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Short Communication

Regulation of Type 1 Inositol 1,4,5-Triphosphate Receptor by Dopamine Receptors in Cocaine-Induced Place Conditioning

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ABSTRACT Recent study shows that type 1 inositol-1,4,5-triphosohate receptors (IP_3Rs) may be involved in amphetamine-induced conditioned preference, but little is known about its role in psychological dependence on cocaine. This study investigated the role and regulation of IP_3R-1 in mice with cocaine-induced place preference. The cocaine-induced place preference was dose-dependently inhibited by intracerebroventricular pretreatment with IP_3R antagonists, 2-aminophenoxyethane-borate (2-APB), and xestospongin C. The levels of IP_3R-1 in the frontal cortex and nucleus accumbens of cocaine-conditioned mice significantly increased, which was completely abolished by SCH23390 and sulpiride, selective dopamine D1 and D2 receptor antagonists, respectively. These findings suggest that IP_3R-1-mediated intracellular signaling pathway may play an important role in the development of cocaine-induced place preference and that the expression of IP_3R-1 is controlled by both dopamine D1 and D2 receptors in the frontal cortex and nucleus accumbens of mice with cocaine-induced place preference. **Synapse 66:180–186, 2012.**

Cocaine is an illicit psychostimulant that is widely abused throughout the world. One of major brain reward circuitry implicated in the development and expression of addictive behaviors is the mesolimbic dopamine pathway, which comprises the ventral tegmental area with its dopaminergic projection to the nucleus accumbens and medial prefrontal cortex (Nestler, 2005).

Among several modulators of intracellular Ca^{2+} concentration to regulate various neuronal functions such as learning and memory in the central nervous system (CNS; Berridge et al., 2000), inositol-1, 4,5-triphosohate receptors (IP_3Rs) present on the endoplasmic reticulum release Ca^{2+} into intracellular spaces from intracellular Ca^{2+} pools in response to a variety of stimuli. Increased concentration of Ca^{2+} mediated by Ca^{2+}-induced Ca^{2+} release (ClCR) as well as membrane depolarization activates IP_3Rs (Taylor et al., 2009). The complete cDNA sequence of three distinct IP_3R-encoding genes (termed as IP_3R-1, IP_3R-2, and IP_3R-3) has been identified and amino acid sequence of these receptors is highly conserved (60–70% similarity) among these three IP_3R isoforms (Blondel et al., 1993). IP_3R-1 is the major neuronal type of IP_3Rs in the CNS, which is predominantly abundant in cerebellar Purkinje cells, cerebral cortex, CA1 region of hippocampus, basal ganglia, and thalamus (Mikoshiba, 1997). IP3R-2 and 3 are expressed in non-neuronal cells and endothelial cells (Grayson et al., 2004). Furthermore, a recent study suggests that IP3R-1 is considered to be involved in synaptic plasticity and amphetamine-induced conditioned preference in dopaminergic neurons of ventral tegmental area

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(Ahn et al., 2010). However, little is known about responses of IP_3R-1 in psychological dependence on cocaine.

In this study, we examined involvement of IP_3Rs, especially focused on IP_3R-1, and its regulatory mechanism in the CNS of mice with cocaine-induced place preference.

Male ddY mice (8 weeks old; Japan SLC, Hamamatsu, Japan), which were housed in a room maintained at 22 ± 1°C, and 55 ± 0.5% humidity with a 12 h light/dark cycle (light on 8:00 A.M. to 8:00 P.M.) for 1 week prior to the experiments, were used. Food and water were available *ad libitum*. All experiments presented in this study were approved by the Animal Research Committee of Kawasaki Medical School and conducted according to the "Guide for Care and Use of Laboratory Animals" of Kawasaki Medical School that is based on the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996.

Place-conditioning procedure was carried out according to the method reported previously (Kurokawa et al., 2010). The conditioning place preference schedule consisted of three phases (preconditioning test, conditioning and postconditioning test). Preconditioning test (day 1): Before the preconditioning test mice were placed on the border of both compartments and the time mice spent was measured. The time mice spent in each compartment during 900-s session was then recorded automatically using an infrared beam sensor (BS-CPP-MS; BrainSienceldea, Osaka, Japan). The compartment mice spent longer time was defined as the preferred compartment and another compartment was defined as the nonpreferred one. Mice spent in one compartment for more than 600 s were excluded from the experiment. The remaining mice were divided into two groups according to place preference, that is, one group consisted of the mice preferring the black compartment and the other consisted of those preferring the white compartment. The baseline preference in each test group for the black and white compartments was ~50%. With such biased assignment, the mice were conditioned in their nonpreferred compartment (drug-paired compartment).

Conditioning test (days 2–7): After the preconditioning test, conditioning sessions were carried out. During this test, mice administered with cocaine (Shionogi, Osaka, Japan) were conditioned in the nonpreferred compartment (drug-paired compartment) and those administered with saline were placed in the preferred compartment (saline-paired compartment). Mice received for three cocaine-paired sessions (days 2, 4, and 6 or 3, 5, and 7) and three saline-paired sessions (days 3, 5, and 7 or 2, 4, and 6), respectively. That is, on days 2, the mice were placed in the cocaine-paired compartment for 1 h immediately after s.c. injection of cocaine (10 mg/kg) or placed in the saline-paired compartment immediately after s.c. injection of saline, and on alternative day (days 3) mice were conditioned in the saline-paired compartment with saline injection or in the cocaine-paired compartment with cocaine treatment, respectively. Such cycle of conditioning was carried out for 6 days. Each of vehicle, 2-aminophenoxyethane-borate (2-APB; a nonselective inhibitor for IP_3Rs; 0.3, 1, 3 nmol/mouse, Sigma-Aldrich, St. Louis, MO), xestospongin C (a nonselective inhibitor for IP_3Rs; 10, 30, 100 pmol/mouse, Sigma-Aldrich), SCH23390 (a dopamine D1 receptor antagonist; 30 nmol/mouse, Sigma-Aldrich), or sulpiride (a dopamine D2 receptor antagonist; 30 nmol/mouse, Sigma-Aldrich) was i.c.v. administered 30 min before s.c. treatment with cocaine (10 mg/kg) or saline. 2-APB, xestospongin C, and sulpiride were dissolved in 10% dimethyl sulfoxide in saline.

Postconditioning test (day 8): On the 8th day after the final conditioning session (day 7), the postconditioning test identical to the preconditioning test was preformed for 900 s. The preference for the drug-paired place was expressed as the mean difference between the duration spent in it during the preconditioning and postconditioning tests. In this study to check dose-response of cocaine-induced place preference to 2-APB and xestospongin C, one mouse was administered one concentration of each drug.

Intracerebroventricular (i.c.v.) administration was carried according to the previous report (Kurokawa et al., 2010). A 2-mm double-needle (tip: 27 G × 2 mm and base: 22 G × 10 mm; Natsume Seisakusho, Tokyo, Japan) attached to 25-mL Hamilton microsyringe was inserted into the unilateral injection site of mice lightly anesthetized with diethyl ether. I.c.v. injection of Vehicle, SCH23390, sulpiride, 2-APB, and xestospongin C were repetitively icv injected into the same site through a small guide hole that was pierced into the skull 2 days before the first injection. The volume of drug solution injected was 4 μL/mouse.

Locomotor activity of mice was measured by an animal-movement analysis system (Actimo-100 system, Shintechno, Fukuoka, Japan), which consists of a rectangular enclosure (30 × 20 cm^2) with a side wall equipped with photosensors at 2-cm intervals as described previously (Kurokawa et al., 2011). Total activity counts in each 10-min segment were automatically recorded for 30 min prior to the injection of and for 30 min after i.c.v. administration of vehicle, SCH23390 (30 nmol/mouse), sulpiride (30 nmol/mouse), 2-APB (3 nmol/mouse), and xestospongin C (100 pmol/mouse).

To minimize the effects of arousal and stress, mice were handled gently and exposed to the testing site several times before measurements as described previously (Narita et al., 2008). Catalepsy was evaluated by placing the animal with both forelegs over a horizontal bar elevated 5 cm from the floor. The time (s)

for which the mouse maintained this position was recorded for up to 60 s. Catalepsy was considered to be finished when the forepaw touched the floor or when the mouse climbed on the bar.

Immediately after the postconditioning test, the animal was decapitated and the nucleus accumbens with its surrounding tissues in the limbic forebrain and frontal cortex were dissected on an ice-cold glass plate. The dissection of the brain tissues for protein analysis and the procedure for electrophoresis were carried out according to the method reported previously (Kurokawa et al., 2010). For immunoblot detection of separated proteins, the membrane was incubated overnight at 4 C with primary antibodies against IP_3R-1 (rabbit polyclonal anti-IP_3R-1, Millipore Bioscience Research Reagents, Temecula, CA) diluted 1:1000 in phosphate-buffered saline (PBS) containing 5% nonfat dried milk and then further incubated for 2 h at room temperature with horseradish peroxidase-conjugated goat anti-rabbit IgG (Southern Biotechnology Associates, Birmingham, AL) diluted 1:5000 in PBS containing 5% nonfat dried milk. Finally, separated proteins were detected by chemiluminescence detection (ECL) reagents (GE Healthcare UK, Buckinghamshire, UK).

Statistical analysis was performed using Prism 5 (Graph Pad). Each of data is presented as the mean ± SEM. The statistical significance of differences between groups was assessed with a one-way and two-way ANOVA test followed by Bonferroni multiple comparisons test or Dunnett's post hoc test where appropriate. A level of probability of 0.05 or less was considered to be significant.

In order to examine the role of IP_3Rs in the development of cocaine-induced place preference, we investigated the effect of 2-APB and xestospongin C reported, IP_3R antagonists (Tumelty et al., 2011), on cocaine-induced place preference using conditioned place preference paradigm. Cocaine-induced place preference was significantly suppressed by i.c.v. pretreatment with 2-APB and xestospongin C in a dose-dependent manner ($F_{(5,54)} = 28.52$, $P < 0.0001$, Fig. 1A; $F_{(5,54)} = 12.77$, $P < 0.0001$, Fig. 1B). 2-APB or xestospongin C alone showed no effects on place preference (Fig. 1A, B). In order to examine whether antagonists for IP_3Rs and DRs themselves produce sedation to modify animal behavior, we examined locomotor activity after i.c.v. treatment with these antagonists. The pretreatment with SCH23390 (30 nmol/mouse), sulpiride (30 nmol/mouse), 2-APB (3 nmol/mouse), and xestospongin C (100 pmol/mouse) showed no significant changes of locomotor activity ($F_{(4, 35)} = 1.215$, $P = 0.32$, Fig. 1C). These results are considered to exclude the possibility that the suppression of cocaine-induced place preference by antagonists for IP_3Rs and DRs is due to the decrease of motor activity. Furthermore, we also investigated whether the pretreatment with SCH23390, sulpiride, 2-APB, and xestospongin C could provoke catalepsy. Catalepsy values were obtained at 15, 30, and 45 min after i.c.v. administration of SCH23390 (30 nmol/mouse), sulpiride (30 nmol/mouse), 2-APB (3 nmol/mouse), and xestospongin C (100 pmol/mouse). The duration of cataleptic postures were not changed by a single i.c.v.-injection of SCH23390, sulpiride, 2-APB, and xestospongin C (Fig. 1D). Statistical analysis was performed with two-way ANOVA followed by Bonferroni test [SCH23390; interaction between treatment and time: $F_{(3,56)} = 0.95$, no significant (NS); effect of treatment, $F_{(1,56)} = 6.44$, $P < 0.05$; effect of time, $F_{(3,56)} = 0.95$, NS; sulpiride; interaction between treatment and time: $F_{(3,56)} = 2.67$, NS; effect of treatment, $F_{(1,56)} = 2.67$, NS; effect of time, $F_{(3,56)} = 2.67$, NS].

For further investigation which subtypes of dopamine receptors, dopamine D1 and D2 receptors (D1 and D2DRs), have regulatory activity on IP_3R-1 expression in the brain of cocaine-conditioned mice, effects of SCH23390 and sulpiride on the increased in IP_3R-1 in the frontal cortex and nucleus accumbens of cocaine-conditioned mice was examined. Increased expression of IP_3R-1 in the frontal cortex and nucleus accumbens by cocaine was completely abolish by i.c.v. injection of SCH23390 and sulpiride at the dose that significantly suppressed the cocaine-induced place preference (frontal cortex; $F_{(3,12)} = 20.76$, $P < 0.01$, nucleus accumbens; $F_{(3,12)} = 16.05$, $P < 0.01$, Fig. 2A; frontal cortex; $F_{(3,12)} = 14.88$, $P < 0.01$, nucleus accumbens; $F_{(3,12)} = 23.27$, $P < 0.001$, Fig. 2B). The cocaine-induced place preference was suppressed by i.c.v. pretreatment with SCH23390 and sulpiride ($F_{(5,42)} = 20.93$, $P < 0.0001$, Fig. 2C).

We also examined the changes of acquisition of cocaine-induced place preference and expression of IP_3R-1 in one and two cocaine conditioning sessions. Cocaine-induced place preference in two cocaine conditioning sessions, whereas it failed to induce place preference in the one cocaine conditioning session (Fig. 2D). Western blot analysis showed significant increases of IP_3R-1 in the frontal cortex and nucleus accumbens in mice with two cocaine conditioning sessions. However, one cocaine conditioning session induced no changes of IP_3R-1 expression (Fig. 2E).

This study demonstrated that a new pathway participating in the cocaine-induced upregulation of IP_3R-1, which can also lead to the expression of cocaine-induced place preference, is mediated by activation of both D1 and D2DRs. I.c.v. administration of 2-APB and xestospongin C significantly suppressed place preference by cocaine. Furthermore, it showed that significant increase of IP_3R-1 protein in the frontal cortex and nucleus accumbens of the cocaine-conditioned mice. These results suggest that IP_3R-1 may be an important player involved in the development of cocaine-induced place preference.

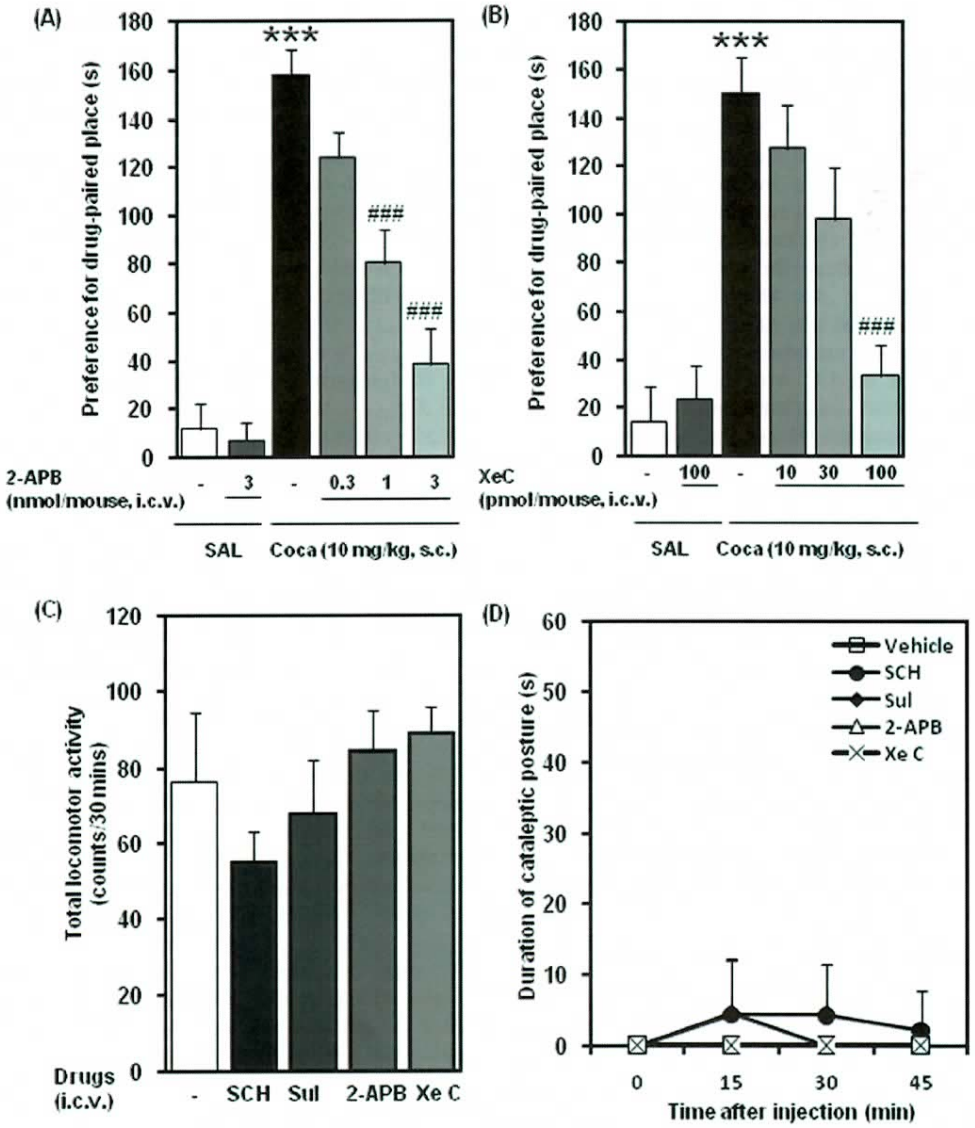

Fig. 1. Effects of IP3R-1 antagonists and dopamine receptor antagonists on mouse behaviors. (**A**) Effect of 2-APB and (**B**) xestospongin C on cocaine-induced place preference. 2-APB (0.3, 1, or 3 nmol/mouse) and xestospongin C (XeC; 10, 30, or 100 pmol/mouse) were i.c.v. administered 30 min before subcutaneous treatment with saline (SAL) and cocaine (Coca; 10 mg/kg). Each of the data represents the mean ± S.E.M. obtained from 10 animals. $^{***}P < 0.001$ vs. vehicle-SAL group, $^{###}P < 0.001$ vs. vehicle-Coca group (Dunnett's test). (**C**) Effects of SCH23390, sulpiride, 2-APB, and xestospongin C on mouse locomotion activity. Total locomotor activity was counted for 30 min after i.c.v. administration of vehicle, SCH23390 (30 nmol/mouse), sulpiride (30 nmol/mouse), 2-APB (3 nmol/mouse), and xestospongin C (100 pmol/mouse). Each column represents the mean ± S.E.M. of eight mice. (**D**) Time-course of expression of catalepsy after administration of SCH23390, sulpiride, 2-APB, and xestospongin C in mice. Catalepsy values were obtained at 15, 30, and 45 min after i.c.v. administration of vehicle, SCH23390 (SCH; 30 nmol/mouse), sulpiride (Sul; 30 nmol/mouse), 2-APB (3 nmol/mouse) and xestospongin C (Xe C; 100 pmol/mouse). Each column represents the mean ± S.D. of eight mice (two-way ANOVA followed by Bonferroni's).

In this study, the cocaine-induced place preference was suppressed by i.c.v. pretreatment with SCH23390 and sulpiride. These data therefore suggest a possibility that there may be a functional and/or regulatory relationship between the expression of IP_3R-1 involved in place preference of cocaine and DRs. As demonstrated in this study, administration of SCH23390 and sulpiride resulted in significant inhibition of the increased expression of IP_3R-1 in the frontal cortex and nucleus accumbens evoked by cocaine. In addition, as demonstrated above, these DR antagonists showed no inhibitory effects on motor activity and cataleptic behavior of mice when measured by locomotor assay and horizontal bar test. Based on our

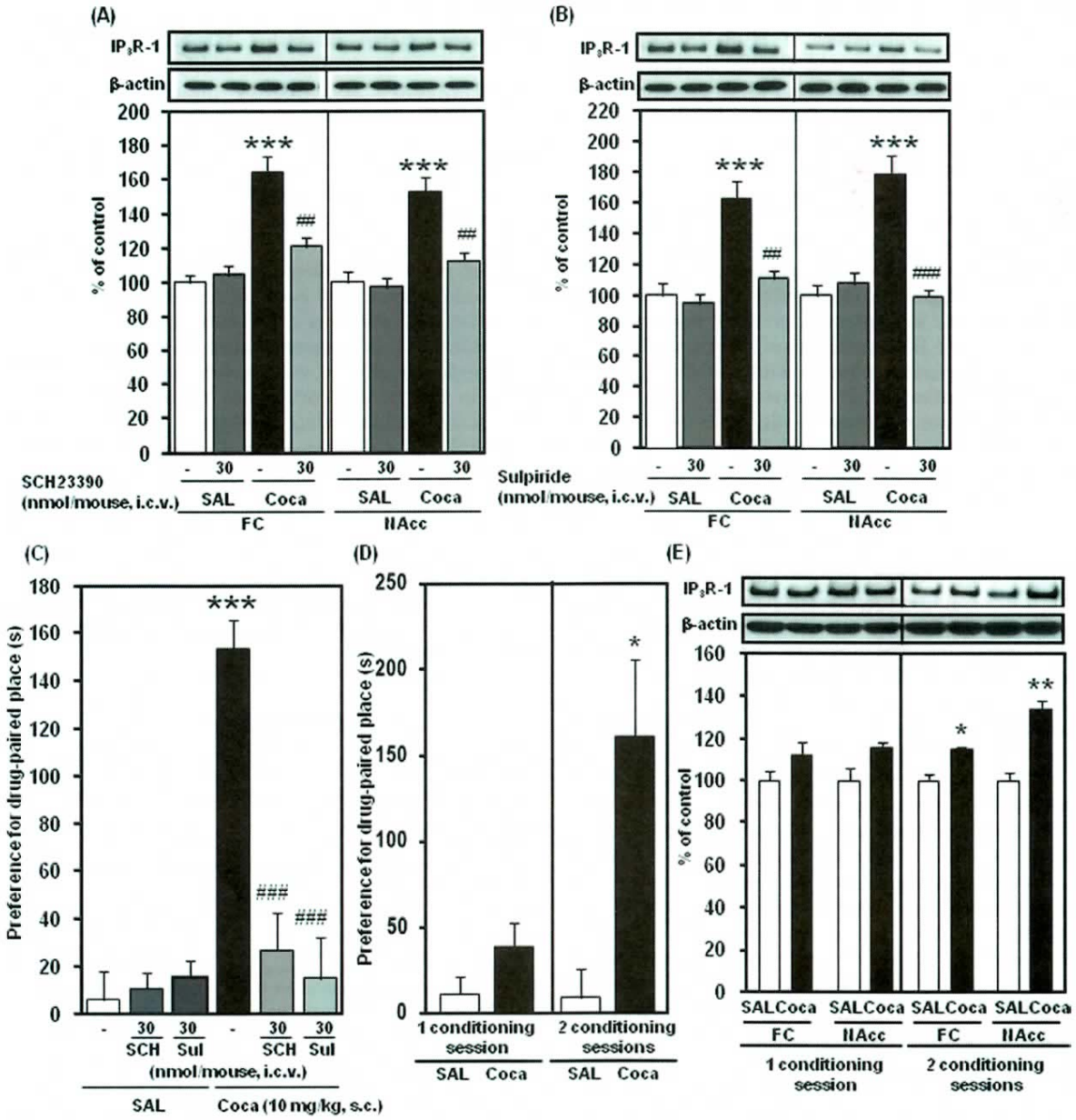

Fig. 2. Effects of SCH23390 and sulpiride on cocaine-induced increase in expression of IP_3R-1 in the frontal cortex and nucleus accumbens and on cocaine-induced place preference in mice. Mice were subcutaneously injected with saline (SAL) or cocaine (Coca) as described in the figure legend of Figure 1. FC, frontal cortex; NAcc, nucleus accumbens. (**A**) Effect of SCH23390 and sulpiride on cocaine-induced increase in expression of IP_3R-1 in the frontal cortex and nucleus accumbens of mice. SCH23390 (30 nmol/mouse) and sulpiride (30 nmol/mouse) 30 min before subcutaneous cocaine (10 mg/kg) or saline injection. The membrane fractions for measuring IP_3R-1 were prepared 24 h after the last conditioning with cocaine or saline. Each column represents the mean + S.E.M. of four mice, each of which was carried out in duplicate. $^{***}P < 0.001$ versus Veh-SAL (Bonferroni's test). $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs. Veh-Coca group (Bonferroni's test). (**C**) Effects of SCH23390 and sulpiride on cocaine-induced place preference in mice. SCH23390 (SCH; 30 nmol/mouse) and sulpiride (Sul; 30 nmol/mouse) were i.v.c. administered 30 min before subcutaneous treatment with saline (SAL) and cocaine (Coca; 10 mg/kg). Each of the data represents the mean ± S.E.M. obtained from eight animals. $^{***}P < 0.001$ vs. vehicle-SAL group, $^{\#\#\#}P < 0.001$ vs. vehicle-Coca group (Bonferroni's test). (**D**) Cocaine-induced place preference in shorter cocaine conditioning sessions. Mice were subcutaneously treated with saline or cocaine (10 mg/kg, s.c.; once per every other day) for 2 or 4 days (during one and two conditioning sessions). Each of the data represents the mean + S.E.M. obtained from eight animals. $^{*}P < 0.05$ vs. SAL (Student's *t*-test). (**E**) IP_3R-1 protein expression in the frontal cortex and nucleus accumbens of mice in shorter cocaine conditioning sessions. The procedure to administer saline and cocaine was same as described above. The membrane fractions for measuring IP_3R-1 were prepared 24 h after the last conditioning (one and two conditioning session) with cocaine or saline. Each column represents the mean + S.E.M. of four mice, each of which was carried out in duplicate. $^{*}P < 0.05$, $^{**}P < 0.01$ versus SAL (Student's *t*-test).

results and the previous data, it is reasonable to consider that the upregulation of IP_3R-1 is mediated through activation of D1 and D2DRs during cocaine intermittent treatment producing place preference.

It has been documented that the blockade of D1 DRs by their antagonists significantly attenuated place preference induced by cocaine (Baker et al., 1998; Nazarian et al., 2004). Conversely, antagonism of D2 DR has no effects on cocaine conditioned place preference (Nazarian et al., 2004). Similarly, methamphetamine-induced place preference was also blocked by D2 DR antagonists (Mizoguchi et al., 2004). On the other hand, several studies have demonstrated that D1 and D2 DRs antagonists have no effects on acquisition of cocaine-induced conditioned place preference (Tzschentke, 2007). However, at present it is difficult to explain the reasons why such difference in the role of DRs in the acquisition of place preference.

We examined the relationship between the acquisition of cocaine-induced place preference and the expression of IP_3R-1 in one and two cocaine conditioning sessions. The upregulation of IP_3R-1 proteins was observed with shorter cocaine-conditioning regimen (two cocaine conditioning sessions) than three sessions, though one conditioning session was not able to induce IP_3R-1 expression. These results suggest that the upregulation of IP_3R-1 is functionally related to the acquisition of cocaine-induced place preference.

DRs are grouped into two subfamilies, D1- and D2-like receptors (Missale et al., 1998). Opposing influences of D1 and D2DR activation on cAMP-dependent signaling have been reported in many studies with D1DRs acting through stimulatory Gs-like $G\alpha_{olf}$, and D2DRs through inhibitory $G\alpha i/o$ protein. Despite these opposing actions on cellular signaling to protein kinase A (PKA) via cAMP, both D1 and D2DRs can similarly mediate reinforcing signals of abuse (Sershen et al., 2010). A recent investigation demonstrates interesting data that $G\beta\gamma$ provides a possible mechanism to explain signals by these receptors to produce rewarding effect of drugs of abuse (Inoue et al., 2007). That is, $G\alpha s$- from the Gs-coupled D1DRs and $G\beta\gamma$ subunits from $G\alpha i/o$-coupled D2DRs can act cooperatively to activate PKA signaling, which may be considered to support the results that the inhibition of either of the receptors fails to stimulate IP_3R-1 expression. However, exact mechanisms of regulatory effects of D1 and D2DRs on IP_3R-1 expression are not clear at present.

This study demonstrates that the increase of IP_3R-1 in the frontal cortex and nucleus accumbens of mice with intermittent administration of cocaine is significantly suppressed by SCH23390 and sulpiride, which indicates that the expression of IP_3R-1 is positively regulated by dopamine D1 and D2 receptors. However, as these effects of SCH23390 and sulpiride were induced by their i.c.v. administration, but not direct injection into the frontal cortex and/or the nucleus accumbens, global dopamine D1 and D2 receptor blockade could be produced to modify the functions of reward circuitry activated by intermittent cocaine administration in other parts of the brain except of two brain regions described above. Therefore, it is noted that the effect of i.c.v. injection of SCH23390 and sulpiride on IP_3R-1 expression in the frontal cortex and nucleus accumbens demonstrated here may be due to possible indirect effects mediated through modified function of other brain regions projecting to the frontal cortex and nucleus accumbens, although such possibility remains to be elucidated.

In conclusion, we demonstrated here that intermittent treatment of mice with cocaine increased IP_3R-1 levels in the frontal cortex and nucleus accumbens. The cocaine-induced place preference was suppressed by 2-APB and xestospongin C. The increased expression of IP_3R-1 in these brain regions of cocaine-conditioned mice were completely inhibited by the blockade of D1 and D2DRs. These findings suggest that IP_3R-1 with an important role in the development of cocaine-induced place preference is regulated by D1 and D2DRs and those antagonists of IP_3R may be possible candidates as therapeutics to treat and/or prevent cocaine dependence.

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