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ABT-724 alleviated hyperactivity and spatial learning impairment in the spontaneously hypertensive rat model of attention-deficit/hyperactivity disorder

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HIGHLIGHTS

- Intermediate/high-dose ABT-724 tested reduced hyperactivity in SHRs.
- Intermediate/high-dose ABT-724 tested improved spatial learning in SHRs.
- No dose of ABT-724 tested altered non-selective attention in SHRs.

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ABSTRACT

Dysfunction of dopamine D4 receptor (D4R) is linked to attention-deficit/hyperactivity disorder (ADHD) as well as ADHD associated cognitive impairment. Here, we tested the possible therapeutic benefit of the D4R-selective agonist ABT-724 in adolescent spontaneously hypertensive rats (SHRs). ABT-724-treated SHRs were administered ABT-724 (0.04 mg/kg, 0.16 mg/kg or 0.64 mg/kg) from postnatal day (P) 28 to P32. Control SHRs and Sprague-Dawley (SD) rats were injected with saline. Then two cohorts of rats were tested in the open field and Làt maze that measured locomotion and non-selective attention (NSA), respectively. Another cohort of rats was subjected to water maze task for evaluation of spatial learning and memory. We found that control SHRs displayed hyperactivity as well as impaired NSA and spatial learning compared with normotensive SD rats. ABT-724 (0.16 and 0.64 mg/kg) treatment alleviated hyperactivity and spatial learning impairment in SHRs. No dose of ABT-724 tested altered NSA in SHRs. Our results raise the possibility that ABT-724 may be used as a therapeutic intervention for ADHD patients during adolescence.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD), one of the most common childhood-onset psychiatric disorders, is characterized by age-inappropriate inattention, impulsiveness and hyperactivity, causing significant social, academic, and occupational impairment in children [11].

Dopamine (DA) dysfunction represents a central factor in ADHD etiology. ADHD is associated with dopaminergic hypofunction characterized by hypoactive tonic and phasic DA components that resulted in reduced post-synaptic efficacy of dopaminergic modulation of neuronal circuits [22]. DA's effects are mediated by a group of D1-like and D2-like receptors. The DA D4 receptor (D4R) in the D2-like class has high affinity for DA and is known to exist in the dopaminergic pathways connecting the striatum to the prefrontal cortex (PFC) [13]. Alterations in the PFC and the fronto-striatal circuitry are thought to be involved in ADHD [5,13]. Evidence has indicated that deficient function of D4R is strongly linked to hyperactivity and inattention [6,7,12,15]. Furthermore, dysfunction of D4R is also associated with poor performance on measures of intelligence and working memory in ADHD patients [1,10,17].

The spontaneously hypertensive rat (SHR) which was bred from progenitor Wistar-Kyoto (WKY) rat is the most widely used animal

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model of ADHD [18,23]. Some studies have shown that the SHR has a hypoactive DA system, in terms of vesicular storage of DA and DA release [4,22]. Furthermore, the SHR has lower levels of D4R gene expression and protein synthesis in the PFC than WKY [16]. In light of these data, it is reasonable to suspect that D4R agonists could be useful for the management of ADHD.

Here, we aimed to investigate the effects of ABT-724, a selective D4R agonist [19], on hyperactivity, inattention and spatial learning and memory in SHRs. The use of WKY as a control for SHR has recently been questioned because it displays signs of depression and abnormal responses on tests of ADHD-like behaviors in comparison to several other rat strains [23]. Thus, we selected the Sprague-Dawley (SD) rat strain which is used most frequently in psychostimulant studies as "normal" rat.

2. Material and methods

2.1. Animals and drugs

Three-week old male rats of SHR and SD strains were obtained from Shanghai Slac Laboratory Animal CO. LTD (Shanghai, China). All rats were housed under standard laboratory conditions with a 12/12 h light/dark cycle (room temperature: 22 °C, humidity: 45–55%). Animals were given ad libitum access to food and water and were acclimated to the colony conditions for one week prior to the experiment. Adolescent SHR rats were used as ADHD is primarily a disease of adolescent humans. All experimental procedures were conducted in accordance with the guidelines set by the National Institutes of Health Guide for the Care and Use of Laboratory Animals. ABT-724 (Tocris Bioscience, USA) was freshly dissolved in sterile saline and administered at 1 ml/kg.

2.2. Experimental design

Five groups of rats were included: SD + saline group; SHR + saline group; SHR + ABT-724 (0.04 mg/kg) group; SHR + ABT-724 (0.16 mg/kg) group, and SHR + ABT-724 (0.64 mg/kg) group. ABT-724-treated SHRs received ABT-724 subcutaneously daily from P28 to P32. Control SD and SHR rats were given subcutaneous injections of corresponding volumes of saline daily during the same period. Each group consists of 24 rats that were divided into 3 different cohorts. One cohort was subjected to water maze task beginning on P27. The other two cohorts underwent open field or Làt maze test on P32, respectively. On days that overlapped with behavioral testing, ABT-724 was administered to rats 5 min before the start of the test.

2.3. Behavioral testing

2.3.1. Open field test

After drug or saline administration on P32, a cohort of rats ($n = 8$/group) was tested in the open field to evaluate locomotor and exploratory behavior. The open field test board consisted of a wooden box (90 cm × 90 cm × 50 cm), with four holes of 4 cm in diameter symmetrically spaced on the floor. The floor of the box was divided into 25 squares of 18 cm × 18 cm (16 peripheral squares and 9 central squares). A 60 W light was situated 1 m above the arena floor. Before each trial, the floor was cleaned thoroughly with 70% ethanol. Rats were placed in the center square of the floor for 30 s, covered with an opaque black casket. After removing the casket, the number of squares crossed (horizontal activity) and rearing frequency (vertical activity, defined as number of times the animals stood on their hind legs) were recorded for analysis of locomotor activity. The number of head dips into the holes was used for analysis of exploratory activity. Behavior was monitored for 5 min.

2.3.2. Làt maze test

The Làt maze test was performed to assess non-selective attention (NSA). The Làt maze consisted of a 60 × 60 × 40 cm wooden box with a 30 × 30 × 40 cm plastic transparent smaller box inserted in the middle. A set of four such boxes was located in a sound attenuated room and each was illuminated by a white, cold 4 W lamp placed 60 cm above the floor in the centre of the wooden cover. Rats ($n = 8$/group) were allowed to explore the resulting corridor (60 cm long, 15 cm wide, and 40 cm high) freely. The movements were tracked over 30 min and recorded by video cameras. The frequency of rearing episodes on the hind limbs by rats was used to index NSA [8].

2.3.3. Morris water maze test

To assess spatial learning and memory, another cohort of rats ($n = 8$/group) was tested in the Morris water maze. The Morris water maze (Institute of Material Medicine, Chinese Academy of Medical Sciences) is composed of the monitor with the video camera set in the ceiling, a computerized tracking system (DMS-2), and a black circular metal tank (150 cm in diameter, 60 cm in height) filled with water (24 ± 2 °C). A set of three such mazes was used. Evaporated milk was added to make the water opaque. Four start positions with white mark were located equidistantly around the edge of the maze, dividing it into four equal quadrants. On P27, each rat was allowed to swim freely in the pool for 120 s for habituation. From P28 to P31, a hidden escape platform (10 cm in diameter, 23 cm in height) was submerged 2.0 cm below the water surface in the middle of the target quadrant (TQ, northeast quadrant). During acquisition training, four trials separated by 30 s were conducted daily for each rat. Each day, the animals were placed into the pool at four different starting points and entry from the North, South, East, or West points was varied in a quasi-random order. The rat was allowed a maximum of 120 s to locate the platform. If the rat did not find the platform within 120 s, it was guided to the location. Path length (cm) to the platform was recorded for analysis of spatial learning ability. For each rat, the data of the four trials per day were averaged. To analyze memory retention, a probe trial was conducted on P32. Each rat was placed into the water diagonally from the TQ and allowed to swim freely for 120 s without the platform present. The time spent swimming in each of the four quadrants of the pool was recorded. The ratio of the amount of time spent in the TQ to that spent in the four quadrants was measured.

2.4. Statistical analysis

All statistical analyses were conducted using SPSS 17.0. Values are expressed as mean ± SEM. One-way ANOVAs followed by Bonferroni post hoc tests were performed to compare multiple groups for open field test, Làt maze, and probe trial data. For analysis of path length data in the water maze test, repeated measures ANOVAs followed by Bonferroni post hoc tests were performed. The level of statistical significance was set at $p \leq 0.05$.

3. Results

3.1. Open field test

A significant group effect was observed in the numbers of square crossings [$F(4, 35) = 7.30$; $p < 0.001$] and rearings [$F(4, 35) = 8.08$; $p < 0.001$] among groups. Compared with saline-treated SHRs, saline-treated SD rats had significantly smaller numbers of square crossings ($p < 0.01$) and rearings ($p < 0.01$) (Fig. 1A and B). SHRs treated with ABT-724 at doses of 0.16 mg/kg and 0.64 mg/kg

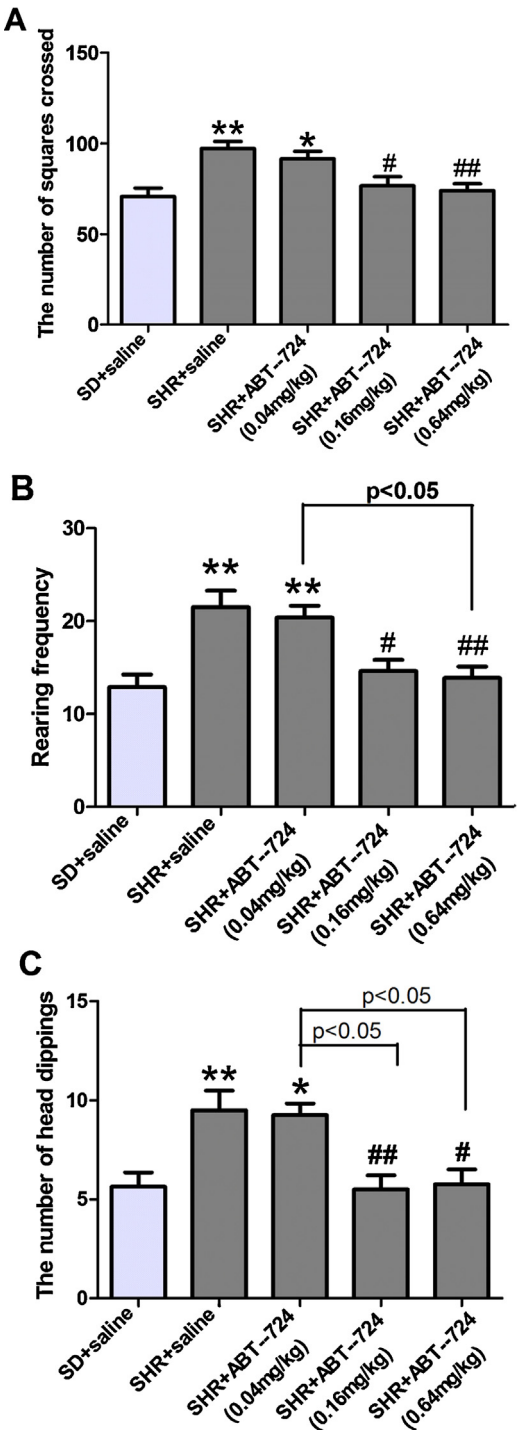

Fig. 1. Open field testing. (A), (B) and (C) Represent horizontal activity, vertical activity and exploratory behavior, respectively. Data are expressed as means ± SEM. * $p < 0.05$, ** $p < 0.01$ vs. SD + saline group; # $p < 0.05$, ## $p < 0.01$ vs. SHR + saline group.

reduced the numbers of square crossings (0.16 mg/kg, $p < 0.05$; 0.64 mg/kg, $p < 0.01$) and rearings (0.16 mg/kg, $p < 0.05$; 0.64 mg/kg, $p < 0.01$) compared with saline-treated SHRs. No difference in locomotor activity existed among saline-treated SD rats and SHRs treated with ABT-724 at doses of 0.16 and 0.64 mg/kg. No difference was observed in locomotor activity between saline-treated SHRs and SHRs treated with ABT-724 at the dose of 0.04 mg/kg.

A significant group effect was observed in the exploratory behavior among groups [$F(4, 35) = 7.28$; $p < 0.001$]. Compared with SD rats, saline-treated SHRs ($p < 0.01$) and ABT-724

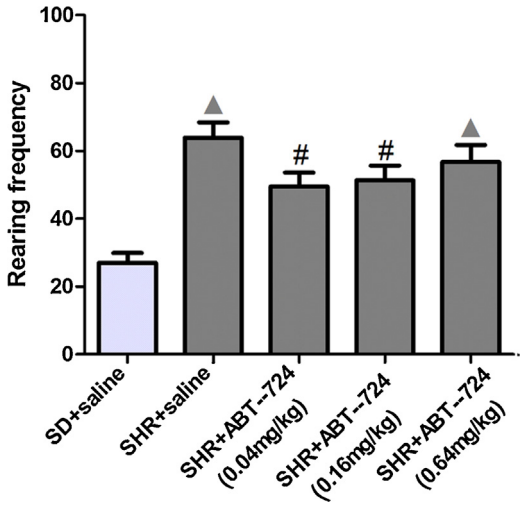

Fig. 2. Non-selective attention in Làt maze. No difference in rearing frequency existed among saline-treated SHRs and SHRs treated with ABT-724 at all three doses tested. Data are expressed as means ± SEM. # $p < 0.01$, ▲ $p < 0.001$ vs. SD + saline group.

(0.04 mg/kg)-treated SHRs ($p < 0.05$) had higher numbers of head dippings (Fig. 1C). The numbers of head dippings were smaller in ABT-724-treated SHRs (0.16 mg/kg, $p < 0.01$; 0.64 mg/kg, $p < 0.05$) than saline-treated SHRs. No difference in the number of head dippings existed among SD rats and SHRs treated with ABT-724 at doses of 0.16 mg/kg and 0.64 mg/kg.

3.2. Làt maze test

There was a group effect in NSA among groups [$F(4, 35) = 10.76$; $p < 0.001$]. The numbers of rearings in saline-treated SD rats were significantly smaller than those of saline-treated SHRs ($p < 0.001$) and ABT-724-treated SHRs at three doses tested ($p < 0.01$, $p < 0.01$ and $p < 0.001$ for 0.04, 0.16 and 0.64 mg/kg, respectively) (Fig. 2). No difference existed among saline-treated SHRs and SHRs treated with ABT-724 at all three doses tested.

3.3. Morris maze test

A repeated measures ANOVA revealed significant effects of group [$F(4, 35) = 6.87$; $p < 0.001$] and day [$F(3, 105) = 291.18$; $p < 0.001$] on spatial learning, without group × day interaction [$F(12, 105) = 1.36$; $p = 0.20$]. During acquisition training, saline-treated SHRs ($p < 0.05$) and SHRs treated with ABT-724 at the dose of 0.04 mg/kg ($p < 0.05$) swam a longer path length to find the platform than SD rats (Table 1). SHRs treated with ABT-724 at doses of 0.16 ($p < 0.05$) and 0.64 mg/kg ($p < 0.05$) had shorter path length than SHRs treated with saline. No differences in path length existed among SD rats and SHRs-treated with ABT-724 at doses of 0.16 and 0.64 mg/kg. There was no significant difference in path length between saline-treated SHRs and SHRs treated with ABT-724 at the dose of 0.04 mg/kg. In addition, we observed no difference in the percentage of time spent in the TQ among groups (Fig. 3).

4. Discussion

As the most widely used animal model of ADHD, SHR displays hyperactivity, inattention and impulsivity which is consistent with the diagnostic criteria for ADHD [18]. In our study, saline-treated SHRs had significantly higher numbers of square crossings and rearings than SD rats in the open field test. Furthermore, saline-treated SHRs also showed higher rearing frequencies in the Làt maze. Thus,

Table 1
Mean daily escape path length in the Morris water maze.

Group	P28 (cm)	P29 (cm)	P30 (cm)	P31 (cm)
Group 1	1423.73 ± 84.14	983.81 ± 89.11	556.52 ± 53.19	169.61 ± 19.39
Group 2*	1417.39 ± 79.52	1092.12 ± 69.18	875.01 ± 75.18	445.10 ± 35.45
Group 3*	1431.33 ± 81.42	1137.67 ± 60.41	801.51 ± 58.95	490.20 ± 43.24
Group 4#	1405.85 ± 68.04	986.38 ± 94.28	559.04 ± 60.48	195.59 ± 17.26
Group 5#	1381.18 ± 85.39	982.54 ± 67.09	549.06 ± 70.02	201.28 ± 25.92

Group 1, SD + saline; Group 2, SHR + saline; Group 3, SHR + ABT-724 (0.04 mg/kg); Group 4, SHR + ABT-724 (0.16 mg/kg), and Group 5, SHR + ABT-724 (0.64 mg/kg). Data are expressed as mean ± SEM.

* $p < 0.05$ compared with SD rats.

\# $p < 0.05$ compared with saline-treated SHRs.

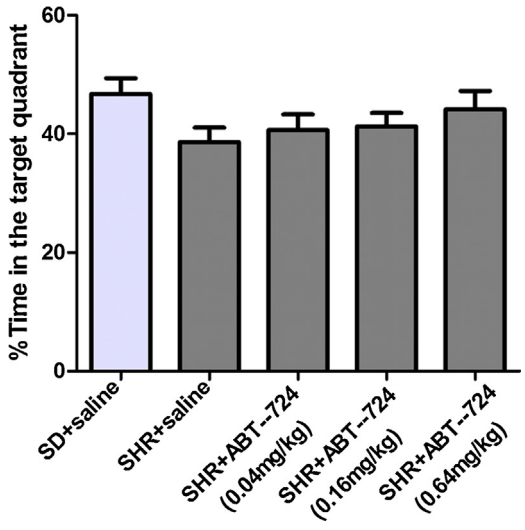

Fig. 3. Memory retention ability evaluated by the probe trial, as shown by the percentage of time spent in the TQ. Data are expressed as means ± SEM. No difference in memory retention among groups.

our results demonstrated that the SHR was indeed hyperactive and had poorer NSA than the normotensive SD rat.

Evidence has indicated that the SHR displays decreased density of D4R in the PFC and increased DA uptake in frontocortical and striatal terminals compared with WKY [16,18]. In humans, polymorphisms of D4R gene are associated with ADHD and D4R is an intriguing target for ADHD treatment [2,25]. Our results indicated that SHRs receiving intermediate or high dose ABT-724 showed attenuated hyperactivity and improved spatial learning ability compared with saline-treated SHRs. In addition, SHRs treated with ABT-724 (0.16 mg/kg and 0.64 mg/kg) showed similar performance with SD rats in the open field and Morris water maze tests. Though the exact mechanisms remained unclear, our results suggested that ABT-724 has therapeutic effects in the SHR model of ADHD.

Hyperactivity is studied most frequently by far in rodent models of ADHD [20]. Erlij et al. have shown that deficient D4R function can lead to hyperactivity and stimulation of D4R by the selective D4 agonist PD 168,077 reduces motor activity in Wistar rats [6]. Similarly, we also found that ABT-724 treatment at intermediate and high doses tested reduced hyperlocomotor activity in SHRs. Mechanisms underlying the beneficial effect of ABT-724 in reducing hyperactivity in SHRs remain mysterious. Future studies investigating the signaling pathways (protein kinase A/DARPP-32, Akt/glycogen synthase kinase 3, and ERK), which were reported to regulate DA-mediated locomotor activity [9], may shed some light on this issue. Notably, SHRs treated with saline and ABT-724 (0.04 mg/kg) exhibited higher exploratory activity, evidenced by increased numbers of head dippings, compared with SD rats in the open field. In contrast, SHRs treated with ABT-724 (0.16 and 0.64 mg/kg) displayed comparable exploratory activity with SD rats. Since ABT-724 treatment led to decreased locomotor activity in SHRs, hyperactivity should be, at least in part, responsible for the higher exploratory activity in SHRs treated with saline and ABT-724 (0.04 mg/kg).

DA system is hypothesized to play a crucial role in regulating attentional processes and D4R polymorphisms are associated with dysregulation and modulation of the attentional system [12,24]. In the Làt maze, saline-treated SHRs showed higher frequency of rearings than SD controls, indicating NSA impairment in SHRs. Moreover, SHRs treated with ABT-724 at three doses tested showed comparable numbers of rearings with saline-treated SHRs. Though evidence has indicated that D4R is more strongly related to inattentive than hyperactive-impulsive symptoms of ADHD [7,15], our results suggested no beneficial effect of ABT-724 in alleviating NSA impairment in SHRs. Consistent with our study, Ruocco et al. also found that intranasal DA administration did not influence NSA in the Naples high excitability rat model of ADHD [21].

Cognitive functioning deficits in executive function, behavioral inhibition and working memory, have also been associated with ADHD in humans. D4R has been suggested to play a role in processes involved in cognition relevant to ADHD and the 7-repeat allele of the D4R gene is associated with poor performance on measures of intelligence in ADHD patients [1,10,14,17]. Our results indicated that saline-treated SHRs showed spatial learning impairment in the acquisition training, evidenced by longer escape distance when compared to normotensive SD rats. SHRs treated with ABT-724 (0.16 mg/kg and 0.64 mg/kg) showed comparable escape distance in comparison with SD rats, suggesting that ABT-724 improved spatial learning ability in SHRs. Consistent with our study, A-412997, a selective DA D4 agonist, has also been shown to improve acquisition in the 5-trial inhibitory avoidance task in SHRs [3]. Though there are reports that demonstrate impairment of spatial memory in SHRs in the water maze [26,27], our findings showed SHRs had intact working memory. These inconsistencies may be due to the use of different control rat strain and apparatus, the age of the rats, or other factors in these studies.

In conclusion, our study demonstrated that ABT-724 decreased hyperactivity and improved spatial learning ability in SHRs. Our findings suggested that D4R stimulation may have therapeutic effects in ADHD. Future research is needed to explore the mechanisms underlying the therapeutic effects of ABT-724 in the SHR model of ADHD.

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