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Chronic Treatment With Aripiprazole Prevents Development of Dopamine Supersensitivity and Potentially Supersensitivity Psychosis

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Background: **Long-term treatment of schizophrenia with antipsychotics is crucial for relapse prevention, but a prolonged blockade of D_2 dopamine receptors may lead to the development of supersensitivity psychosis. We investigated the chronic effects of aripiprazole (ARI) on dopamine sensitivity.** ***Methods:*** **We administered ARI (1.5 mg/kg/d), haloperidol (HAL; 0.75 mg/kg/d), or vehicle (VEH) via minipump for 14 days to drug-naive rats or to rats pretreated with HAL (0.75 mg/kg/d) or VEH via minipump for 14 days. On the seventh day following treatment cessation, we examined the effects of the treatment conditions on the locomotor response to methamphetamine and on striatal D_2 receptor density (N = 4-10/condition/experiment).** ***Results:*** **Chronic treatment with HAL led to significant increases in locomotor response and D_2 receptor density, compared with the effects of chronic treatment with either VEH or ARI; there were no significant differences in either locomotor response or D_2 density between the VEH- and ARI-treated groups. We also investigated the effects of chronic treatment with HAL, ARI, or VEH preceded by HAL or VEH treatment on locomotor response and D_2 density. ANOVA analysis indicated that the rank ordering of groups for both locomotor response and D_2 density was HAL-HAL > HAL-VEH > HAL-ARI > VEH-VEH.** ***Conclusions:*** **Chronic treatment with ARI prevents development of dopamine supersensitivity and potentially supersensitivity psychosis, suggesting that by reducing excessive sensitivity to dopamine and by stabilizing sensitivity for an extended period of time, ARI may be helpful for some patients with treatment-resistant schizophrenia.**

Key words: D_2 dopamine receptor/locomotor activity/partial agonist/radioligand binding assay/rat/striatum

Introduction

For decades, the standard schizophrenia treatment protocol has included the administration of D_2 dopamine receptor blockers as effective antipsychotics, especially for the amelioration of psychotic symptoms.[1] Long-term, continuous treatment with antipsychotic agents is emphasized as a treatment strategy to encourage remission in people with schizophrenia because the chance of relapse is decreased if pharmacotherapy continues uninterrupted.[2] However, even among stabilized patients maintained on optimal doses of antipsychotic depot therapy, significant rates of relapse have been reported.[3] It is widely recognized that a small reduction in antipsychotic dosage or a short-term interruption in antipsychotic drug therapy can induce an acute exacerbation of psychotic symptoms and that the dose of antipsychotics needed to reduce such symptoms tends to increase with each relapse.[4,5] There may be multiple causes for this phenomenon, including the development of the disease itself. One of the possible explanations, however, may be the development of supersensitivity psychosis associated with long-term treatment with D_2 receptor blockers.[6–10]

Aripiprazole (ARI), an atypical antipsychotic that is commercially known as a dopamine partial agonist, is clinically used to treat schizophrenia. Treatment with ARI has been associated with the lowest rate of rehospitalization (71% risk reduction) among antipsychotics in clinical use, including both first- and second-generation antipsychotics,[11] which suggests that, compared with other antipsychotics, ARI may more efficiently lower the risk of relapse or prevent a worsening of psychotic symptoms. We hypothesized that these clinical consequences might be related to certain unique effects of ARI on the development of supersensitivity psychosis.

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Dopamine supersensitivity in animals has been used as a model of supersensitivity psychosis in humans. Experimental rats chronically or subchronically treated with D_2 receptor antagonists develop dopamine supersensitivity in terms of behavior and movement, with increased striatal D_2 receptor density.[12–16] Based on the unique pharmacokinetic effects of ARI on D_2 receptors, eg, partial agonism, we hypothesized that chronic treatment with ARI not only does not induce dopamine supersensitivity but actually reduces the dopamine supersensitivity induced by D_2 receptor antagonists. In order to test these 2 hypotheses in the present study, we investigated the effects of chronic ARI treatment on (*a*) the behavioral sensitivity of experimental rats to methamphetamine (MAP) and (*b*) the density of striatal D_2 receptors.

Methods

Animals

Male Sprague Dawley rats (CLEA Japan Inc.) weighing 240-260 g were used. The animals were housed in groups of 2 per cage and were maintained under standard conditions (12 h-12 h light-dark cycle: lights on from 0700 to 1900 h; room temperature, 22 ± 2°C; humidity, 55 ± 5%) with free access to food and water. Experiments were performed in accordance with the *Guide for the Care and Use of Laboratory Animals* (1996).

Drugs

Aripiprazole (ARI; 1.5 mg/kg/d; a gift from Otsuka Pharmaceutical Co., Ltd.) and haloperidol (HAL; 0.75 mg/kg/d; Toronto Research Chemicals Inc.) were dissolved in a 2% glacial acetic acid/H_2O solution (pH adjusted to 3.0-3.8 with NaOH). These drugs were given via an Alzet osmotic minipump (model 2ML2; 14-day delivery; DURECT Corp.). Methamphetamine-HCl (MAP; 1.0 mg/kg; Dainippon Pharmaceutical, Ltd.) was dissolved in 0.85% saline and administered intraperitoneally (i.p.) in a volume of 1 ml/kg body weight.

The dose of HAL, 0.75 mg/kg/day, was determined based on data from a previous report,[16] and the dose of 1.5 mg/kg/day of ARI was equivalent to the dose of HAL, according to human clinical studies.[17] In a preliminary study, we examined the effects of these drugs on MAP-induced locomotion on the third day and the seventh day after the administration via minipump to the rats. As regards the total locomotor activity observed for 60 min after MAP injection, compared with the VEH-treated group, the ARI- and HAL-treated groups exhibited significantly smaller amounts of activity, ie, 74.2% (±SEM 0.5) and 94.9% (±SEM 0.2) less activity on the third day and 75.5% (±SEM 5.8) and 40.0% (±SEM 12.3) less activity on the seventh day, respectively. In other words, both the ARI and HAL treatments significantly suppressed MAP-induced hyperlocomotion ($P < .05$; one-way ANOVA).

[^{3}H]raclopride (80.1 Ci/mmol) was purchased from PerkinElmer Life Science. Other chemicals were purchased commercially.

Minipump Implantation

An Alzet osmotic minipump containing either vehicle (VEH; 2% glacial acetic acid/H_2O solution), HAL, or ARI was implanted under 5% pentobarbital sodium anesthesia. A 1.5-cm-wide incision was made in each animal's lower back, and hemostats were used to loosen connective tissue between the scapulae. Minipumps were inserted to lie on either side of the scapulae, with the flow moderator pointed away from incision. When a subsequent pump was implanted in exchange for a former one, the most recent pump was inserted on the other side of the scapulae across from the former pump. The incision was closed using 9-mm surgical staples and cleaned with 70% ethanol.

Groups and Procedures

Experiment 1 was designed to test whether or not chronic treatment with ARI induces dopamine supersensitivity (figure 1). Forty-five rats were divided into 3 groups (n = 15 each) that received the following treatments: (1) ARI at 1.5 mg/kg/d for 14 days (ARI group), (2) HAL at 0.75 mg/kg/d for 14 days (HAL group), and (3) VEH for 14 days (VEH group). Within each group, 10 rats were subjected to MAP-induced locomotion tests (Experiment 1a; n = 10 rats per treatment protocol), and the other 5 rats were used for radioligand binding assays (Experiment 1b; n = 5 rats per treatment protocol).

Experiment 2 was designed to determine whether chronic treatment with ARI reduces dopamine supersensitivity induced by chronic treatment with HAL (figure 1). Forty-eight rats were divided into 4 groups (n = 12 per group) that received the following treatments: (1) HAL at 0.75 mg/kg/d for 14 days, followed by ARI at 1.5 mg/kg/d for 14 days (HAL-ARI group); (2) HAL at 0.75 mg/kg/d for 14 days, followed by HAL at 0.75 mg/kg/d for 14 days (HAL-HAL group); (3) HAL at 0.75 mg/kg/d for 14 days, followed by VEH for 14 days (HAL-VEH group); and (4) VEH for 14 days, followed by VEH for 14 days (VEH-VEH group). All the drugs used for the first 14-day period were administered via minipump; the minipumps were then exchanged to administer the second set of drugs for the second 14-day period. Within each treatment group, 8 rats were subjected to MAP-induced locomotion tests (Experiment 2a; n = 8 per treatment protocol), and the other 4 rats were subjected to radioligand binding assays (Experiment 2b; n = 4 per treatment protocol).

Tests of MAP-Induced Locomotion

On the seventh day following treatment cessation (removal of the minipumps), MAP-induced locomotion

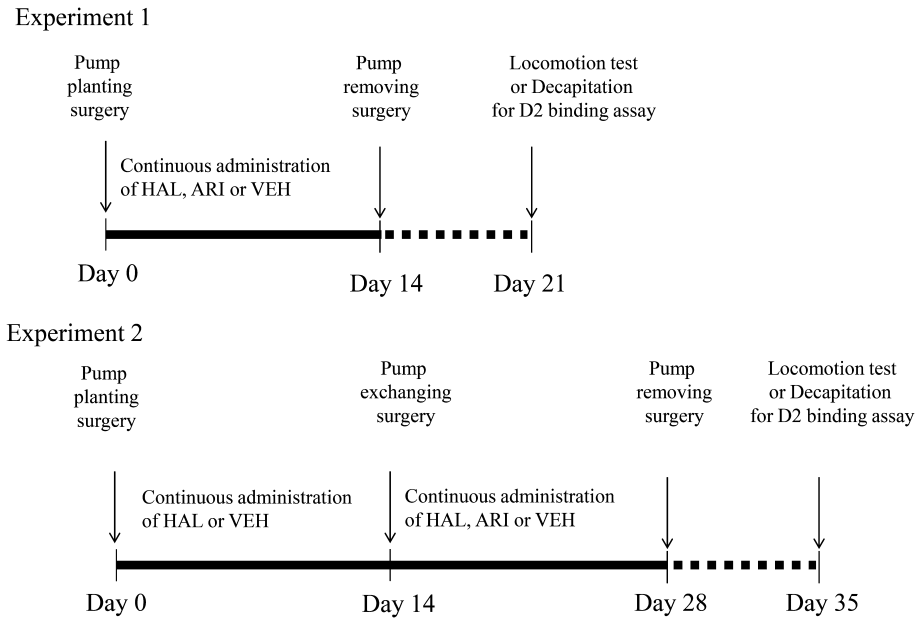

Fig. 1. Graphic depiction of the sequence of treatment and testing for experiments 1 and 2. In Experiment 1, an Alzet osmotic minipump was implanted into each rat, and drugs were administered starting on Day 0. The minipump was removed on Day 14, and the evaluation of either locomotor response to methamphetamine or the decapitation to evaluate D_2 receptor binding occurred on Day 21, ie, on the seventh day following treatment cessation. In Experiment 2, a minipump was implanted into each rat, and drugs were administered starting on Day 0; the first minipump was exchanged for a second minipump on Day 14. The second minipump was removed on Day 28, and the evaluation of either locomotor response to methamphetamine or the decapitation to evaluate D_2 receptor binding occurred on Day 35, ie, on the seventh day following the cessation of 2 consecutive treatment periods (total, 28 days). HAL indicates 0.75 mg/kg/d of haloperidol; ARI, 1.5 mg/kg/d of aripiprazole; and VEH, 2% glacial acetic acid/H_2O solution as vehicle.

was measured (Experiment 1a and 2a). Locomotor activity was assessed using an animal movement analysis system (Scanet SV-10; MATYS).[18] One hour before MAP injection, animals were placed in clear Plexiglas cages (30 × 48 × 60 cm), which were equipped with a row of 96 photocell beams placed 3 cm above the floor of the cage. Photocell beam breaks were detected and recorded by a computer. Data collected for 180 min were used for the analysis.

Radioligand Binding Assays

On the seventh day following treatment cessation (removal of the minipumps), the rats were sacrificed by decapitation, and the striata (rostal neo-striatum) were rapidly dissected. Tissues were stored at −70°C until use. Radioligand binding assays for striatal D_2 receptors were performed (Experiments 1b and 2b). Tissue samples (60-80 mg wet weight) of striata were homogenized for 15 s in 40 volumes (w/v) of ice-cold 50 mM Tris-HCl buffer (pH 7.4) containing 120 mM NaCl and 5 mM KCl, and the homogenates were then centrifuged (40 000*g*, 15 min, 4°C). The pellets were suspended and centrifuged twice in the same buffer.

The binding assays were carried out according to procedures described previously,[19] with slight modifications. Briefly, 100 μl of membrane homogenate was added to tubes containing 50 μl of [^{3}H]raclopride to yield a final assay volume of 500 μl. Binding to D_2 receptors was measured with 6 concentrations (0.25, 0.5, 1, 2,4, 8 nM) of [^{3}H]raclopride. The samples were incubated for 60 min at 25°C, and specific binding was determined in the presence of 300 μM (-)-sulpiride. The incubated samples were rapidly run through Whatman GF/B glass filters pretreated with 0.5% polyethyleneimine for at least 2 h, using a Brandell 24-channel cell harvester (Biochemical Research Laboratory). The filters were washed twice with 4 ml cold buffer. Radioactivity was determined using a liquid scintillation counter. In the final incubation tubes, the protein concentration was approximately 0.2 mg/ml, as determined by the Lowry method in 50 μl aliquots of membrane preparation. The Bmax and Kd values for D_2 receptors in each rat were calculated by a nonlinear regression curve fit using GraphPad Prism 5.01 software for Windows.

Statistical Analysis

In order to determine treatment effects, all data were analyzed using one-way ANOVA followed by 2-tailed Bonferroni's multiple comparison test or Fisher's least significant difference test (only for locomotion data from 3 groups). All statistical calculations were carried out with SPSS 12.0J software for Windows.

Results

Experiment 1a: Effects of Chronic Treatment on Behavioral Sensitivity to MAP

In Experiment 1a, we examined the effects of chronic treatment with HAL (0.75 mg/kg/d), ARI (1.5 mg/kg/d), or VEH, delivered to rats via minipump for 14 days, on the locomotor response of rats to MAP (1.0 mg/kg/injection) on the seventh day following treatment cessation. The injection of MAP induced hyperlocomotion in each group. Hyperlocomotion peaked about 20 min after the administration of MAP and then gradually declined during the observation period (figure 2A). As regards the total locomotor activity for the 60-min period after the MAP injection, the HAL group exhibited a significantly greater amount of activity than either the VEH

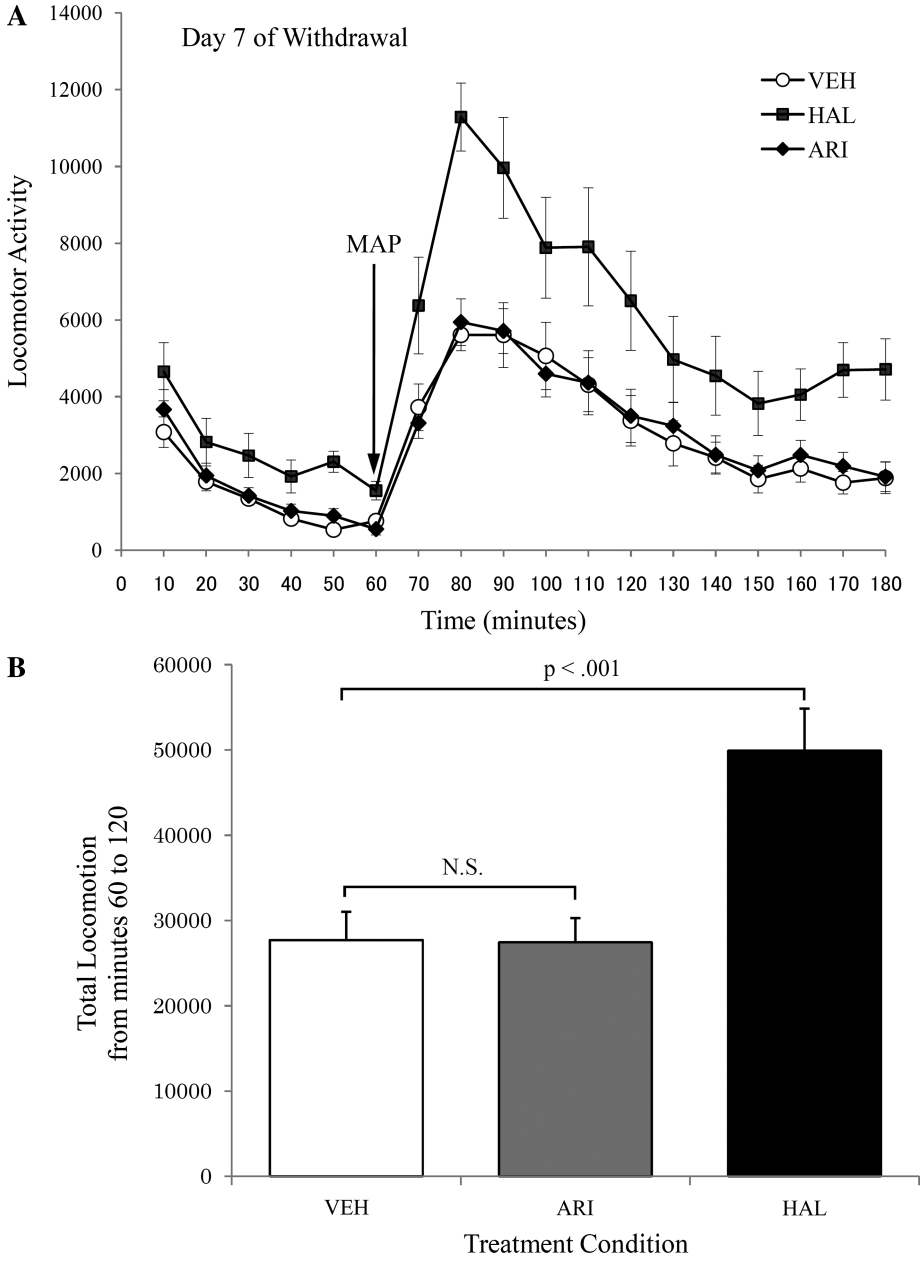

Fig. 2. The effects of chronic treatment with haloperidol (0.75 mg/kg/d, HAL), aripiprazole (1.5 mg/kg/d, ARI), or vehicle (VEH) on the locomotor response to methamphetamine (1.0 mg/kg i.p. injection, MAP). Drugs or vehicle were administered via an implanted minipump for 14 days, and locomotor tests were performed on the seventh day following treatment cessation. In (A), following MAP injection in each group, locomotor activity increased, peaked approximately 40 min after the injection of MAP, and then decreased with time. In (B), the total locomotor response was defined as the total locomotor activity measured for 60 min after MAP injection. The HAL group showed significantly higher activity levels than either the VEH or ARI group, whereas there was no significant difference in the activity levels between the VEH group and ARI group (one-way ANOVA with Bonferroni's tests; $F_2 = 11.44$; $P < .001$ [VEH vs HAL and ARI vs HAL]; $P = .999$ [VEH vs ARI]). $N = 10$ in each group. Error bars indicate the SEM.

group or the ARI group (ie, averaged about 80% more activity), whereas there was no significant difference in locomotor activity in response to MAP between the VEH group and ARI group ($P < .001$, figure 2B).

Experiment 1b: Effects of Chronic Treatment on Striatal D_2 Receptor Binding

In Experiment 1b, we examined the effects of chronic treatment with HAL (0.75 mg/kg/d), ARI (1.5 mg/kg/d), or VEH, delivered to rats via minipump for 14 days, on the density and affinity of striatal D_2 receptors, as determined on the seventh day following treatment cessation. As regards the Bmax value (ie, density) of the D_2 receptors, the HAL group showed a significantly higher Bmax value than either the VEH group or the ARI group (ie, averaged 153% and 126% higher, respectively), whereas there were no significant differences between the VEH group and the ARI group ($P < .001$; figure 3B). On the other hand, as regards the Kd value (ie, affinity) of the D_2 receptors, ANOVA revealed a slightly significant difference among the 3 groups, although post hoc analyses did not show any significant difference between any pairing of the 3 groups studied ($P < .05$; figure 3A).

Experiment 2a: Effects of Chronic Treatment Preceded by Chronic HAL Treatment on Behavioral Sensitivity to MAP

In Experiment 2a, we examined the effects of chronic treatment with HAL (0.75 mg/kg/d), ARI (1.5 mg/kg/d), or VEH, delivered to rats via minipump for 14 days, which had been preceded by a 14-day course of HAL (0.75 mg/kg/d) or VEH treatment, also delivered via minipump, on the locomotor response of rats to MAP (1.0 mg/kg/injection), as measured on the seventh day following treatment cessation. MAP injection induced hyperlocomotion in each group. Hyperlocomotion peaked approximately 20 min after the administration of MAP and then gradually declined during the observation period (figure 4A). As regards the total locomotor activity observed for 60 min after MAP injection, both the HAL-HAL group and the HAL-VEH group showed significantly greater amounts of activity (ie, averaged 120% and 99% more activity, respectively) than the VEH-VEH group, yet there was no significant difference between the VEH-VEH group and the HAL-ARI group in this regard ($P < .05$; figure 4B). Furthermore, the total locomotion value of the HAL-ARI group was significantly lower than that of the HAL-HAL group, ie, by an average of 38%, whereas there was no significant difference between the HAL-HAL group and the HAL-VEH group ($P < .05$; figure 4B). Consequently, the rank order of the total locomotor response to MAP was HAL-HAL > HAL-VEH > HAL-ARI > VEH-VEH.

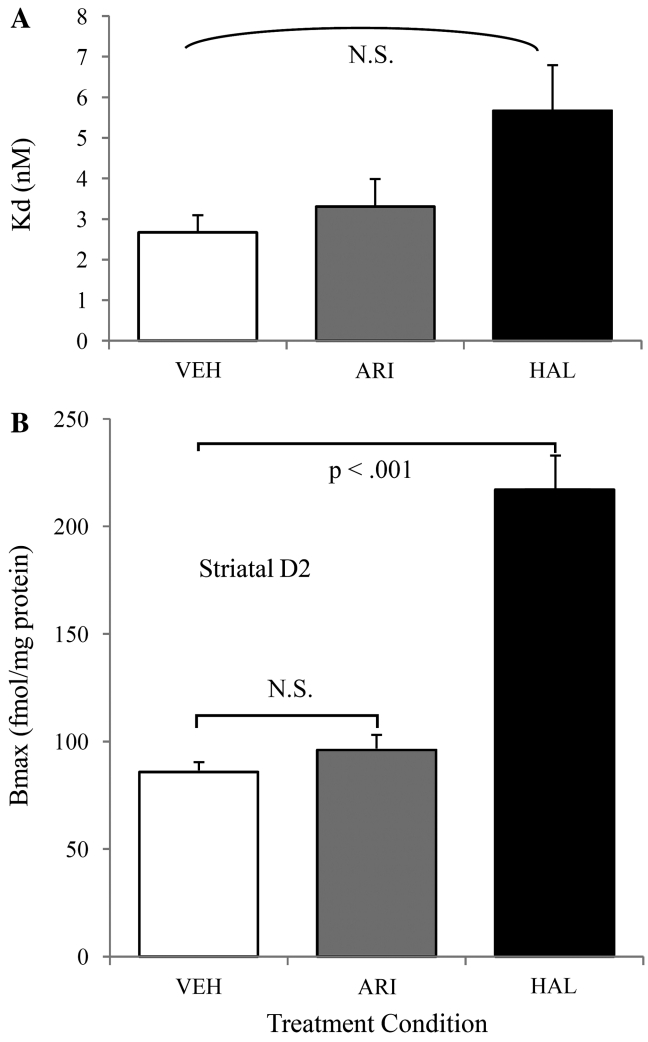

Fig. 3. The effects of chronic treatment with haloperidol (0.75 mg/kg/d, HAL), aripiprazole (1.5 mg/kg/d, ARI), or vehicle (VEH) on Kd (A) and Bmax (B) of striatal D_2 receptors. Drugs were administered via an implanted minipump for 14 days, and the animals were decapitated on the seventh day following treatment cessation. In (A), the Kd value showed significant treatment effects by one-way ANOVA ($P = .048$), although no significant difference was seen in the post hoc analysis by Bonferroni's multiple comparison tests. In (B), the Bmax value of the HAL group was significantly higher than that of either the VEH group or the ARI group, whereas there was no significant Bmax value difference between the VEH group and ARI group (one-way ANOVA with Bonferroni's tests; $F_2 = 50.55$; $P < .001$ [VEH vs HAL and ARI vs HAL]; $P = 1.00$ [VEH vs ARI]). $N = 5$ in each group. The error bars indicate the SEM.

Experiment 2b: Effects of Chronic Treatment Preceded by Chronic HAL Treatment on Striatal D_2 Receptor Binding

In Experiment 2b, we examined the effects of chronic treatment with HAL (0.75 mg/kg/d), ARI (1.5 mg/kg/d), or VEH, delivered to rats via minipump for 14 days, which had been preceded by a 14-day course of HAL (0.75 mg/kg/d) or VEH treatment, also delivered via minipump, on the density and affinity of striatal

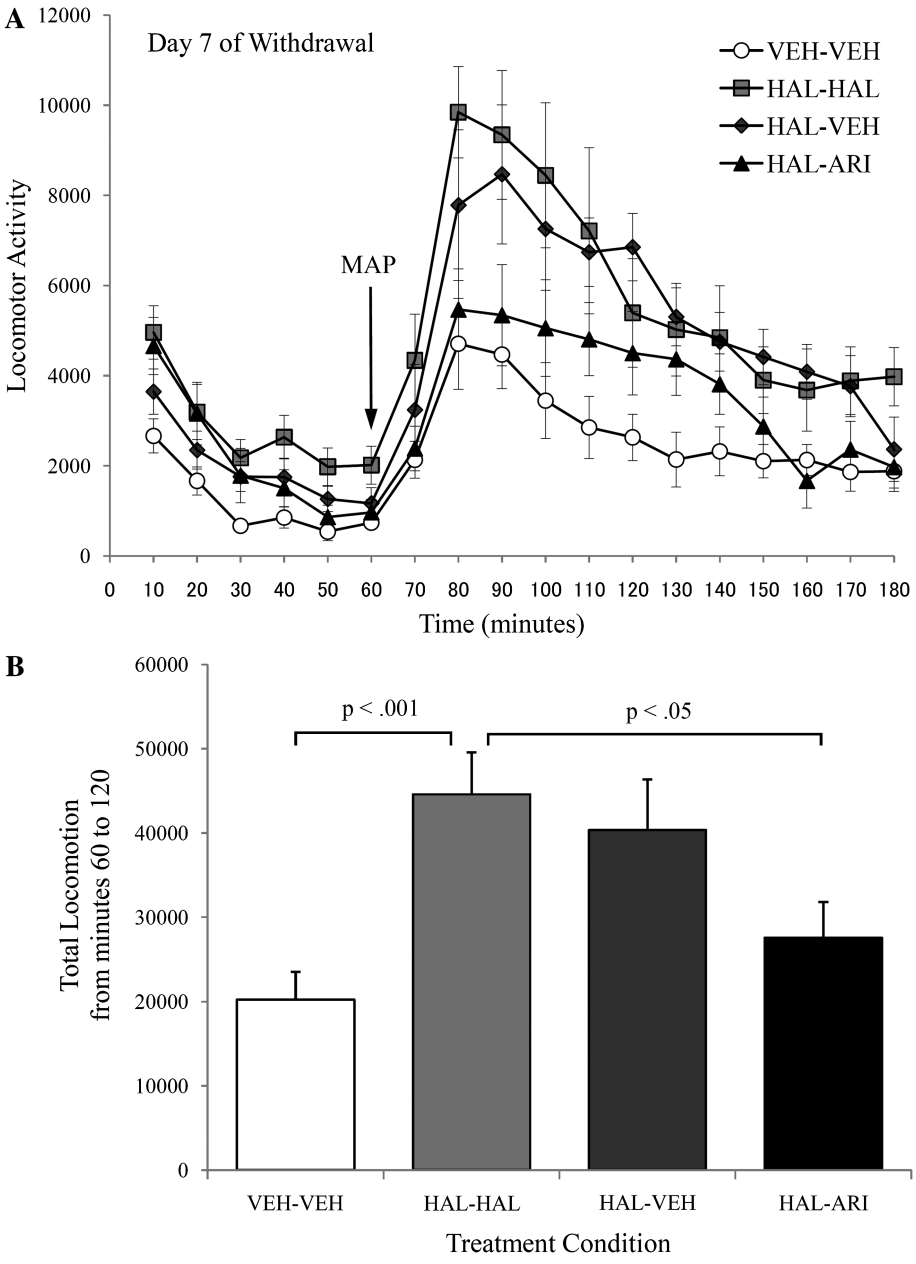

Fig. 4. The effects of chronic treatment with haloperidol (0.75 mg/kg/d, HAL-HAL), aripiprazole (1.5 mg/kg/d, HAL-ARI), or vehicle (HAL-VEH), preceded by chronic treatment with HAL (0.75 mg/kg/d) or VEH (VEH-VEH), on the locomotor response to methamphetamine (1.0 mg/kg i.p. injection, MAP). Either HAL or VEH was administered via an implanted minipump for 14 days and then the minipump was exchanged for a second minipump, by which drugs were administered for an additional 14 days. Locomotor tests were performed on the seventh day following the cessation of the entire 28-day treatment period. In (A), following MAP injection of each group, locomotor activity increased, peaked about 40 min after the MAP injection, and then decreased with time. In (B), the total locomotor response was defined as the total locomotor activity measured for 60 min after MAP injection. The HAL-HAL group and the HAL-VEH group both exhibited significantly higher levels of activity than the VEH-VEH group, whereas there was no significant difference in the activity levels between the VEH-VEH and the HAL-ARI groups (one-way ANOVA with Bonferroni's tests; $F_3 = 5.64$; $P < .01$ [VEH-VEH vs HAL-HAL]; $P < .05$ [VEH-VEH vs HAL-VEH]; $P = 1.00$ [VEH-VEH vs HAL-ARI]). Although there was no significant difference among the HAL-HAL, HAL-VEH, and HAL-ARI groups (one-way ANOVA; $F_2 = 2.97$; $P = .073$), visual inspection of this figure reveals that the total locomotion for the 3 groups could be arranged in the following descending order of magnitude: HAL-HAL > HAL-VEH > HAL-ARI. Analysis of variance with a polynomial contrast (ie, the linear component) revealed a significant linear trend across these 3 groups ($F_1 = 5.49$; $P < .05$). In the post hoc analyses of total locomotor activity, the HAL-ARI group showed significantly less activity than the HAL-HAL group, whereas there was no such significant difference between the HAL-HAL group and the HAL-VEH group (Fisher's least significant difference tests; $P < .05$ [HAL-HAL vs HAL-ARI]; $P = .565$ [HAL-HAL vs HAL-VEH]). The rank ordering of groups in terms of the total locomotor response to MAP was HAL-HAL > HAL-VEH > HAL-ARI > VEH-VEH. $N = 8$ in each group. Error bars indicate the SEM.

D_2 receptors, as determined on the seventh day following treatment cessation. As regards the Bmax value (ie, density) of the D_2 receptors, the HAL-HAL group showed significantly higher Bmax values than either the VEH-VEH or the HAL-ARI group (ie, averaged 240% and 97% higher, respectively), whereas there was no significant difference between the HAL-ARI group and the VEH-VEH group ($P < .05$; figure 5B). Furthermore, the Bmax value in the HAL-ARI group was significantly lower (ie, an average of 49% lower) than that of the HAL-HAL group, whereas no significant differences were observed between the HAL-HAL and the HAL-VEH groups ($P < .05$; figure 5B). Consequently, the rank order of the D_2 density was HAL-HAL > HAL-VEH > HAL-ARI > VEH-VEH, which was the same ranking as seen in the locomotor study. On the other hand, as regards the Kd values (ie, affinity) of the D_2 receptors, there were no significant differences among the 4 groups ($P < .05$; figure 5A).

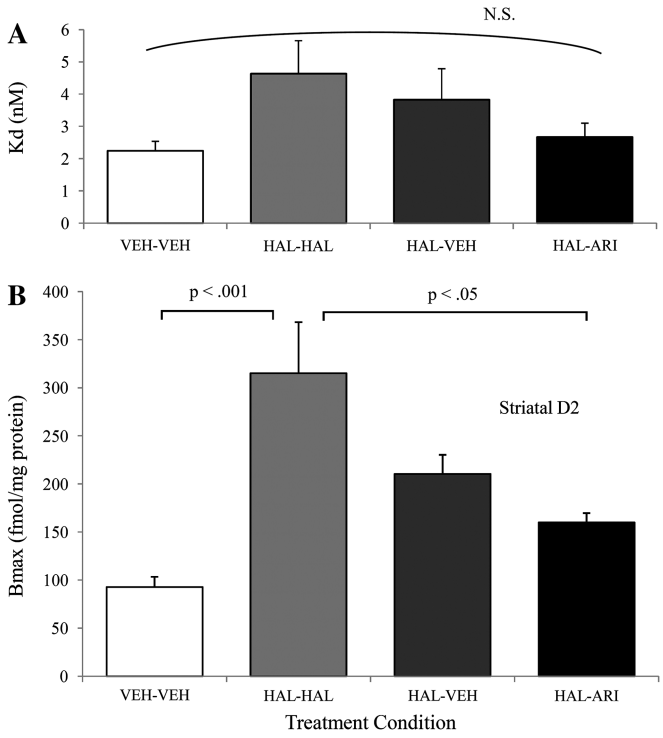

Fig. 5. The effects of chronic treatment with haloperidol (0.75 mg/kg/d, HAL-HAL), aripiprazole (1.5 mg/kg/d, HAL-ARI), or vehicle (HAL-VEH), preceded by chronic treatment with HAL (0.75 mg/kg/d) or VEH (VEH-VEH), on Kd (A) and Bmax (B) of striatal D_2 receptors. Either HAL or VEH was administered via an implanted minipump for 14 days and then the minipump was exchanged for a second minipump, by which drugs were administered for an additional 14 days. The animals were decapitated on the seventh day following the cessation of the entire 28-day treatment period. In (A), there was no significant difference in the Kd value of any of the groups (one-way ANOVA; $F_3 = 2.13$; $P = .150$). In (B), the Bmax value of the HAL-HAL group was significantly higher than that of either the VEH-VEH group or the HAL-ARI group (one-way ANOVA with Bonferroni's tests; $F_3 = 10.33$; $P < .001$ [HAL-HAL vs VEH-VEH]; $P < .05$ [HAL-HAL vs HAL-ARI]). There was also a significant difference between Bmax values among the HAL-HAL, HAL-VEH, and HAL-ARI groups (one-way ANOVA; $F_2 = 5.72$; $P < .05$). In the post hoc analyses on the Bmax value, the HAL-ARI group had a significantly lower value than that of the HAL-HAL group, whereas there was no significant difference between the Bmax values of the HAL-HAL group and the HAL-VEH group (Bonferroni's tests; $P < .05$ [HAL-HAL vs HAL-ARI]; $P = .156$ [HAL-HAL vs HAL-VEH]). The rank ordering of groups in terms of D_2 density was HAL-HAL > HAL-VEH > HAL-ARI > VEH-VEH. $N = 4$ in each group. Error bars indicate the SEM.

Discussion

In the present study, we investigated the effects of chronic treatment with minipump-administered HAL, ARI, or VEH on the sensitivity of rats to dopamine, as measured by the locomotor response to MAP and the density of striatal D_2 receptors on the seventh day following treatment cessation. Chronic treatment with HAL significantly increased the rats' locomotor response and the striatal D_2 density compared with the values observed after chronic treatment with either VEH or ARI. Moreover, there were no significant differences between the VEH and ARI groups in terms of locomotor response or D_2 density. We also investigated the effects of chronic treatment with HAL, ARI, or VEH following chronic treatment with HAL or VEH on locomotor response and D_2 receptor density. The ANOVA analysis indicated the same rank ordering of groups in terms of either locomotor response or D_2 receptor density, ie, HAL-HAL > HAL-VEH > HAL-ARI > VEH-VEH. These results indicate that chronic treatment with HAL induces dopamine supersensitivity, which is retained for an extended period of time, and is exacerbated by additional HAL treatment. In contrast, chronic treatment with ARI does not induce dopamine supersensitivity, and it reduces the supersensitivity induced by the preceding chronic treatment with HAL.

In order to investigate the effects of chronic antipsychotic treatment, we implanted rats with an Alzet osmotic minipump, which enabled the continuous administration of drugs at a constant rate. It has been reported that a protocol of either single or twice-daily injection, such as that adopted in most previous studies, may not suffice as a preclinical model because the half-life of antipsychotic agents is, on average, 4 to 6 times faster in rodents than in humans.[20] For instance, the half-life of HAL is 1.5 h in rodents vs 12-36 h in humans[21,22] and that of ARI is 1.9-2.2 h in rodents vs 47-68 h in humans.[23,24] Kapur et al[20] suggested that only when doses 5 times higher than the optimal single injection were administered by minipump were clinically comparable D_2 occupancies obtained. Thus, the present study protocol serves as an appropriate animal model of chronic antipsychotic treatment.

In the present study, we found that chronic treatment with ARI did not induce behavioral supersensitivity, which result may have been due to the maintenance of

stable striatal D_2 receptor density, in accord with the findings of a previous study.[25] Interestingly, we also observed that chronic treatment with ARI reduced the dopamine supersensitivity previously induced by chronic HAL treatment, as determined based on both behavioral testing and D_2 receptor density. In other words, ARI left baseline dopamine sensitivity intact in drug-naive rats, while it reduced sensitivity in rats that had already developed supersensitivity. Although it was already known that chronic exposure to agonists often induces desensitization that correlates with a decrease in the number of targeted receptors,[26] ARI did not induce desensitization in drug-naive rats. One explanation for these results could be related to compensatory systems of dopamine neurotransmission. Although it is still controversial whether ARI is a D_2 receptor partial agonist,[27–29] ARI is thought to possess some dopamine agonistic activity.[30] Hence, in drug-naive rats, ARI allows for natural dopaminergic neurotransmission, and such compensatory functioning may not be involved. On the other hand, in supersensitive rats, ARI yields excessive dopaminergic neurotransmission due to increased D_2 receptor density, and thus compensatory systems may be induced, which in turn would reduce D_2 receptor density, as suggested in the present study. In other words, ARI may stabilize sensitivity to dopamine by regulating compensatory systems of dopamine neurotransmission.

Chronic treatment with D_2-antagonistic antipsychotics in some cases induces dopamine supersensitivity, which may cause supersensitivity psychosis and may ultimately be related to treatment-resistant schizophrenia. In fact, it has been estimated that more than half of treatment-resistant schizophrenia cases may be related to supersensitivity psychosis.[31] The results of the present study suggest that chronic ARI administration may reduce the risk of supersensitivity psychosis, which might be related to a lower rate of rehospitalization. Although a transient worsening of psychosis can appear in certain supersensitized patients due to relatively excessive agonistic effects,[32] ARI may be a helpful agent for patients with treatment-resistant schizophrenia by reducing excessive sensitivity to dopamine.

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