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Review

The role of age, genotype, sex, and route of acute and chronic administration of methylphenidate: A review of its locomotor effects

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Abstract

Children with attention deficit hyperactivity disorder (ADHD) are treated for extended periods of time with the psychostimulant methylphenidate (MPD). The psychostimulants cocaine, amphetamine, and MPD exhibit similar structural configuration and pharmacological profile. The consequence of the long-term use of psychostimulants such as MPD as treatment for ADHD in the developing brain of children is unknown. Repeated treatment with psychostimulants has been shown to elicit adverse effects in behavior, such as dependence, paranoia, schizophrenia, and behavioral sensitization. Behavioral sensitization and cross-sensitization between two drugs are used as experimental markers to determine the potential of a drug to develop dependence/addiction. Although there are many reviews written about behavioral sensitization involving psychostimulants, scarcely any have focused specifically on MPD-elicited behavioral sensitization and cross-sensitization with other psychostimulants. Moreover, the response to MPD and the expression of ADHD vary among females and males and among different populations due to genetic variability. Since the interpretation and synthesis of the data reported are controversial, this review focuses on the adverse effects of MPD and the role of age, sex, and genetic composition on the acute and chronic effects of MPD, such as MPD-elicited behavioral sensitization and cross-sensitization with amphetamine in animal models. Animal models of drug-induced locomotor stimulation, particularly locomotor sensitization, can be used to understand the mechanisms underlying human drug-induced dependence.

Keywords: Behavioral sensitization; Cross-sensitization; Methylphenidate (Ritalin); Amphetamine; Psychostimulants; Genetic strains; Age; Gender; Drugs of abuse; Dependence; Locomotor activity

Contents

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1. Introduction

The psychostimulant methylphenidate (MPD), commonly known as Ritalin, is the most prescribed drug treatment for attention deficit hyperactivity disorder (ADHD) [1,60,102,164]. Children with ADHD are treated with the drug for several (4–9) years [7,41,81,82,102,112,178]. Concerns about the possible overuse of MPD in young children have been disseminated both in the media and scientific publications [1,81,82]. They are the result of: (1) the rapid increase in the MPD usage, (2) an increase in the number of preschool-aged children diagnosed with ADHD and treated with MPD, and (3) lack of information on the long-term consequences of psychostimulants on brain development [1]. Moreover, there are controversial reports whether MPD treatment has the potential to elicit drug dependence as other psychostimulants, such as cocaine and amphetamine [72,81]. Additional concerns are the possible adverse effects produced by such psychopharmacological intervention in a developing brain [102]. During childhood, crucial neurodevelopment occurs with the production and elimination of numerous neuronal connections, i.e., synaptic pruning. Repeated treatment with psychostimulants can result in the initiation and intensification of biochemical and behavioral manifestations that ultimately lead to modulation of these critical developmental processes and produce plasticities in the cellular components of the central nervous system (CNS) and thus cause dependence of the drug and behavioral sensitization. Behavioral sensitization refers to the progressive augmentation of behavioral responses to the repetitive use of psychostimulants that develop as a result of enduring drug response [76,146,188]. One of the experimental markers in animals that indicate the potential of a psychostimulant becoming a drug of abuse is behavioral sensitization and cross-sensitization with other psychostimulants that result in altering the body's homeostasis [77]. Therefore, this review will address the role of age in response to acute and chronic MPD in rats.

Ethnicity and race are associated with certain biological dispositions due to differences in the individual's genetic composition [112]. Similarly, strain is associated with certain genetic composition in animals. Different ethnicities/strains have different genetic composition that may lead to differences in a subject's response to acute and chronic drug treatment and drug liability. It was reported that genetic factors influence activity of the CNS [40]. Therefore, this review will address the role of genetic/strain in response to MPD in rats.

The consequences and mechanisms of drugs are not identical in females and males. Sex differences in response to drugs in general and to psychostimulants in particular may be an important variable to consider in the tendency and vulnerability of the subject to express side effects of the drug, as well as in the treatment of behavioral disorders and prevention of drug abuse and addiction. Studies in humans and rodents using cocaine and amphetamine indicate that female subjects express a more rapid and robust behavioral sensitization than their male counterparts and that their symptoms of drug side effects are also more serious than those of male subjects [17,62,88]. This indicates that sex-based research is important. Thus, this review will also address the role of sex in acute and chronic effects of MPD in rats.

Prospective studies following hyperactive children and normal controls into adulthood have found that hyperactive adults with a history of ADHD in their childhood are more likely than controls to have substance-use disorders [102]. Moreover, several studies support the link between ADHD and substance-use disorders [58,102,108]. The chronic use of psychostimulants, such as cocaine and amphetamine, elicits behavioral sensitization [74,76]. Behavioral sensitization is characterized by the progressive increase in response to repeated exposure of a psychostimulant and is used as an experimental model to determine the potential of a drug to develop dependency [19,147,148]. Repeated use of one psychostimulant has also resulted in cross-sensitization with other psychostimulants, a phenomenon involving an augmented response that occurs when pretreatment with one stimulant leads to a greater sensitivity to another stimulant [3,19,92,160]. Cross-sensitization between two psychostimulants indicates a hypersensitivity to the incentive properties of these drugs and that these two drugs have similar incentive and adverse properties [94]. Under certain conditions, MPD has been shown to have abuse potential comparable to cocaine and amphetamine [81]. Since behavioral sensitization serves as an experimental model to study the potential of a drug to elicit incentive and/or adverse effects [77,147,148] and because the use of MPD has rapidly increased in recent years [60,82,154,196], this review will relate to MPD-elicited behavioral sensitization and cross-sensitization, as well as the role of age, genetic composition, and sex on the effects of MPD.

2. Pharmacology of methylphenidate (MPD)

Methylphenidate hydrochloride is a CNS stimulant that closely relates to the structure of dextroamphetamine [78,132], an isomer of amphetamine [173]. The neuropharmacological profile of MPD is also similar to that of cocaine [181]. The drug was first synthesized in 1944 and was used initially as an analeptic for several types of barbiturate-induced coma [183]. It was later used as a drug to improve memory in depressed elderly or brain tumor patients [100,120]. Since then its usage has been extended to improve the alertness in children with emotional, behavioral, and learning difficulties [178,185]. MPD is highly effective in treating ADHD [25]. In addition, MPD may also be useful in providing relief from intractable pain as well as taking addicted patients off cocaine and antidepressants [79]. It also helps to combat narcolepsy and chronic fatigue [30,79,100].