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Influence of aripiprazole on the antidepressant, anxiolytic and cognitive functions of rats

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Abstract:
Recent research has suggested that cognitive disorders are a persistent trait of mental illnesses such as schizophrenia. Cognitive deficits in the course of schizophrenia may be due to the disease and/or drug therapy, especially with old-generation drugs.
Several clinical experiments have indicated the beneficial effects of new-generation antipsychotics on cognitive processes in patients treated for mental disorders.
Aripiprazole is a new, atypical antipsychotic with a unique mechanism of action, which may have positive effects on cognitive functions.
The aim of this study was to investigate the effects of aripiprazole on spatial memory in the Morris water maze and antidepressant activity in the Porsolt test. In addition, we examined whether aripiprazole had any side effects in the chimney test. The behavioral tests showed that aripiprazole improved spatial memory in rats and had antidepressant and anxiolytic effects after a single treatment; however, aripiprazole impaired motor coordination after repeated administration.
We concluded that aripiprazole could be an effective antipsychotic for the treatment of patients with schizophrenia or bipolar disorder who have associated anxiety and cognitive deficits.

Key words:
aripiprazole, cognitive function, animal model, rats

Abbreviations: 5-HT – endogenous serotonin receptor, ARI – aripiprazole, BSE – square entries in the black compartment, BWT – transition between the two compartments, CMC – carboxymethylcellulose, D_2/D_3 – dopamine receptors, DA – dopamine, DH – drug-induced helplessness test, EFs – escape failures, EPS – extrapyramidal symptoms, FST – forced swimming test, PCP – phencyclidine, WSE – square entries in the white compartment

Introduction

Aripiprazole (ARI) is a new atypical antipsychotic that was approved for the treatment of schizophrenia in 2002 [49]. Two years later, its therapeutic indications were extended for use in acute manic and mixed episodes associated with bipolar disorder. In addition, ARI was approved as an adjunct therapy for major depressive disorder in 2007. Aripiprazole is sometimes referred to as a third-generation antipsychotic [19] and differs from other typical and atypical antipsychotics by improving both positive and negative symptoms of psychosis without inducing extrapyramidal side effects or an increase in serum prolactin [22].

Compared to other antipsychotic drugs, ARI has a unique pharmacology. It is a partial agonist at D_2 and D_3 dopamine receptors, and behaves as an antago-

nist in hyperdopaminergic states and an agonist in hypodopaminergic states [19]. Interestingly, studies have suggested that the pharmacological profile of ARI may be due to functional selectivity rather than partial agonist activity [42]. The phenomenon of functional selectivity suggests that a ligand acting at a single G protein-coupled receptor causes dissimilar degrees of activation for different effector pathways [46].

ARI is a partial agonist at dopamine D_2 and serotonin 5-HT_{1A} and 5-HT_7 receptors, whereas it is an antagonist at serotonin 5-HT_{2A} and 5-HT_6 receptors [52]. It also acts as a 5-HT_{2C} partial agonist, which may underlie the minimal weight gain seen in the course of therapy [53]. In addition, ARI has moderate affinity to histamine receptors, α-adrenergic receptors and the serotonin transporter, which contribute to ARI's improved tolerability profile [1].

Because of its activity, ARI has been described as a dopamine-serotonin system stabilizer. It can reduce dopaminergic neurotransmission in situations in which dopamine activity is high and enhance neurotransmission in situations in which dopamine activity is low [16]. ARI also simultaneously maintains a balance in other important areas of dopaminergic neurotransmission, such as regulation of motor function and prolactin release. In clinical practice, these effects should translate into a low incidence of extrapyramidal symptoms (EPS) and prolactin elevation [7]. Controlled trials have examined ARI in combination with an antimanic mood stabilizer. Overall, the results of these trials have indicated that hospitalized patients with acute mania of moderate or greater severity with or without psychotic symptoms show a greater mean reduction in manic symptoms and greater initial response rates with the combination treatment. ARI monotherapy is approved for the acute treatment of bipolar mania/mixed states and maintenance for individuals with recent manic or mixed episodes [28, 45].

Regardless of intrinsic 5-HT_{1A} affinity, atypical antipsychotic blockade of 5-HT_{2A} may promote the ability of 5-HT_{1A} receptor stimulation to increase dopamine release [31].

Cognitive dysfunction is accompanied by a number of mental illnesses. Schizophrenia is a mental disorder that involves changes in central nervous system (CNS) neurotransmission (e.g., dopaminergic and serotonergic) compared to healthy individuals [10, 50]. In patients with schizophrenia, impairment of cognitive functions may result from both the symptoms of the disease and the type of pharmacotherapy. ARI is a new antipsychotic drug that may be an alternative to current antipsychotic drugs that adversely affect cognitive processes.

The aim of this paper was to assess the impact of ARI on behavioral functions of rats with particular emphasis on memory after single and multiple dosing. We wanted to verify that the test dose of medication did not cause sedation, which could have a negative impact on cognitive processes. In addition, we wanted to assess the antidepressant and anxiolytic effects of ARI in rats. After testing 6 different doses from 1 to 12 mg/kg (dose response), a dose of 6 mg/kg was selected (unpublished studies) because this dose did not adversely affect animal mobility in the activity meter test and showed antidepressant effects after subacute administration in the Porsolt test.

Materials and Methods

Animals

The present study used male Wistar rats (180–200 g) that were obtained from a licensed breeder (Sadowski, Poznań, Poland; licensed by Ministry of Agriculture in Warszawa, Poland). The rats were housed in standard laboratory conditions with a 12-h light/dark cycle (lights on at 6:00 a.m.) in a temperature controlled room (20–21°C) at 60% humidity with free access to granulated standard food and tap water.

All procedures related to the use of rats in these experiments were conducted with due respect to ethical principles regarding experiments on animals. The study protocol was approved by the Local Ethical Commission for Research on Animals in Poznań.

The rats were housed 10 per cage. Each test involved two groups of rats: an experimental group (10 rats) and a control group (10 rats).

Drugs

Carboxymethylcellulose sodium (CMC) pure was obtained from Koch-Light Laboratories (London, England). Aripiprazole (6 mg/kg) – Abilify, was obtained from Otsuka Pharmaceutical Europe, Bristol-Myers Squibb Polska. The rats were administered ARI or vehicle intraperitoneally (*ip*) for 14 days. The tests were carried out on day 1, day 7 and day 14. On each of the test days, the treatment was given 30 min before the

test. Between the tests with different assays, there was 24-h washout period. The controls were given CMC only (2 ml, *ip*) according to the same schedule. Separate groups of animals were used for different tests.

Measurement of locomotor activity in rats

Locomotor activity was measured using eight 20.5 × 28 × 21 cm wire grid cages with two horizontal infrared photocell beams along the long axis (3 cm above the floor). Photocell interruptions were recorded by electromechanical counters in an adjacent room. After 30 min of habituation to the novel cage, rats were treated with VAL, and photocell activity was recorded at 10-min intervals for 1 h. This test provided an index of basal locomotor activity of rats in a familiar environment, which was necessary to indicate the presence of central stimulant or sedating effects of the drug used in the novelty test.

Measurement of immobility time in the Porsolt forced swimming test

We used the Porsolt forced swimming test to measure immobility [34]:
a) Pretest: 24 h prior to the experiments, the rats were individually placed in plexiglass cylinders (height 40 cm, diameter 18 cm) containing water (25°C) up to 17 cm of the cylinder's height. Fifteen minutes later, the rats were removed to a 30°C drying room for 30 min.
b) Test: ARI was administered 24 h after the pretest. Thirty minutes after drug administration, the rats were placed in the cylinders and immobility was measured for 5 min. A rat was judged to be immobile when it remained floating in the water in an upright position and only made very small movements necessary to keep its head above water. The total duration of immobility over the 5-min period was recorded by an observer unaware of the treatment applied to the rats.
c) We also examined drug effects after prolonged administration (7 and 14 days).

The water was changed after the observation of each rat.

Morris water maze test [30]

The water maze apparatus was a circular basin (diameter = 180 cm, height = 50 cm) filled with water (approximately 22–24°C) to a depth of 24 cm, and pieces of Styrofoam were hiding an escape platform (diameter = 8 cm) that was placed 1 cm below the water surface (learning place, invisible condition). Many extra-maze visual cues surrounding the maze were available, and the observer remained in the same location for each trial.

The rats were placed in the water facing the midpoint section of the wall at one of 4 equally spaced locations: north (N), east (E), south (S) and west (W). The pool was divided into 4 quadrants: NW, NE, SE and SW. The rats were allowed to swim freely until they found and climbed onto the platform. If a rat failed to locate the platform within 60 s, it was placed on the platform for 5 s. Each rat was submitted to 6 trials per day, and the starting position was changed at each trial (starting on the N side, followed by E, S, and W sides, in that order). The intertrial interval was 5 min between trials 1–3 and 4–6 and 10 min between trials 3 and 4. For the first 3 days of maze testing, the submerged platform was placed in the NW quadrant. The platform was subsequently placed in the SE quadrant for the following 2 days. After these 5 testing days, there was a period of 7 days without any testing. On day 6, the rats were retested with the platform located in the same position as it had been on day 5. On day 7 (one day later), the platform was lifted above water level and placed in the SW quadrant. On the test day, each rat was subjected to a one probe trial consisted of 6 individual trials. The total number of times each rat crossed the probe target area and the time of the probe trial swim were recorded by the observer. The time of each of the 6 trials was noted, and a mean value for each rat was calculated. The same procedures were followed in the chronic experiments.

On day 7 (one day later), the platform was lifted above water level and placed in the SW quadrant, and rats were injected with ARI 30 min before the test. After prolonged administration of ARI (7 and 14 days), the drug effects were tested as described for the 7th day of the Morris water maze test procedure.

Chimney test

Motor impairment was quantified with the "chimney test", which was described by Boissier. Motor coordination was evaluated using the "chimney test" as originally described for mice [5]. In this test, rats had to climb backwards up a plastic tube (57 mm inner diameter, 452 mm long), and motor impairment was indicated by the inability of the animals to climb backwards up the transparent tube within 60 s.

Anxiolytic effects

The anxiolytic effects were determined in a two-compartment exploratory test. The apparatus employed to test "approach-avoidance behavior" was a conventional open field (100 × 100 cm) with a white floor divided into 25 (5 × 5 cm) equal squares by a black grid. This surface was divided into two different compartments. One compartment consisted of a squared area (40 × 40 cm) in one corner of the open field, with all the surfaces blackened and a roof fitted 35 cm from the floor to prevent light from entering from above, and the second compartment consisted of the remaining white part of the open field, which was uniformly lit by a fluorescent lamp.

At the beginning of the test, the rat was placed in the white area in the corner of the compartment. The number of transitions between the two-compartments (BWT), square entries in the black compartment (BSE) and square entries in the white compartment (WSE) were recorded for a 5-min period. An event was recorded whenever the rat crossed a line on the grid or the compartment border with all four legs.

Statistical analysis

The data are shown as the mean values ± SEM. The data distribution pattern was not normal (unlike Gaussian function).

Statistical analyses for the memory test, locomotor activity, two-compartment exploratory test and antidepressant test were carried out using the nonparametric Mann-Whitney U test for unpaired data and ANOVA Friedman two-way analysis of variance (ANOVA) test for paired data. Statistical significance was tested using Dunn's *post-hoc* test.

The motor performance data were tested using Fisher's exact probability test.

Results

Effects of single and repeated administration of ARI on locomotor activity in the activity meter

A single dose of ARI (6 mg/kg) administered 30 min before the test did not produce a statistically significant difference in locomotor activity compared to the control group. There was also no effect after 7 days of treatment. Interestingly, there was a statistically significant difference in locomotor activity after 14 days of treatment ($p < 0.05$ *vs.* control group) (Tab. 1).

Evaluation of the antidepressant effects of ARI after single and repeated administration using the Porsolt test

Single administration of ARI (6 mg/kg) 30 min before the test did show a statistically significant reduction in the immobility time of the rats. In addition, we did not observe a statistically significant reduction in the immobility of the rats after 7 or 14 days of ARI administration (Tab. 2).

Tab. 1. Influence of single and repeated ARI administration on locomotor activity measured in the activity meter test

Drug	Activity counts [$\bar{x}$ ± SEM]			Friedman H [2, 29]
	Single administration	Chronic treatment		
		7 days	14 days	
Control 0.5% CMC (0.5 ml/rat)	113.6 ± 8.6	93.8 ± 3.1	96.6 ± 4.5	2.9
ARI (6 mg/kg, *ip*) 30 min before the test	104.0 ± 4.9	91.3 ± 4.0	75.4 ± 4.8*	12.9
Mann-Whitney U test	p = 0.3450	p = 0.6273	p = 0.0047	

* Statistically significant difference ($p < 0.05$) *vs.* control group. Number of animals = 10

Tab. 2. Influence of single and repeated ARI administration on antidepressant actions measured in the Porsolt test

Group	Immobility time (s) [$\bar{x}$ ± SEM]			Friedman H [2, 29]
	Single administration	Chronic treatment		
		7 days	14 days	
Control 0.5% CMC (0.5 ml/rat)	206.2 ± 5.8	229.3 ± 11.2	250.2 ± 5.9	10.5
ARI (6 mg/kg, *ip*) 30 min before the test	187.1 ± 8.4*	227.4 ± 14.0	259.5 ± 6.3	9.4
Mann-Whitney U test	p = 0.0402	p = 0.9168	p = 0.2955	

* Statistically significant difference ($p < 0.05$) *vs.* control group. Number of animals = 10

Evaluation of the effects of ARI on memory after single and repeated administration using the Morris test (escaped latencies)

After single administration of ARI (6 mg/kg) 30 min before the test, we observed reductions in the escape latencies, which indicated improved memory function. After chronic treatment (7 and 14 days) with ARI (6 mg/kg) 30 min before the test, we observed the same effect: reductions in the escape latencies, which indicated improved memory function (Tab. 3).

Evaluation of the effects of ARI on memory after single and repeated administration using the Morris test (number of crossed quadrants)

After single administration of ARI (6 mg/kg) 30 min before the test, we observed a reduced number of crossed quadrants, which indicated improved memory function. After chronic treatment (7 and 14 days) with ARI (6 mg/kg) 30 min before the test, we observed the same effect: reduced number of crossed quadrants, which indicated improved memory function (Tab. 4).

Evaluation of the effects of ARI on motor coordination after single and repeated administration using the chimney test

Single administration of ARI (6 mg/kg) 30 min prior to the test did not contribute to the reduction of motor coordination in rats. In addition, only 10% reduction ($p < 0.05$ *vs.* control group, n = 10) was observed after 7 days and no decrease in motor coordination occurred after administration of ARI for 14 days.

Evaluation of the effects of ARI on anxiolytic actions after single and repeated administration using the two-compartment exploratory test

Neither single nor 7-day administration of ARI had an impact on the rats' behaviors in the two-compartment exploratory test compared to the control group. After

Tab. 3. Influence of single and repeated ARI administration on memory measured in the Morris test (number of escape latencies)

Drug	Escape latency (s) [$\bar{x}$ ± SEM]			Friedman H [2, 29]
	Single administration	Chronic treatment		
		7 days	14 days	
Control 0.5% CMC (0.5 ml/rat)	14.1 ± 1.5	7.3 ± 1.2	6.0 ± 0.7	8.9
ARI (6 mg/kg, *ip*) 30 min before the test	10.2 ± 1.1*	4.6 ± 0.2*	3.6 ± 0.3*	11.5
Mann-Whitney U test	p = 0.0504	p = 0.0395	p = 0.0055	

* Statistically significant difference ($p < 0.05$) *vs.* control group. Number of animals = 10

Tab. 4. Influence of single and repeated ARI administration on memory measured in the Morris test (number of crossed quadrants)

Drug	Crossed quadrants [$\bar{x}$ ± SEM]			Friedman H [2,29]
	Single administration	Chronic treatment		
		7 days	14 days	
Control 0.5% CMC (0.5 ml/rat)	3.6 ± 0.5	2.6 ± 0.3	0.9 ± 0.2	6.5
ARI (6 mg/kg, *ip*) 30 min before the test	2.6 ± 0.3	1.1 ± 0.2*	0.4 ± 0.1*	9.1
Mann-Whitney U test	p = 0.1035	p = 0.0006	p = 0.0382	

* Statistically significant difference ($p < 0.05$) *vs.* control group. Number of animals = 10

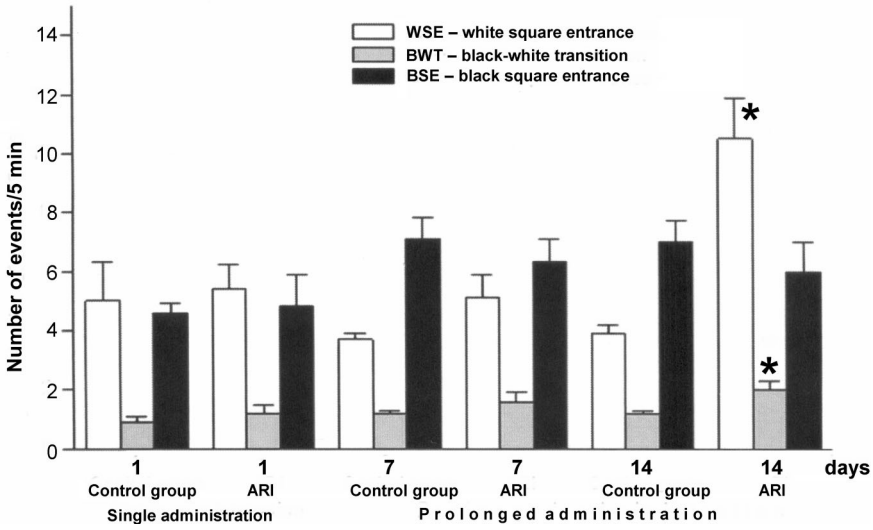

Fig. 1. Influence of single and repeated ARI administration on anxiolytic activities measured in the "two-compartment exploratory test". * Statistically significant difference ($p < 0.05$) *vs.* control group. Number of animals = 10

14 days of treatment, however, there was a statistically significant increase in the WSE and BWT parameters, which indicated an anxiolytic effect (Fig. 1).

Discussion

Contemporary therapy of mental diseases involves treatment of primary symptoms of the disease and attempts to improve disturbed cognitive functions in the patients (e.g., learning memory). Cognitive deficits may be modified with an appropriate, state-of-the-art pharmacotherapy involving new-generation drugs.

Apart from their efficacy in treating the key symptoms of mental illnesses, atypical antipsychotics cause minimal adverse effects in the extrapyramidal system and have little potential of resulting in dyskinesias in long-term therapy [4]. Undoubtedly, an important side effect of older generation antipsychotic drugs is the ability to cause sedation, which may be one of the direct causes of cognitive impairment.

In the present study, we examined locomotor activity and found that ARI (6 mg/kg) only decreased locomotor activity in the rats after 14 days of treatment. The study by Natesan et al. showed that administration of ARI alone produced significant decreases in spontaneous locomotor activity in rodents [32], the decrease in spontaneous locomotor activity was seen

at all doses tested, including the lowest dose of 1 mg/kg, which agreed with other literature showing depressed locomotor activity at similar doses in rodents [51, 54].

In another trial with ARI, results showed a decrease in total locomotor activity in a dose-dependent manner. The time course of changes in locomotor activity revealed that ARI (0.3 and 1.0 mg/kg) caused a marked locomotor suppression 1 h after administration. In contrast to the single treatment, repeated treatment with ARI (0.01–0.1 mg/kg) had no effect on locomotor activity [31]. These discrepancies may result from the use of different dosage forms and/or the use of different rat populations.

Another trial that used a rotarod test for motor coordination concluded that no disturbances were observed following ARI treatment with any dose tested (3, 10 and 30 mg/kg) when testing was performed at 8 rpm. When animals were tested at 16 rpm, however, deficits emerged in animals treated with 10 and 30 mg/kg of ARI at 1 and 3 h posttreatment, and significant deficits were still seen in animals treated with 30 mg/kg at 6 h posttreatment. Importantly, deficits produced by the highest dose tested (i.e., 30 mg/kg) were considerably small [33]. The present study showed that ARI only had a significant effect on motor coordination after 7 days of treatment.

Memory has been regarded as one of the major areas of cognitive deficit in schizophrenia [29]. Interestingly, the present study found that administration of ARI (6 mg/kg once a day) improved memory as assessed by the Morris test. Single administration and repeated administration for 7 and 14 days resulted in a shorter time for the rats to reach the platform in the water maze. In addition, the number of crossed quadrants was significantly reduced after repeated administration of ARI for 7 and 14 days compared with control, which indicated improved spatial memory.

Further research on the impact of ARI on memory in rats has shown that after single (1.0 mg/kg) and repeated (0.03 and 0.1 mg/kg) treatment during a period of 7 days, ARI ameliorated PCP-induced impairment of recognition memory; however, the single treatment significantly decreased the total exploration time during the training session. Another study demonstrated that the ameliorating effect of ARI on recognition memory in PCP-treated mice was blocked by cotreatment with the dopamine D_1 receptor antagonist SCH23390 and the serotonin 5-HT_{1A} receptor antagonist WAY100635. Cotreatment with the D_2 receptor antagonist raclopride, however, had no effect on the ability of ARI to ameliorate recognition memory in PCP-treated mice. These results suggested that the ameliorative effect of ARI on PCP-induced memory impairment is associated with dopamine D_1 and serotonin 5-HT_{1A} receptors [43]. Interestingly, studies have shown that the activation of 5-HT_{1A} receptors in the prefrontal cortex enhances the activity of dopaminergic neurons in the ventral tegmental area and causes mesocortical dopamine release [14]. Accumulating evidence has suggested that the dopaminergic system in the prefrontal cortex is involved in cognitive function [12, 13, 40, 46], and it is possible that the memory-enhancing effects of ARI presented in this paper are mediated by the prefrontal cortical dopaminergic system.

In two clinical studies with patients suffering from schizophrenia or schizo-affective disorders, treatment with ARI improved working memory [9, 23]. Anxiety and depressive disorders share many features, which suggests a common set of physiological substrates. Interestingly, two published clinical observations have reported that dysphoria and suicidal tendency were among the serious side effects of ARI [24, 31], which is in agreement with some preclinical findings that ARI increases escape failures (EFs) at 5 and 10 mg/kg in the drug-induced helplessness test (DH). Based on the learned helplessness model of depression, increases in EFs in the DH are proposed to reflect a drug-induced depressive-like state, which is a contributing factor to neuroleptic dysphoria in humans. Interestingly, altering the level of anxiety experienced by the rat in the DH test could lead to a change in EFs (i.e., reducing anxiety would make the rat less motivated to escape the shock) [2].

In the present study, single administration of ARI (6 mg/kg) failed to show a statistically significant reduction in the immobility times of the rats. Dopamine has been implicated in mood regulation [3, 27], and brain extracellular DA levels have been shown to be decreased in rats after the forced swimming test (FST) [38]. Therefore, studies have concluded that DA is involved in the activity of antidepressants in animal models of depression [21, 27, 35, 36]. Indeed, DA receptor agonists, including D_2 agonists, have been shown to elicit antidepressant effects of animals in the FST [21, 27]. Moreover, D_2 receptor agonists (e.g., bromocriptine) have shown antidepressant effects in humans [8, 42]. Indeed, both DA receptor agonists

and antagonists (e.g., olanzapine) can be used as an augmentation strategy in patients with treatment-resistant depression [11]. The influence of the dopaminergic system in the FST is relatively difficult to study due to an aversive phenomenon developed during the test. Interestingly, the placement of animals in water for the FST has been shown to produce a spontaneous liberation of DA, and the maximal level of DA in the brain would be rapidly attained [37]. This phenomenon may explain the results obtained in the present study, namely shortened immobility time, after a single treatment of ARI. This effect, however, has no clinical significance. It may be that the lack of IT changes after ARI administration for 7 or 14 days can be explained with drug accumulation and adaptive changes in the CNS after chronic administration, which is an effect that cannot be observed after a single administration. The DA release effect after a rat was placed in water – which seems responsible for IT reduction – could have not occurred or could only have occurred in such a mild manner that it did not affect the test parameter due to DA level stabilization by ARI, which shows such activities upon multiple administration.

Snigdha et al. proposed a social interaction test as a model for negative and depressive-like symptoms in rats [43] and demonstrated that ARI had a beneficial effect in reversing PCP-induced social behavior deficits. Snigdha et al. have previously demonstrated that acute treatment with ziprasidone, which acts as a partial agonist at the 5-HT_{1A} receptor and an antagonist at D_2 and 5-HT_{2A} receptors (similar to ARI) [39], improved the social interaction deficits induced by PCP [48]. Unlike ARI, however, ziprasidone is devoid of partial D_2 agonism. Interestingly, 5-HT_{1A} receptor activation selectively augments cortical dopamine levels, which results in improvements in social behavior deficits [43].

Although ARI alone did not affect the duration of immobility in the tail suspension test, Kamei observed that a combined treatment of ARI and a subeffective dose of fluoxetine significantly decreased the duration of immobility in the tail suspension test, which was in agreement with the forced swim test results presented in this paper. Kamei hypothesized that the decrease in immobility time with ARI-fluoxetine coadministration in the tail suspension test model of depression in mice was associated with the combined effect of stabilizing activity on the DA system and the activation of 5-HT_{1A} receptors [25].

Another study that examined mice in the FST demonstrated that inactive doses of ARI (0.03 and 0.06 mg/kg) potentiated subthreshold doses of the selective serotonin reuptake inhibitors (SSRIs) paroxetine and citalopram (4 and 8 mg/kg) and the serotonin and norepinephrine reuptake inhibitors (SNRIs) venlafaxine and milnacipran (4 and 8 mg/kg). In contrast, this augmentation activity of ARI was not found when ARI was combined with drugs that do not inhibit the reuptake of 5-HT (2 and 4 mg/kg desipramine and 4 and 8 mg/kg bupropion). The combination of ARI with antidepressants did not produce any psychostimulant effects, which indicated that the anti-immobility effect was related to the antidepressant-like activity [6]. The FST has been shown to induce a significant increase in DA in mice [35, 36], which supports the inference that, depending upon the stress state, a partial dopaminergic agonist might be effective [6].

Aripiprazole also has a unique receptor profile that may make it more likely to be a superior agent (in relation to older drugs) in the treatment of schizophrenia with a comorbid social anxiety. As noted by Snigdha et al., ARI has a number of possible mechanisms of action that may be important in the treatment of depressive and anxiety disorders. At serotonin receptors, ARI acts as a 5-HT_{1A} receptor partial agonist, a 5-HT_{2C} receptor partial agonist and a 5-HT_{2A} receptor antagonist. ARI also acts as a dopamine D_2 receptor partial agonist and has possible actions at adrenergic receptors. Furthermore, ARI may have possible neuroprotective effects [44].

In an animal study, ARI (1 mg/kg, *ip*) inhibited marble-burying behavior, which has been considered to be an animal model of obsessive-compulsive disorder [20]. Although the mechanism mediating ARI-induced inhibition of marble-burying behavior is unclear, the partial antagonistic effects of 5-HT_{2A} and DA D_2 receptors may be involved in the ARI-mediated inhibition of marble-burying behavior. Interestingly, Egashira et al. found that WAY100635 had no effect on the ARI-mediated inhibition of marble-burying behavior – these findings suggested that ARI inhibits the marble-burying behavior *via* 5-HT_{1A} receptor-independent mechanisms [15]. In present study, the results obtained during testing in the two-compartment exploratory test showed that ARI (6 mg/kg) only induced an anxiolytic effect after 14 days of administration. This effect may be due to adaptive changes that occur in the CNS. Traditionally,

researchers have thought that the onset of the antipsychotic response is delayed for 2–3 weeks after the initiation of drug therapy; thus, priority was given to studying neurobiological changes that emerged after the delay [17]. This led to a focus on various late-onset phenomena, such as delayed depolarization [18] or delayed onset of neuroplasticity [26]. One interesting phenomenon is that stable dopamine D_2 receptor blockade can be achieved within hours after drug administration, but substantial improvement of symptoms is usually not observed until 2–3 weeks later [47].

In conclusion, the antipsychotic ARI can have a positive impact on the realm of cognitive processes, which is important in the treatment of schizophrenia. The present study was in agreement with cited evidence suggesting that only combined treatments of ARI and antidepressant drugs (even subeffective doses) exert an antidepressant effect. These effects may appear when the 5-HT system is activated and appear to implicate complex regulations between dopamine and serotonin receptors.

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