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Long-term Effects of Aripiprazole Treatment during Adolescence on Cognitive Function and Dopamine D2 Receptor Expression in Neurodevelopmentally Normal Rats

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Objective: This study aimed to investigate the long-term effects of aripiprazole treatment during adolescence on behavior, cognitive function, and dopamine D2 receptor (D2R) expression in adult rats.
Methods: Adolescent male Sprague-Dawley rats were injected intraperitoneally with aripiprazole, risperidone, or vehicle control for 3 weeks (postnatal day 36–56). After a 2-week washout period, locomotion, anxiety, and spatial working memory were evaluated in adulthood (postnatal day 71–84), using an open field test, elevated plus maze, and Y-maze, respectively. In addition, we assessed D2R levels in the dorsolateral and medial prefrontal cortex (PFC), dorsal and ventral striatum, and hippocampus using western blot analysis.
Results: Spontaneous alternation performance (SAP) in the Y-maze, a measure of spatial working memory, differed significantly among the 3 groups ($F = 3.89$, $p = 0.033$). A *post-hoc* test confirmed that SAP in the aripiprazole group was significantly higher than that in the risperidone group (*post-hoc* test $p = 0.013$). D2R levels in the medial PFC ($F = 8.72$, $p = 0.001$) and hippocampus ($F = 13.54$, $p < 0.001$) were different among the 3 groups. D2R levels in the medial PFC and hippocampus were significantly lower in the aripiprazole-treated rats than that in the risperidone-treated rats (*post-hoc* test $p = 0.025$ and $p < 0.001$, respectively) and controls (*post-hoc* test $p < 0.001$, all).
Conclusion: This study showed that aripiprazole treatment in adolescence could influence cognitive function and dopaminergic neurotransmission into early adulthood.

KEY WORDS: Aripiprazole; Adolescent; Cognition; Dopamine D2 receptors; Animal models.

INTRODUCTION

Since the introduction of atypical antipsychotics (AAPs) with relatively minor side effects, prescriptions of AAPs have increased in adolescent patients with mental illness.[1)] In particular, AAPs are commonly used off-label to control anger, irritability, violence, and mood instability in adolescent patients with non-psychotic disorders such as attention-deficit/hyperactivity disorder, oppositional defiant disorder, and depressive disorder.[2)] However, the US Food and Drug Administration has approved the use of AAPs in pediatric and adolescent patients only for the treatment of schizophrenia, bipolar disorder, autism, and Tourette's syndrome.[3)] There is insufficient evidence for the off-label use of AAPs in non-psychotic adolescent patients, and there are many disagreements about its efficacy and safety.[4)] Moreover, little is known about the effects of AAP treatment during adolescence on brain development or the subsequent changes in behavior, mood, and cognitive function that may persist long after AAP withdrawal.

It is difficult to directly assess the effects of AAPs on human brain development. Instead, animal studies can indirectly predict behavioral and neurochemical changes following AAP treatment during adolescence. Some behavioral studies have reported that neurodevelopmentally normal animals treated with risperidone or olanzapine during adolescence developed altered locomotion and

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reward behaviors in adulthood.[5,6] Risperidone or olanzapine treatment during adolescence has also been suggested to alter the dopaminergic, GABAergic, and glutamatergic neurotransmitter systems in the rat brain, especially in the prefrontal cortex (PFC) and nucleus accumbens.[7-9] However, few studies have addressed the long-lasting effects of aripiprazole treatment during adolescence on behavior, cognitive function, or neurotransmission systems in adulthood. Aripiprazole has a unique pharmacological profile as a dopamine D2 receptor (D2R) partial agonist with partial agonistic activity at the serotonin-1A receptor and antagonistic activity at the serotonin-2A receptor,[10] and it has been often prescribed to treat several non-psychotic conditions in adolescent patients due to its high tolerability.[11]

This study investigated changes in behavior, cognitive function, and levels of D2R in adult rats after chronic adolescent treatment with aripiprazole. To this end, we administered aripiprazole, risperidone, or vehicle to neurodevelopmentally normal rats during adolescence, and evaluated their locomotion, anxiety, and spatial working memory in adulthood using behavioral tests. In addition, we examined D2R levels in PFC, striatum, and hippocampus of the rat brain via western blot analysis.

METHODS

Materials

Aripiprazole and risperidone (SML0935-50MG and #R3030-10MG, respectively; Sigma-Aldrich, St. Louis, MO, USA) were dissolved in 25% hydroxypropyl-β-cyclodextrin (332593-25G; Sigma-Aldrich) acidified with HCl and titrated to pH 5.5 to 6.0 with NaOH as described previously,[12] and then diluted 10-fold with 0.9% normal saline. The respective vehicle control was 0.9% normal saline in 2.5% hydroxypropyl-β-cyclodextrin acidified with HCl and titrated to pH 5.5 to 6.0. Antibodies for western blot analysis against D2R (ab5084P) were purchased from EMD Millipore (Billerica, MA, USA).

Animals and Housing

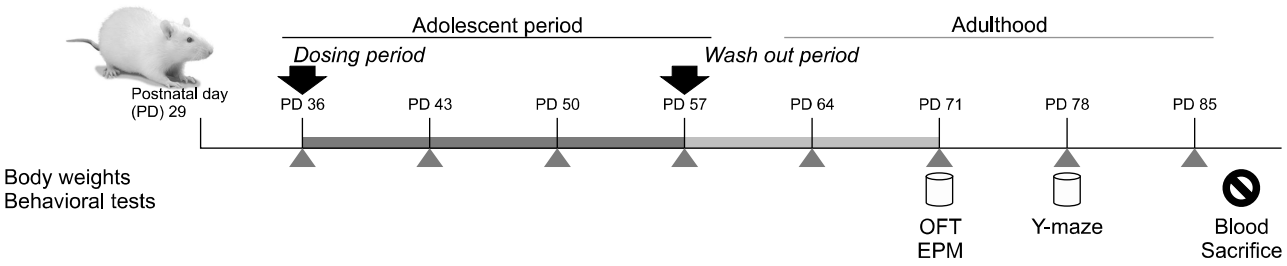
Specific-pathogen-free male (postnatal day [PD] 29) Sprague-Dawley rats purchased from OrientBio (Seongnam, Korea) were maintained in the laboratory animal facility of the National Center for Mental Health (23 ± 2°C, 50 ± 10% relative humidity and 12-hour light/dark cycle). They were allowed *ad-libitum* access to water and a commercial diet of Altromin 1214 (Altromin GmbH., Lage, Germany). The animals were acclimatized for 7 days prior to beginning the study. All animal experiments were approved by the Institutional Animal Care and Use Committee of the National Center for Mental Health (approval number: NCMH-1703-001-001-02).

Experimental Design

The general study scheme is depicted in Figure 1. Animals were randomly divided into aripiprazole, risperidone, and control groups, and each group consisted of 10 male rats. The drug treatment period from PD 36 to PD 56 in the rats was equivalent to the period of mid-late adolescence in humans.[13,14] The rats received an intraperitoneal (i.p.) injection of drugs or vehicle control for 3 weeks. A staggered drug treatment pattern, slowly titrated from a low starting dose, was used to mimic a clinical setting. The AAP doses were initiated during the first week of treatment at 1.5 mg/kg/day for aripiprazole and 0.5 mg/kg/day for risperidone, and then increased over the second and third weeks of treatment to 3 mg/kg/day for aripiprazole and 1 mg/kg/day for risperidone. The proposed dosages were selected based on preclinical efficacy or occupancy studies. Some previous studies had compared effects of oral aripiprazole (1 mg/kg three times a day [t.i.d.]) and risperidone (0.3 mg/kg t.i.d.) treatment during adolescence on behaviors and the dopamine system in rats.[15-17] Sub-chronic treatment with 1.0 mg/kg/day i.p. risperidone was reported to induce changes in forebrain receptor levels in adolescent rats.[18] In addition, it has been previously reported that, at the selected doses, aripiprazole and risperidone treatment reaches 60% to 80% D2R occupancy in the rat brain.[19] Based on the body surface area formula for dosage translation between humans and rats,[20] the selected doses were within the recommended dose ranges for the psychiatric treatment.

Behavioral Tests

After the 2-week washout period, behavioral tests were carried out from PD 71 to PD 84 (which was equivalent to adulthood in humans) in the following sequence: open field test (OFT), elevated plus maze (EPM), and Y-maze, as described below. The rats' activities in the behavioral tests were analyzed using SMART 3.0® video tracking software (Panlab, Barcelona, Spain).



Group	Test-item	Duration (animal age; wk)	Route	Animal No.	Final dose level (mg/kg/day)	Final dose concentration (mg/ml)	Dose volume (ml/kg)
1	Aripiprazole	5-7	IP	10	3	0.3	10
2	Risperidone	5-7	IP	10	1	0.1	10
3	Control (vehicle)	5-7	IP	10	0	0	10

Fig. 1. Study scheme. Timeline and group table illustrate the timing of treatment, the experimental measures obtained, and dosage. OFT, open field test; EPM, elevated plus maze; IP, intraperitoneally.

Open Field Test

The OFT has often been used to assess locomotion,[21] and the procedure was performed according to previous reports.[22] The open field consisted of a 60 × 60 × 40 cm high plastic enclosure, and the field was divided into 25 squares, defined as 9 central and 16 peripheral squares. Each rat was placed in the central square and allowed to move freely and explore the environment for 10 seconds. Next, a video camera above the center of the arena recorded the behavior of the rats for 5 minutes. The arena was cleaned between tests with 75% ethanol. The rats' locomotion at the periphery and the center were analyzed.

Elevated Plus Maze

The EPM is one of the most widely used tests for measuring anxiety-like behaviors in laboratory rodents.[21] The apparatus consisted of two 45 × 10 cm open arms and two 45 × 10 × 45 cm closed arms. Open and closed arms were cross-shaped; the cross center was a 10 × 10 cm open platform. The maze was 50 cm above the ground. The rats were placed on the central platform facing an open arm. A video camera above the maze was used to record the activity of the animals for 5 minutes. Test variables included the number of open and closed arm entries as well as the time spent in the center, open arms, and closed arms. When the head and forelimbs of a rat were in one arm, it was recorded as one entry.

Y-maze

The Y-maze spontaneous alternation paradigm is used to assess spatial working memory in rodents and is based on the innate tendency of rodents to explore a prior unexplored arm of a Y-maze.[23] The Y-maze apparatus, made of Plexiglas, had three identical arms (45 × 10 × 35 cm) placed at 120° with respect to each other. Each rat was placed at the end of one arm and allowed to freely explore the apparatus for 8 minutes. A rat was considered to have entered an arm when the head and forelimbs were positioned in the arm runway. We assessed spontaneous alternation performance (SAP), a measure of working memory, which was defined as actual alternation (total arm entries)/possible alternations (total arm entries − 2) × 100. Alternations were operationally defined as successive entries into each of the 3 arms on overlapping triplet sets. Alternate arm returns (AAR) and same arm returns (SAR) in the Y-maze (AAR = alternate arm returns/total arm entries × 100, SAR = same arm return/total arm entries × 100) were used as indicators of memory impairment.[24]

Necropsy

All animals were subjected to a necropsy examination at PD 86 to 87, which included evaluation of the cranial cavity and external surfaces of the brain. All tissue samples of the brain (dorsolateral and medial PFC, dorsal and ventral striatum, and hippocampus) were obtained after exsanguination under isoflurane anesthesia. Coronal brain slices (0.5 mm thick) were prepared, and all steps of

the preparation were carried out in ice-cold rodent brain matrix for further analysis.

Western Blot Analysis

To quantify D2R expression, tissues were lysed by RIPA lysis buffer without EDTA (R4100-050; GeneDepot, Barker, TX, USA) containing Phosphatase Inhibitor Cocktail (P2300; GeneDepot) and Protease Inhibitor Cocktail (P3100). Prepared cell lysates with sodium dodecyl sulfate were run on an 8% polyacrylamide gel, and transferred onto a polyvinylidene fluoride membrane (162-0174; Bio-rad, Hercules, CA, USA) via the semidry transfer method. The membrane was blocked with 5% skimmed milk with tris-buffered saline-tween (TBS-T) for 1 hour, and incubated with antibodies against D2R (ab5084P; EMD Millipore) dissolved in 5% bovine serum albumin in TBS-T, overnight in a cold room (5 ± 3°C). The membrane was incubated with a Goat anti-Rabbit IgG coupled with horseradish peroxidase (#31460; Thermo Fisher Scientific, Rockford, IL, USA). The expression of the endogenous control β-actin was probed (sc-47778 HRP; Santa Cruz Biotechnology, Dallas, TX, USA). Blots were visualized using Clarity™ Western ECL Substrate (170-5060) with ChemiDoc™ XRS+ System (170-8256; Bio-rad) and measured using Image Lab™ software (170-9690; Bio-rad).

Statistical Analyses

We compared the distance traveled in the peripheral and central areas and total distance traveled in the OFT, the number of open and closed arm entries and the time spent in the center, open arms, and closed arms of the EPM, and the SAP, AAR, and SAR in the Y-maze, among the aripiprazole, risperidone, and control groups using analysis of variance (ANOVA), followed by pair-wise comparisons using the least significant difference (LSD) *post-hoc* test. In addition, we compared D2R levels in dorsolateral and medial PFC, dorsal and ventral striatum, and hippocampus among the 3 groups in the same way. All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). The p values less than 0.05 were considered statistically significant.

RESULTS

Behavioral Tests

In the OFT, we found no differences in distance traveled at the periphery ($F = 0.26$, $p = 0.775$), in the center ($F = 0.99$, $p = 0.386$), or total distance traveled ($F = 0.32$, $p = 0.727$), among the 3 groups. In the EPM, there were also no significant differences in the number of open arm entries ($F = 0.11$, $p = 0.901$) or closed arm entries ($F = 0.43$, $p = 0.658$) as well as time spent in the center ($F = 0.51$, $p = 0.606$), open arms ($F = 0.23$, $p = 0.797$), and closed arms ($F = 0.36$, $p = 0.704$). In the Y-maze, we found a significant difference in SAP among the 3 groups ($F = 3.89$, $p = 0.033$). LSD *post-hoc* test confirmed that there was a significant difference between aripiprazole and risperidone groups ($p = 0.013$), and there was also a marginal difference between aripiprazole and control groups ($p = 0.054$)

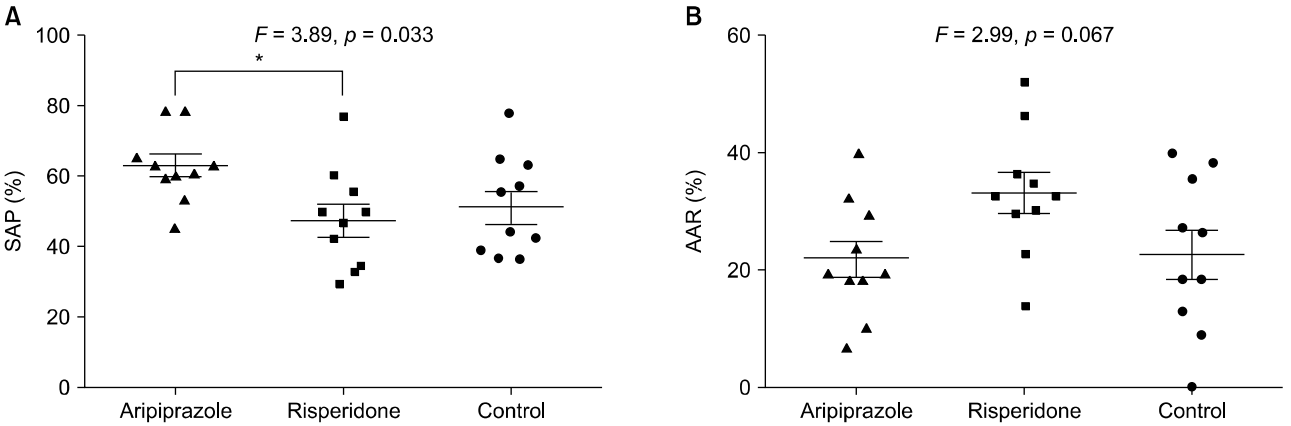


Fig. 2. Differences in spatial working memory among groups of adult rats treated with aripiprazole (3 mg/kg/day), risperidone (1 mg/kg/day), and vehicle (control) during adolescence. Spontaneous alternation performance (SAP) (A) and alternate arm returns (AAR) (B) in Y-maze.
*p=0.013 in the least significant difference *post-hoc* test.

(Fig. 2). Comparing the 3 groups using ANOVA revealed no significant difference in AAR ($F = 2.99$, $p = 0.067$), but showed a trend where AAR was higher in the risperidone group (mean±standard error of mean [SEM], 33.30 ± 10.71) than that in the aripiprazole group (mean ± SEM, 22.14 ± 10.05) (Fig. 2). Furthermore, we observed no difference in SAR among the 3 groups ($F = 1.55$, $p = 0.230$). The detailed results of OFT, EPM, and Y-maze are shown in Table 1.

Table 1. Behavioral analyses of adult rats treated with aripiprazole (3 mg/kg/day), risperidone (1 mg/kg/day), and vehicle (control) during adolescence

Behavioral test	Aripiprazole	Risperidone	Control
Open field test			
Distance traveled in the peripheral area (cm)	1,340.38 ± 86.67	1,334.85 ± 209.97	1,188.82 ± 186.38
Distance traveled in the central area (cm)	235.59 ± 27.52	380.11 ± 107.09	277.22 ± 67.88
Total distance traveled (cm)	1,575.97 ± 90.18	1,714.96 ± 300.41	1,466.04 ± 214.76
Elevated plus maze			
Number of open arm entries (n)	3.00 ± 0.60	2.90 ± 0.74	2.60 ± 0.58
Number of closed arm entries (n)	17.50 ± 2.45	14.30 ± 2.07	15.70 ± 2.81
Time spent in the center (sec)	79.09 ± 7.57	65.70 ± 11.75	75.87 ± 9.62
Time spent in the open arms (sec)	44.62 ± 11.95	37.84 ± 14.29	32.73 ± 10.97
Time spent in the closed arms (sec)	176.28 ± 14.58	196.46 ± 22.07	191.40 ± 15.12
Y-maze			
Spontaneous alternation performance (%)*	63.48 ± 3.10†	47.57 ± 4.72	51.51 ± 4.60
Alternate arm returns (%)	22.14 ± 3.18	33.30 ± 3.39	22.89 ± 4.18
Same arm returns (%)	5.77 ± 1.69	7.86 ± 2.11	11.09 ± 2.57
Number of total arm entries (n)	22.7 ± 1.80	24.7 ± 1.95	20.5 ± 2.25

Values are presented as mean ± standard error of mean.
*Significantly different among aripiprazole, risperidone, and control groups ($p < 0.05$ in ANOVA).
†Aripiprazole vs. risperidone ($p < 0.05$ in the least significant differenc *post-hoc* test).

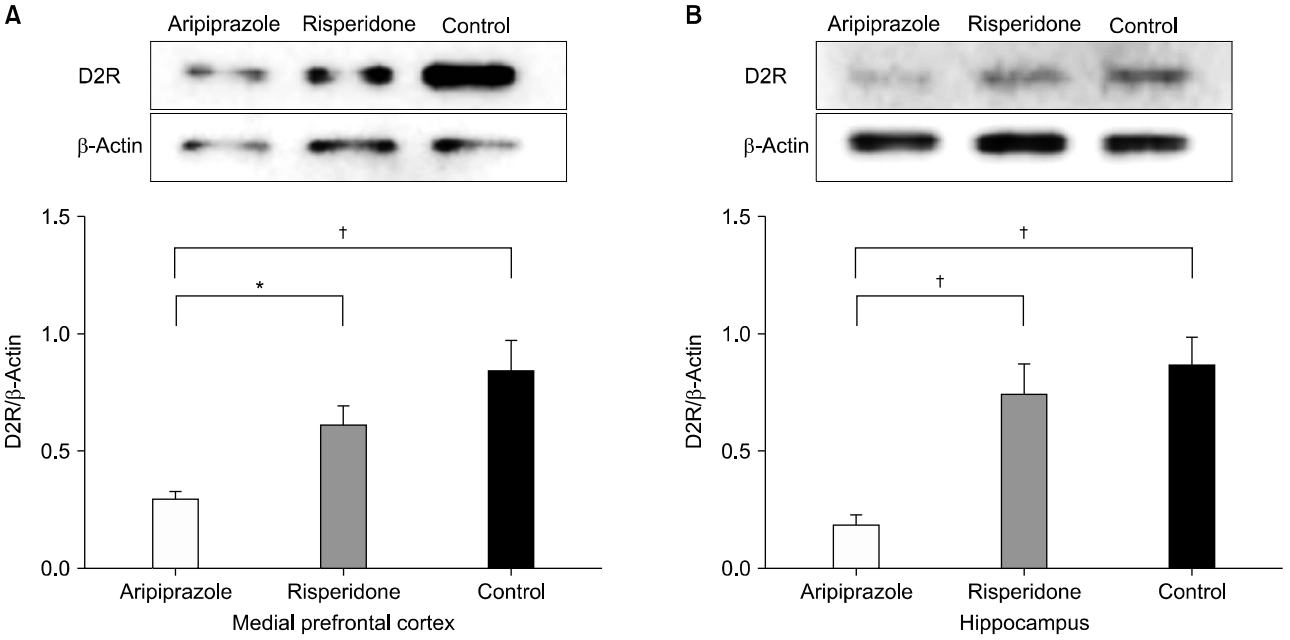


Fig. 3. Differences in dopamine D2 receptor (D2R) levels in the medial prefrontal cortex (A) and the hippocampus (B) among groups of adult rats treated with aripiprazole (3 mg/kg/day), risperidone (1 mg/kg/day), and vehicle (control) during adolescence. Data are presented as mean ± standard error of mean.
*$p = 0.025$, †$p < 0.001$ in the least significant difference *post-hoc* test.

Table 2. Dopamine D2 receptor protein expression of adult rats treated with aripiprazole (3 mg/kg/day), risperidone (1 mg/kg/day), and vehicle (control) during adolescence in the Western Blot assay

Brain region	Aripiprazole	Risperidone	Control
Dorsolateral prefrontal cortex	1.15 ± 0.076	1.02 ± 0.047	1.78 ± 0.419
Medial prefrontal cortex*	0.30 ± 0.031 †, ‡	0.61 ± 0.090	0.85 ± 0.130
Dorsal striatum	0.28 ± 0.035	0.21 ± 0.019	0.20 ± 0.042
Ventral striatum	0.04 ± 0.004	0.08 ± 0.020	0.05 ± 0.008
Hippocampus*	0.20 ± 0.031 †, §	0.76 ± 0.123	0.88 ± 0.115

Values are presented as mean ± standard error of mean (% of β-actin).
*Significantly different among aripiprazole, risperidone, and control groups ($p < 0.05$ in ANOVA).
†Aripiprazole vs. control ($p < 0.001$ in the least significant differenc [LSD] *post-hoc* test).
‡Aripiprazole vs. risperidone ($p < 0.05$ in LSD *post-hoc* test).
§Aripiprazole vs. risperidone ($p < 0.001$ in LSD *post-hoc* test).

Neurochemical Outcomes

D2R levels were significantly different among the 3 groups in the medial PFC ($F = 8.72$, $p = 0.001$) and hippocampus ($F = 13.54$, $p < 0.001$) (Fig. 3). LSD *post-hoc* test confirmed that D2R levels in the medial PFC were significantly lower in the aripiprazole group than in the risperidone ($p = 0.025$) and control ($p < 0.001$) groups. D2R levels in the hippocampus were also significantly lower in the aripiprazole group than in risperidone ($p < 0.001$) and control ($p < 0.001$) groups. D2R levels were not significantly different among the 3 groups in the dorsolateral PFC ($F = 2.71$, $p = 0.085$), dorsal striatum ($F = 1.50$, $p = 0.241$), and ventral striatum ($F = 1.90$, $p = 0.170$). The detailed results of D2R levels in dorsolateral and medial PFC, dorsal and ventral striatum, and hippocampus are shown in Table 2.

DISCUSSION

In this study, we found that aripiprazole treatment during adolescence had different effects from risperidone treatment during adolescence on the cognitive function and dopaminergic system of adult rats. Specifically, adult rats treated with aripiprazole during adolescence showed higher performance in the spatial working memory task than did rats treated with risperidone. In addition, aripiprazole-treated rats expressed lower D2R levels in the medial PFC and hippocampus compared to risperidone-treated rats and controls.

Cognitive outcomes following antipsychotic treatment during adolescence have been examined in a small number of animal studies. According to Xu *et al.*,[25] chronic haloperidol treatment in adolescent mice decreased the performance in the Y-maze and Morris water maze. Milstein *et al.*[7] reported that adult rats treated with olanzapine during adolescence had deficits in working memory and fear conditioning. In this study, we investigated changes in spatial working memory that persisted into early adulthood after adolescent exposure to aripiprazole, risperidone, and vehicle. In the Y-maze, aripiprazole-treated rats showed not only significantly higher SAP but also marginally lower AAR than risperidone-treated rats, indicating that aripiprazole-treated rats had better spatial working memory than risperidone-treated rats. Moreover, aripiprazole-treated rats showed marginally higher SAP compared to controls. To the best of our knowledge, this is the first animal study on the long-term effects of aripiprazole treatment during adolescence on cognitive function. Meanwhile, in this study, we did not observe altered locomotion and anxiety-like behaviors in aripiprazole-treated rats. De Santis *et al.*[17] reported that adult rats treated with aripiprazole during adolescence spent more time in the open part of EPM than did controls, indicating anxiolytic behaviors. Further animal study is needed on the behavioral outcomes following aripiprazole treatment during adolescence.

In this study, we observed that aripiprazole-treated rats showed higher cognitive performance than risperidone3-treated rats. As mentioned above, aripiprazole has a unique pharmacological profile as a partial agonist at D2R and may influence brain development during adolescence in a different manner than D2R antagonists.[10] Moreover, considering the finding that aripiprazole-treated rats showed a marginal increase in cognitive performance when compared to the control, we can hypothesize that aripiprazole may have a positive effect on adolescent cog-

nitive development. Some animal studies have provided evidence of the cognitive-enhancing effects of aripiprazole.[26,27] There have been clinical studies suggesting its cognitive-enhancing effects in patients with schizophrenia.[28-30] A recent PET study showed that greater striatal D2/3R occupancy by aripiprazole was related with increased performance in working memory tasks in patients with schizophrenia.[31] However, a previous PET study conducted in healthy adults administered with aripiprazole demonstrated a decrease in cognitive performance and frontal metabolism associated with greater D2/3R occupancy.[32] Considering the evidence that there is a large difference between adulthood and the developing brain in the dopamine system with reference to dopamine concentration, innervation, and receptor density,[33] aripiprazole treatment may have a different impact on the dopamine system during adolescence than in adulthood.

Some studies have reported long-lasting alterations in dopaminergic neurotransmission induced by chronic AAP treatment in neurologically intact adolescent animals. An increase in D2R levels in the medial PFC, nucleus accumbens, and hippocampus was observed in adult rats previously treated with olanzapine during adolescence.[7,34] Chronic risperidone treatment during adolescence was also reported to upregulate D2R in the same brain regions.[8] In this study, we observed that aripiprazole-treated rats had significantly lower D2R levels in the medial PFC and hippocampus compared to risperidone-treated rats and controls. This finding conflicts with the above-mentioned studies that reported an upregulation of D2R in these brain regions. We assume that this discrepancy is due to different mechanisms of action of aripiprazole, a D2R partial agonist. According to Li *et al.*,[35] aripiprazole preferentially increases dopamine release in the medial PFC and hippocampus of the rat brain. The increase in dopamine release could reactively suppress the expression of dopamine receptors in the medial PFC and hippocampus. In addition, we can hypothesize that the change of D2R levels in the medial PFC and hippocampus may be related to the higher cognitive performance in the aripiprazole-treated rats. The medial PFC and hippocampus are known to jointly contribute to spatial working memory.[36] Local infusion of D2R selective dopaminergic drugs into the medial PFC and hippocampus of rats has been reported to have a significant influence on spatial working memory.[37,38] Our hypothesis is indirectly supported by a previous study reporting that chronic treatment with haloperidol, a potent D2R antagonist, decreased the SAP of mice in Y-maze experiments and increased D2R levels in the hippocampus.[25]

This study has some methodological limitations. First, this study did not include an analysis of dose-dependent differences of AAP administration. In particular, the interpretation of the results requires careful consideration because the effects of dose difference between aripiprazole and risperidone cannot be excluded. Second, we evaluated only spatial working memory using the Y-maze. Further studies are needed to evaluate the effects of adolescent exposure to aripiprazole on comprehensive cognitive function, using additional assessment tools such as the Morris water maze or fear conditioning. Third, the neurochemical effects of adolescent exposure to aripiprazole on other dopaminergic properties, such as dopamine release and dopamine D1 receptor expression, were not analyzed in this study. Finally, the effects of housing conditions of laboratory rats should be considered when interpreting the results of this study.

Within the discussed limitations, this study provides preclinical evidence that long-term exposure to aripiprazole during adolescence can influence cognitive function and dopaminergic neurotransmission into early adulthood. Further research is needed to investigate the long-term effects of aripiprazole treatment during adolescence on cognitive function in animal models of neuropsychiatric disorders.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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