Drug Reinforcement in a Rat Model of Attention Deficit/Hyperactivity Disorder – The Spontaneously Hypertensive Rat (SHR)

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Abstract: The co-occurrence of drug addiction in adults with attention deficit hyperactivity disorder (ADHD) is very common, but its etiology remains largely unknown. Therefore, animal models to study this kind of psychiatric comorbidity are needed. The Spontaneously Hypertensive Rat (SHR) strain shows neurochemical and behavioral characteristics which make it a suitable model of ADHD. Compared with their normotensive controls (Wistar-Kyoto) and with some other rat strains, SHR rats drink more ethanol and are more sensitive to its anxiolytic/stimulant effects. They also show increased sensitivity to psychostimulants, opioids and cannabinoids. Furthermore, chronic treatment with methylphenidate, the first-choice drug to treat ADHD, during adolescence, changes the ethanol intake and the behavioral effects of cocaine in adult SHR rats. Regarding sex differences, females are more sensitive to psychostimulants and drink more ethanol than males, an important condition because in adulthood, more females suffer from ADHD than males. Taken together, the reviewed findings indicate that the SHR strain is a promising tool for studies on drug addiction and, possibly, its relationship with ADHD.

Keywords: Drug dependence, alcoholism, psychiatric comorbidity, dopamine, sex differences.

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a complex condition characterized by behavioral and cognitive symptoms, such as inattention and impulsivity/hyperactivity. ADHD is one of the most common childhood neuropsychiatric disorders and, in more than 50% of children with ADHD, the symptoms can persist into adolescence and adulthood [1, 2]. It is now estimated that 4% of adults suffer from ADHD [3, 4]. Moreover, the association between ADHD and other psychiatric disorders is very common, and substance use disorder (SUD) is one of the most prevalent disorders co-occurring with ADHD. Early-onset SUD and higher rates of abuse of and dependence on alcohol and other drugs have been reported in patients with ADHD in comparison with normal control subjects [5-10]. However, the etiology of this psychiatric comorbidity remains largely unknown, at least in part, due to the lack of animal models.

ADHD and SUD show similarities in terms of neurotransmission systems and anatomical structures (e.g., mesolimbic dopaminergic system) [11-14]. Moreover, ADHD is often treated with psychostimulants such as methylphenidate (MPD) or amphetamine (AMPH). The potential for the abuse of these drugs is well documented, but whether pharmacotherapy in ADHD patients contributes to the exceptionally high rates of SUD remains controversial [9]. There is evidence to show that therapeutic treatment of ADHD increases the risk of drug addiction [6], whereas other studies have reported that this treatment reduces the risk of SUD [15]. Nevertheless, pharmacological treatment of ADHD is especially dangerous in patients with SUD as one-third of medicated ADHD patients report having abused their psychostimulant medication [7]. Thus, the identification of the neurobiological mechanisms underlying the association between ADHD and SUD is necessary as this condition may further complicate the diagnosis and treatment of the individuals [8, 9].

Several animal models of ADHD in rodents have been proposed and although they have received criticism, they have undoubtedly proportioned advances in our knowledge in this field. These models include the Wistar-Kyoto Hyperactive Rat (WKHY), Naples High-Excitability Rat, Dopamine (DA) Transporter Knockout Mouse, Coloboma Mutant Mouse, 6-Hydroxydopamine-Lesioned Rat and others [see, for review, 16, 17]. However, the most validated animal model of ADHD is the Spontaneously Hypertensive Rat (SHR). SHR rats show behavioral and neurochemical characteristics, which makes them a useful model of ADHD [16-20]. Hence, it is logical to speculate whether the SHR strain may also constitute a model for the study of SUD. Here we review the findings regarding the effects of drugs of abuse on the behavior of SHR rats and discuss the potential appropriateness of the use of this strain to study the relationship between ADHD and SUD.

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THE SHR STRAIN AS AN ANIMAL MODEL OF ADHD

The SHR strain was developed at the Kyoto University, Japan, about 45 years ago. It was derived from the Wistar-Kyoto strain (WKY) by selective breeding for arterial hypertension [21]. The inbred SHR and WKY (normotensive controls) strains became a model widely used to study hypertension [22, 23]. Besides physiological studies, a considerable number of investigations were dedicated to the behavioral characteristics of these strains. Based on these characteristics, some authors propose the SHR strain as a genetic model of ADHD [17, 24, 25]. When compared with WKY rats and with some other rat strains, SHR rats show a sustained attention deficit, hyperactivity in some situations and motor impulsiveness [16, 17, 19]. Moreover, they are novelty-seekers and risk-takers [26]. Several of these behavioral characteristics are present in young SHRs prior to the establishment of hypertension, suggesting that hypertension and behavior in SHR rats are, at least partially, independent phenotypes. Genetic and neurochemical abnormalities potentially associated with the behavioral profile of SHR rats have been reported. For example, Mill and collaborators [27] have shown several variations in the DA transporter gene (DAT1) between SHR and WKY rats. Alterations in DAT1 could affect DA reuptake and metabolism, which is consistent with the DAergic hypothesis of ADHD [28]. Accordingly, the number of tandem repetitions in the DAT1 gene is associated with ADHD in humans [29]. An extensive review on the characteristics, usefulness and limitations of the SHR strain as a model of ADHD is outside the scope of this article. Excellent reviews on this issue have been published [16, 17, 19, 25].

PSYCHOSTIMULANTS

As mentioned earlier, psychostimulants are the first-choice drugs in the treatment of ADHD [see, for review, 30]. Thus, the majority of studies have investigated the effect of psychostimulants on the ADHD-like symptoms (hyperactivity, impulsivity and inattentiveness) of SHR rats. In this section, with the exception of locomotion, the effect of psychostimulants on ADHD-related behaviors will not be discussed.

Several studies have reported that SHR rats show an increased response to psychostimulants as compared to other strains. SHR rats injected with MPD showed an increased behavioral sensitivity compared to WKY and Sprague-Dawley (SD) rats [31, 32]. SHR rats also displayed higher levels of locomotor stimulant response to AMPH than WKY rats [33]. It was recently reported that SKF-81297 (10 mg/kg), a full and selective D1 receptor agonist, elicited a more pronounced stimulatory effect in SHR than in WKY rats. This effect was accompanied by higher levels of c-fos mRNA expression, a marker of neuronal activity, in the *nucleus accumbens* and adjacent cortical regions, in SHR rats compared to WKY rats [34]. Furthermore, SHR rats were more sensitive to cocaine-induced analgesia than Wistar [35] and LEW rats (Pamplona *et al.*, unpublished data). Some authors suggest that hyperlocomotion and analgesia reflect the positive reinforcing or euphorigenic properties of drugs as these phenomena result from activation of common neuronal pathways [36, 37]. Conversely, similar levels of hyperlocomotor responses to psychostimulants were observed in SHR and WKY adult rats treated with MPD, AMPH or GBR-12909, a dopamine uptake inhibitor [38], an effect that was also observed in adolescent SD, WKY and SHR rats treated with MPD [39]. Finally, a greater increase in locomotion after treatment with MPD [40] or AMPH [41] was observed in WKY and SD rats in comparison to SHR rats.

Repeated exposure to psychostimulants can induce behavioral sensitization that is characterized by a progressive increase in the behavioral effects of the drug, and may be involved in the development of drug addiction [42]. We have recently demonstrated that male SHR rats display more cocaine-induced behavioral sensitization than Lewis (LEW) rats, whereas similar levels of sensitization were found among females. When challenged with cocaine after a two-week drug-free period, LEW and SHR rats of the two sexes showed similar levels of behavioral sensitization [43]. Moreover, Cailhol and Mormède [44] reported that SHR rats showed higher levels of cocaine-induced behavioral sensitization when compared to WKHA, but not to WKY, rats. In a subsequent study, the authors reported similar levels of cocaine sensitization for these three strains [45]. On the other hand, repeated MPD treatment (2.5 mg/kg, IP) induced sensitization in SD, but with a weak effect and with no effect in WKY and SHR rats, respectively. Repeated administration of a higher MPD dose (10 mg/kg), however, induced tolerance (a reduction in activity) in SD, WKY and SHR rats [31]. In adolescent rats, chronic treatment with MPD (0.6, 2.5 and 10 mg/kg, IP) failed to elicit sensitization in SD, WKY and SHR rats [39]. In studies comparing rats of both sexes, SHR females are more sensitive to both the acute effect of psychostimulants and the sensitization produced by these drugs than SHR males [44, 45].

Only one study has evaluated the enduring effects of chronic MPD administration to adolescent SHR rats on their sensitivity to psychostimulants in later life. Augustyniak and collaborators [46] have reported that SHR rats given MPD during adolescence (post-natal day 35 to 44) showed a reduced cocaine-seeking behavior when tested in adulthood in the place-preference paradigm.

In summary, the majority of the aforementioned studies report that SHR rats are more sensitive to psychostimulants when compared to other rat strains. This result may be due to an altered DAergic system in SHR rats. However, discrepant findings exist and this probably results from a complex interplay between the level of activation of the DAergic system and environmental factors [e.g., 47].

ETHANOL

Some studies have compared SHR with other strains regarding the sensitivity, tolerance and consumption of ethanol. Khanna *et al*. [48] have reported that SHR rats are more sensitive to ethanol in the jumping test and consumed significantly more ethanol than WKY rats in both the two-bottle choice and the limited access models. However, a similar magnitude of acute tolerance development was observed between the strains [48]. Da Silva and collaborators [26] have reported that SHR rats are more sensitive to the anxiolytic/stimulant effects of ethanol when compared to the inbred LEW strain. This finding is interesting because the anxiolytic effect of ethanol is considered an important motivational factor underlying the intention to drink in humans

[49]. Accordingly, compared with LEW and other rat strains, SHR rats drank higher amounts of ethanol in the two-bottle choice paradigm [26, 50-52, but see 53]. Other studies, however, have reported that WKHA [54, 55] and WKY [56] rats drank more ethanol than SHR rats. Moreover, ethanol injections induced a conditioned taste aversion in WKY and SHR rats whereas the WKHA rats are much more resistant, a result that may be interpreted as a differential sensitivity to the aversive properties of ethanol [54]. Regarding sex differences, SHR females are less sensitive to the aversive effects of ethanol and consume much more ethanol than SHR males [50, 51, 53-55], an important condition because in adulthood, more females suffer from ADHD than males.

We have recently reported that SHR females, but not males, treated chronically with MPD during pre/peri-adolescence (post-natal day 23 to 38) displayed higher anxious-like behavior and greater ethanol intake than controls when they were tested in adulthood [57]. Soeters and collaborators [56] have recently confirmed that male SHR rats treated with methylphenidate during pre/peri-adolescence (post-natal day 21 to 35) show similar levels of ethanol consumption than controls tested in adulthood. These findings suggest that MPD treatment during adolescence may induce, at least in females, persistent changes in emotionality and ethanol consumption in adult SHRs [57].

Overall, the results suggest that SHR rats are more sensitive to the anxiolytic/stimulant effects of ethanol and drink voluntarily greater amounts of ethanol than other strains. As proposed by Da Silva [26], the higher intake of ethanol in SHR rats compared to other strains might be attributable to the presence of some motivational factors associated with the "ADHD trait" of the SHR strain. On the basis of drinking and personality types, alcoholic individuals have been divided into Type 1 and Type 2 classes [58]. The Type 1 alcoholic shows a low degree of novelty seeking and a high degree of harm avoidance. On the other hand, the Type 2 alcoholic shows a high degree of novelty seeking and a low degree of harm avoidance. Therefore, considering that SHR rats show high levels of novelty seeking, low levels of harm avoidance, and drink high amounts of ethanol, they could represent a useful model of a specific type of alcohol misuse, Type 2 alcoholism. Interestingly, stronger characteristics of Type 2 alcoholism, regardless of gender, have been reported in alcoholics with ADHD compared to alcoholics without ADHD [59].

CANNABINOIDS, OPIOIDS AND NICOTINE

Few studies have evaluated the behavioral effects of cannabinoids, opioids and nicotine in SHR rats. The findings concerning these three neurotransmission systems are grouped and summarized below.

It was found that the density of the main cannabinoid receptor (CB1 receptor) is lower in the prefrontal cortex of adolescent SHR rats when compared with WKY rats [60]. Beltramo and colleagues [61] reported that AM404, an inhibitor of anandamide transport, increases the frequency of rearing and reduces horizontal locomotion in young SHR but not in WKY rats. We have shown that administration of WIN 55,212, a CB1 receptor agonist, increases the locomotion in adolescent SHR rats, an effect not seen in SHR adults, and in WIS adults or adolescents [62]. In a recent study, we observed that treatment with WIN 55,212 induced conditioned place preference in SHR rats, both in adults and adolescents, whereas the same treatment elicited conditioned place aversion in WIS adults, and produced no effects in WIS adolescents. The rewarding and aversive effects of WIN 55,212 were CB1-mediated and not related to blood pressure [Pandolfo *et al*., unpublished data]. The rewarding effects specifically observed for SHR rats are interesting as cannabis is the illicit drug most abused by ADHD patients.

Regarding opioids, it has been observed that morphine and selective kappa receptor agonists produced greater analgesic effects in SHR rats than in WKY rats [63-65]. An increased sensitivity of SHR rats to morphine was also observed for some physiological variables, such as cardiovascular and thermal effects, in comparison with WKY rats [64, 66, 67]. Pharmacodynamic or pharmacokinetic factors may account for behavioral and physiological differences as increased density of opioid receptors [68] and increased levels of morphine after IP injections have been found in the brain of SHR rats compared to WKY rats [69].

Although nicotine is the drug most consumed by ADHD patients, very few studies have investigated this system in animal models of ADHD. It was reported that young and adult SHR rats have a reduced number of central nicotinic acetylcholine receptors in some brain areas compared to age-matched WKY and WIS rats [70, 71]. In addition, chronic nicotine treatment induced upregulation of nAChR in WKY rats while no significant increase was observed in SHR rats [72]. These findings suggest that SHR and WKY rats may have differential behavioral responses to nicotine; however, to our knowledge, no behavioral studies on the effects of nicotine in SHR rats have been published.

Taken together, the results described above indicate that SHR rats appear to be more sensitive to the behavioral effects of cannabinoids and opioids than other rat strains. Further studies concerning cannabis and nicotine effects in SHR rats would be particularly useful given that these are the drugs most abused by ADHD patients.

CONCLUDING REMARKS

Although research is at very early stage in the field, the findings reviewed above suggest that SHR rats are more sensitive to the behavioral effects of psychostimulants, cannabinoids and opioids than other rat strains. Moreover, SHR rats are more sensitive to the anxiolytic/stimulant effects of ethanol and drink large amounts of ethanol compared to other rat strains (Table **1**). Given the key role of the DA system in the etiology of both ADHD and drug addiction [12-14, 28], alterations to this system may explain, at least in part, the behavioral profile of SHR rats [53]. A possible link between the increased drug sensitivity/intake and the ADHD-like phenotype of SHR rats is illustrated in Fig. (**1**).

The ADHD-like phenotype of SHR rats is determined by the interaction of genes with the environment. Some of the behavioral and neurochemical characteristics displayed by SHR rats persist in adulthood and may contribute to the increased sensitivity and drug intake of SHR rats. Hence, environmental manipulations (e.g., stress, environmental enrichment, pharmacological treatment), that are known to

Table 1. Main Effects of Some Drugs of Abuse in Spontaneously Hypertensive Rats, SHR, an Animal Model of Attention Deficit Hyperactivity Disorder, ADHD

Drug/Treatment	Measure	Strain of Rats/Sensitivity	References
Acute Cocaine, MPD, AMPH, SKF	Motor; analgesia	SHR > WKY; SD; WIS; LEW	[31-35]
Acute MPD, AMPH, GBR	Motor	SHR = WKY; SD	[38, 39]
Acute MPD, AMPH	Motor	SHR < WKY; SD	[31, 40, 41]
Repeated Cocaine	Motor	SHR > LEW; WKHA	[43, 44]
Repeated Cocaine	Motor	SHR = WKY; WKHA	[31, 45]
Repeated MPD	Motor	SHR < SD	[31]
Acute Ethanol	Motor/Anxiolytic	SHR > LEW	[26]
Ethanol	Drinking	SHR > WKY; LEW	[26, 48, 50-52]
Ethanol	Drinking	SHR = WKY	[54, 55]
Ethanol	Drinking	SHR < LEW; WKHA; WKY	[53-56]
Acute AM; WIN	Motor	SHR > WKY; WIS	[61, 62]
Repeated WIN	Drug-seeking behavior	SHR > WIS	Pandolfo *et al.*, unpublished data
Acute Morphine	Analgesia	SHR > WKY	[63-65]
Repeated MPD during adolescence	Cocaine-seeking behavior	Adult SHR: MPD pre-exposed < vehicle pre-exposed	[46]
Repeated MPD during adolescence	Ethanol drinking	Adult SHR: MPD pre-exposed > vehicle pre-exposed	[57]
Repeated MPD during adolescence	Ethanol drinking	Adult SHR: MPD pre-exposed = vehicle pre-exposed	[56, 57]

Abbreviations: MPD, methylphenidate; AMPH, amphetamine; SKF, SKF-81297 (a full and selective D1 receptor agonist); GBR, GBR-12909 (a dopamine uptake inhibitor); AM, AM404 (an inhibitor of anandamide transport); WIN, WIN 55,212 (a CB1 receptor agonist). WKY, Wistar-Kyoto; WKHA, Wistar-Kyoto hyperactive; SD, Sprague-Dawley; WIS, Wistar; LEW, Lewis.

influence brain function and maturation, during critical stages of development (e.g., peri-natal period, adolescence) might change the behavior of adult SHR rats in terms of drug sensitivity and intake. Studies on SHR adolescents are particularly important because profound changes occur in the DA system during adolescence and because many people start to abuse drugs during this period [73]. These investigations may contribute to a better understanding of the ADHD-like and drug-induced behaviors in the SHR model.

Although the behavioral findings described in this article (locomotion, sensitization, analgesia, conditioned place-preference, voluntary ethanol intake) provide us with important information on the pharmacology of abused drugs in SHR rats, there are no studies describing their profile of drug intake in the self-administration paradigm, the most widely accepted animal model of drug addiction. Through the use of this model, it was recently reported that high reactivity to novelty predicts a high propensity to initiate cocaine self-administration, whereas impulsivity predicts a switch to compulsive drug-taking in rats [74]. Accordingly, sensation seeking and impulsivity in humans are considered risk factors for drug addition [58, 75]. Considering that SHR rats have high levels of novelty seeking and impulsivity [25, 26], and show impaired extinction of a previously reinforced behavior [76], we predict that they might display increased drug self-administration and that this behavior may become compulsive. Future studies are required to investigate these possibilities.

Finally, some limitations of the SHR strain as a model for the study of SUD should be considered. First, there is no "perfect" control strain for comparison with SHR rats. This is supported by the heterogeneity of inbred strains obtained from different sources, the impact of different environmental conditions on behavior, and the controversy regarding the use of WKY rats as controls [see, e.g., 77]. Therefore, in our opinion, the best controls are strains of rats that display, when tested in similar and well controlled environmental settings, a contrasting behavioral phenotype (probably reflecting differences in brain function) when compared to SHR rats. Second, although there is genetic and pharmacological evidence of dissociation between hypertension and behavior in SHR rats [51, 78], the hypertension in these animals as a confounding factor in the study of the effects of drugs can not be completely overlooked. In conclusion, despite some limitations, the reviewed findings indicate that the SHR strain is a promising tool for the study of drug addiction and, possibly, its relationship with ADHD.

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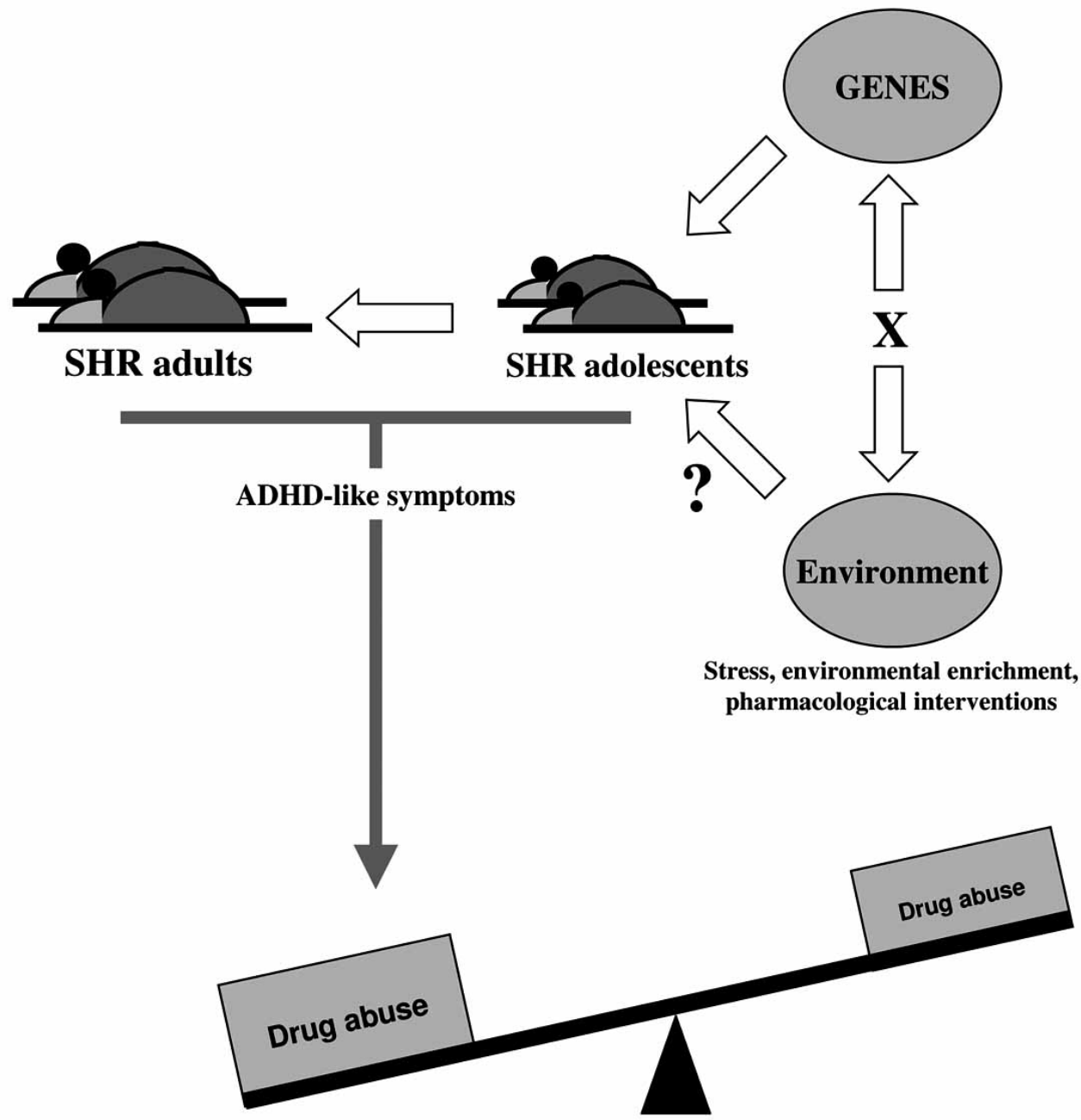

Fig. (1). Possible relationship between drug sensitivity and ADHD-like phenotype of SHR rats. The ADHD-like behavioral and neurochemical characteristics of SHR rats that are determined by the interaction between genes and the environment, may contribute to their increased drug sensitivity and drug intake. Environmental manipulations (e.g., stress, environmental enrichment, pharmacological treatment) during critical stages of development (e.g., peri-natal, adolescence) might change the ADHD-like behavior of SHR rats and their drug sensitivity/intake.

Key Learning Objectives:

- The co-occurrence of drug addiction with ADHD is very common, but its etiology remains largely unknown. The objectives of this review are to summarize the findings regarding the effects of drugs of abuse on the behavior of SHR rats, often proposed as an animal model of ADHD, and to discuss the potential usefulness of this strain for studying the relationship between ADHD and drug addiction.

Future Research Directions:

- To investigate the drug-induced behavior of SHR rats through the use of the self-administration paradigm, the most widely accepted animal model of drug addiction.
- To study the impact of environmental manipulations (e.g., stress, environmental enrichment, pharmacological treatment) during critical stages of development on the sensitivity to and intake of drugs of abuse in SHR rats.

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