is doubled for those with ADHD, going from 10% to over 20%. Figures for ADHD and SUD range from 9.5% to 58%. MPD is becoming more widely used as a recreational

drug and as a cognitive enhancer [1]. Rats are commonly used as animal models in MPD research because they have many pharmacological and behavioural characteristics with humans. Differences in sex and how long MPD continues to affect tolerance or sensitization during repetitive (chronic) usage are a few problems that were not addressed in earlier investigations. Lately, it has been demonstrated that the short-term consequences of MPD can lead to drug abuse [3]. Studies on animals have revealed that MPD has a sizable impact on the dopaminergic neuronal system, providing indications of its potential for addiction [11]. Another animal study has demonstrated that the introduction of MPD treatment at a particular point in adolescence has varied long-term effects. neurological transmission [12, 13]. Although MPD use has been extensively covered in the media, the high rates of prescription and misuse among teenagers and adults of both sexes necessitate a more thorough and conclusive examination of its consequences. The goal of the current study is to determine how long MPD's effects will continue after a subject has used it. To evaluate the long-term effects of MPD, behavioural expressions of tolerance and/or sensitization were examined. These two factors—behavioral tolerance and sensitization—are frequently employed as biomarkers to assess the duration of a drug's effects and if it has the capacity and characteristics to cause dependence [4, 14–16]. The study sheds light on how long MPD will remain in the body and whether it has the potential to become an addictive drug.

Discussion

The study looked over how long six days of MPD ingestion in a row would continue to show behavioural consequences. The study's key conclusions are: 1) Five distinct locomotor behaviour expressions were measured; they all responded to acute MPD treatment similarly but differently to chronic MPD exposure, indicating that each of the five locomotor behavioural expressions is controlled by a unique neural circuit. 2) The same dose of chronic MPD (0.6 mg/kg, 2.5 mg/kg, or 10.0 mg/kg) resulted in behavioural tolerance in some rats and behavioural sensitization in others. One of the experimental indicators for dependence and addiction is behavioural sensitization or tolerance. 3) After six daily MPD exposures of 0.6 mg/kg, 2.5 mg/kg, or 10.0 mg/kg, the effects of the MPD rechallenge at ED 11 show that behavioural sensitization has occurred. during the six daily MPD exposures, or behavioural tolerance. While MPD re-challenge at ED 27, 36, and 42 shows that behavioural sensitization and tolerance persist for extended periods of time

with intensity changes. 4) Both male and female rats exposed to MPD exhibit its effects on locomotor activity for extended periods of time. The research builds on earlier studies that looked at the acute and long-term effects of MPD, also known as Ritalin, in male and female WKY strain rats. Field arrays are used in this investigation to assess the differences between acute and repetitive (chronic) behavioural effects of MPD administration, we measured the locomotor behavioural expression (indices) of Wistar Kyoto (WKY) rats in groups of males and females in response to three different doses of MPD: 0.6 mg/kg, 2.5 mg/kg, and 10.0 mg/kg. In numerous studies [30,31], rats demonstrated a behavioural response to stimulants that was comparable to that of humans. The open field array is a time and money-saving alternative to research that rely on more advanced technology, such as brain implants, for monitoring the locomotor behaviour of five rats. various neural circuitry. Our experience supports using five of the 20 data points provided by the open field array system we used, which has three levels of 16 sensors each and measures the following parameters: horizontal activity (HA), total distance (TD) travelled, numbers of movements (NM), vertical activity (VA), and frequency of stereotypical movement (SM) activity expression. These assessments have shown to be useful in detecting behavioural changes brought on by both acute and chronic MPD use.

The more recent, better-tech solutions can distinguish between the five neural circuits involved in behaviour, but they come at a higher cost, with more invasive harm to the individuals. Results processing may be more difficult since isolating the circuits can hide tolerance and ANOVA analysis with sensitization. Individual movement behaviours and specific neural circuits and cellular alterations may be related to one another, and this relationship may be discovered by combining open field tests with some more recent technologies. At the highest MPD dose of 10.0 mg/kg, half of the rats displayed behaviour that was decreasing with chronic exposure as compared to the initial MPD dose, while the other half showed further significant increases in response after washout as compared to the initial exposure that elicited the greatest response in 80% of the subjects. Males were more likely than females to experience persistent MPD effects (86% vs. 66% respectively), while females did not experience an increase in vertical activity even after receiving the lowest dose of MPD. The difference in activity levels between the sexes as well as the later sexual maturity of female specimens may be influenced by hormonal impacts. Given the contentiousness of treating millions of people The acknowledged disparities between males and females in children with MPD indicate that

more research into sex differences in usage is necessary since they could affect clinical judgements for human patients. The differences in how the five types of locomotor behaviour are expressed between the sexes and between them suggest that each of these is regulated by a different neuronal circuit and that MPD affects each neuronal circuit differently. This suggests that distinct neuronal circuits are involved and that each one needs to be identified and given a separate study to determine how MPD affects it. The WKY rat model was employed in the current study to examine the impact of sex in a non-ADHD rat model. Yet more research is necessary to see whether MPD in ADHD models using SHR rats and potentially other. In particular, sex effects on persistent behavioural alterations and consequent propensity towards SUD are being studied in genetic strains, both with early and late onset of MPD. The use of the open field assay may also be increased, enabling more affordable research to be conducted at a larger scale, by studies that give correlation between the results of the open field assay, electrophysiological measures, and histological analysis.

REFERENCES

1. Kim MG, Kim J, Kim SC, Jeong J. Twitter analysis of the nonmedical use and side effects of methylphenidate: Machine learning study. *J Med Internet Res*. 2020;22(2):e16466.
2. Kollins SH, MacDonald EK, Rush CR. Assessing the abuse potential of methylphenidate in nonhuman and human subjects: a review. *Pharmacol Biochem Behav*. 2001;68(3):611-27.
3. Mac Avin M, Teeling M, Bennett KE. Trends in attention-deficit and hyperactivity disorder (ADHD) medications among children and young adults in Ireland: a repeated cross-sectional study from 2005 to 2015. *BMJ Open*. 2020;10(4):e035716.
4. Dafny N, Yang PB. The role of age, genotype, sex and route of acute and chronic administration of methylphenidate: a review of its locomotor effects. *Brain Res Bull*. 2006;68(6):393-405.
5. Cheung K, Verhamme KMC, Herings R, Visser LE, Stricker BH. Methylphenidate Treatment Initiated During Childhood Is Continued in Adulthood in Half of the Study Population. *J Child Adolesc Psychopharmacol*. 2019;29(6):426-32.
6. Ponnou S, Haliday H. ADHD Diagnosis and Drug Use Estimates in France: A Case for Using Health Care Insurance Data. *J Atten Disord*. 2021;25(10):1347-50.
7. Cândido RCF, Perini E, Pádua CM, Junqueira DR. Prevalence of and factors associated with the use of methylphenidate for cognitive enhancement among university students. *Einstein (Sao Paulo)*. 2019;18:eAO4745.
8. Faraone SV, Wilens T. Does stimulant treatment lead to substance use disorders? *J Clin Psychiatry*. 2003;64 Suppl 11:9-13.
9. Jordan CJ, Lemay C, Dwoskin LP, Kantak KM. Adolescent d-amphetamine treatment in a rodent model of attention deficit/hyperactivity disorder: impact on cocaine abuse vulnerability in adulthood. *Psychopharmacology (Berl)*. 2016;233(23-24):3891-3903.
10. Jordan CJ, Taylor DM, Dwoskin LP, Kantak KM. Adolescent D-amphetamine treatment in a rodent model of ADHD: Pro-cognitive effects in adolescence without an impact on cocaine cue reactivity in adulthood. *Behav Brain Res*. 2016;297:165-79.
11. Ponchio RA, Teodorov E, Kirsten TB, Coelho CP, Oshiro A, Florio JC, et al. Repeated methylphenidate administration during lactation reduces maternal behavior, induces maternal tolerance, and increases anxiety-like behavior in pups in adulthood. *Neurotoxicol Teratol*. 2015;50:64-72.
12. Harvey RC, Sen S, Deaciuc A, Dwoskin LP, Kantak KM. Methylphenidate treatment in adolescent rats with an attention deficit/hyperactivity disorder phenotype: cocaine addiction vulnerability and dopamine transporter function *Neuropsychopharmacology*, 2011;36(4):837-47.
13. Yetnikoff L, Arvanitogiannis A. Differential sensitivity to the acute and sensitizing behavioral effects of methylphenidate as a function of strain in adolescent and young adult rats. *Behav Brain Funct*. 2013;9:38.
14. Venkataraman SS, Joseph M, Dafny N. Concomitant behavioral and prefrontal cortex neuronal responses following acute and chronic methylphenidate exposure in

- adolescent and adult rats. *Brain Res Bull.* 2019;144:200-12.
15. Venkataraman SV, Reyes Vázquez C, Claussen CM, Dafny N. Does MPD affect adolescent and adults differently: concomitant behavioral and PFC neuronal © 2022 - Medtext Publications. All Rights Reserved. 028
16. Venkataraman SS, Claussen C, Kharas N, Dafny N. The prefrontal cortex and the caudate nucleus respond conjointly to methylphenidate (Ritalin). Concomitant behavioral and neuronal recording study. *Brain Res Bull.* 2020;157:77-89.
17. Broussard E, Reyes-Vazquez C, Dafny N. Methylphenidate dose-response behavioral and neurophysiological study of the ventral tegmental area and nucleus accumbens in adolescent rats. *Eur J Neurosci.* 2019;50(4):2635-52.
18. Yang PB, Amini B, Swann AC, Dafny N. Strain differences in the behavioral responses of male rats to chronically administered methylphenidate. *Brain Res.* 2003;971(2):139-52.
19. Yang PB, Swann AC, Dafny N. Chronic methylphenidate modulates locomotor activity and sensory evoked responses in the VTA and NAC of freely behaving rats. *Neuropharmacology.* 2006;51(3):546-56.
20. Yang PB, Cuellar DO, Swann AC, Dafny N. Age and genetic strain differences in response to chronic methylphenidate administration. *Behav Brain Res.* 2011;218(1):206-217.
21. Gaytan O, Ghelani D, Martin S, Swann A, Dafny N. Methylphenidate: Diurnal effects on locomotor and stereotypic behavior in the rat. *Brain Res.* 1997;777(1-2):1-12.
22. Claussen C, Dafny N. Caudate neuronal recording in freely behaving animals following acute and chronic dose response methylphenidate exposure. *Pharmacol Biochem Behav.* 2015;136:21-30.
23. Ihezue SA, Thomas MM, Dafny N. Acute and chronic methylphenidate administration in intact and VTA-specific and nonspecific lesioned rats. *J Neural Transm (Vienna).* 2019;126(2):173-82.
24. Kharas N, Yang P, Castro-Alvarado D, Rose K, Dafny N. Exposure to methylphenidate in adolescence and adulthood modulates cross-sensitization to amphetamine in adulthood in three genetically variant female rat strains. *Behav Brain Res.* 2019;362:36-45.
25. Karim TJ, Aksel C, Kharas N, Reyes-Vasquez C, Dafny N. Caudate nucleus neurons participate in methylphenidate function: Behavioral and neuronal recordings from freely behaving adolescent rats. *Brain Res Bull.* 2018;142:241-52.
26. Gaytan O, Sirpada S, Swann A, Dafny N. Blockade of sensitization to methylphenidate by MK-801: Partial dissociation from motor effects. *Neuropharmacology.* 2001;40(2):298-309.
27. Lee MJ, Yang PB, Wilcox VT, Burau KD, Swann AC, Dafny N. Does repetitive Ritalin injection produce long-term effects on SD female adolescent rats? *Neuropharmacology.* 2009;57(3):201-7.
28. Venkataraman SS, Claussen C, Joseph M, Dafny N. Concomitant behavioral and PFC neuronal activity recorded following dose-response protocol of MPD in adult male rats. *Brain Res Bull.* 2017;130:125-37.
29. Salman T, Nawaz S, Ikram H, Haleem DJ. Enhancement and impairment of cognitive behaviour in Morris water maze test by methylphenidate to rats. *Pak J Pharm Sci.* 2019;32(3):899-903.
30. Salman T, Nawaz S, Waraich RS, Haleem DJ. Repeated administration of methylphenidate produces reinforcement and downregulates 5-HT-1A receptor expression in the nucleus accumbens. *Life Sci.* 2019;218:139-46.
31. Thanos PK, Robison LS, Steier J, Hwang YF, Cooper T, Swanson JM, et al. A pharmacokinetic model of oral methylphenidate in the rat and effects on behavior. *Pharmacol Biochem Behav.* 2015;131:143-53.
32. Floren S, King N, Carrasco A, Dafny N. Glutamate and dopamine in the VTA participate differently in the acute and chronic effect of methylphenidate. *Behav Brain Res.* 2020;380:112390.
33. King N, Floren S, Kharas N, Thomas M, Dafny N.

- Glutamatergic signaling in the caudate nucleus is required for behavioral sensitization to methylphenidate. *Pharmacol Biochem Behav.* 2019;184:172737.
34. Ming T, Dafny N. Glutamatergic signaling in the nucleus accumbens modulates the behavioral response to acute and chronic methylphenidate. *J Exp Neurol.* 2021;2(1):49-61.
 35. Miller EM, Quintero JE, Pomerleau F, Huettl P, Gerhardt GA, Glaser PEA. Chronic Methylphenidate Alters Tonic and Phasic Glutamate Signaling in the Frontal Cortex of a Freely-Moving Rat Model of ADHD. *Neurochem Res.* 2019;44(1):89-101.
 36. Coelho-Santos V, Cardoso FL, Magalhães A, Ferreira-Teixeira M, Leitão RA, Gomes C, et al. Effect of chronic methylphenidate treatment on hippocampal neurovascular unit and memory performance in late adolescent rats. *Eur Neuropsychopharmacol.* 2019;29(2):195-210.
 37. Coelho-Santos V, Cardoso FL, Leitão RA, Fontes-Ribeiro CA, Silva AP. Impact of developmental exposure to methylphenidate on rat brain's immune privilege and behavior: Control versus ADHD model. *Brain Behav Immun.* 2018;68:169-82.
 38. Yang PB, Swann AC, Dafny N. Methylphenidate treated at the test cage--dose dependent sensitization or tolerance depend on the behavioral assay used. *Crit Rev Neurobiol.* 2007;19(1):59-77.
 39. Amini B, Yang PB, Swann AC, Dafny N. Differential locomotor responses in male rats from three strains to acute methylphenidate. *Int J Neurosci.* 2004;114(9):1063-84.
 40. Jin C, Rockhold RW, Hoskins B, Ho IK. Comparisons of cocaine receptors in brain regions from WKY and SHR. *Brain Res Bull.* 1991;27(6):853-6.
 41. Somkuwar SS, Kantak KM, Bardo MT, Dwoskin LP. Adolescent methylphenidate treatment differentially alters adult impulsivity and hyperactivity in the Spontaneously Hypertensive Rat model of ADHD. *Pharmacol Biochem Behav.* 2016;141:66-77.
 42. Watanabe HK, Hoskins B, Ho IK. Effects of subacute treatment with cocaine on activities of N-demethylase, UDP-glucuronyltransferase and sulfotransferase in WKY and SHR rat liver--sex and strain differences. *Life Sci.* 1988;42(1):79-86.
 43. Cailhol S, Mormède P. Strain and sex differences in the locomotor response and behavioral sensitization to cocaine in hyperactive rats. *Brain Res.* 1999;842(1):200-5.
 44. Ashkenazy EP, Yang PE, Taber KH, Dafny N. Methylphenidate (Ritalin): Behavioral studies in the rats. *Int J Neurosci.* 2007;117(6):757-94.
 45. Roessner V, Sagvolden T, Dasbanerjee T, Middleton FA, Faraone SV, Walaas SI, et al. Methylphenidate normalizes elevated dopamine transporter densities in an animal model of the attention-deficit/hyperactivity disorder combined type, but not to the same extent in one of the attention-deficit/hyperactivity disorder inattentive type. *Neuroscience.* 2010;167(4):1183-91.
 46. Somkuwar SS, Darna M, Kantak KM, Dwoskin LP. Adolescence methylphenidate treatment in a rodent model of attention deficit/hyperactivity disorder: dopamine transporter function and cellular distribution in adulthood. *Biochem Pharmacol.* 2013;86(2):309-16.