7-Hydroxy-N,N’-di-n-propyl-2-aminotetraline, a Preferential Dopamine D₃ Agonist, Induces c-fos mRNA Expression in the Rat Cerebellum

Tadashi Ishibashi*, Junko Wakabayashi# and Yukihiro Ohno

Discovery Research Laboratories I, Research Division, Sumitomo Pharmaceuticals Co., Ltd., 3-1-98 Kasugadake-naka, Konohana-ku, Osaka 554-0022, Japan

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ABSTRACT—The effects of a preferential dopamine D₃ receptor agonist 7-hydroxy-N,N’-di-n-propyl-2-aminotetralin (7-OH-DPAT) on c-fos mRNA expression in the rat cerebellum were studied by Northern blot analysis. 7-OH-DPAT (0.003 – 10 mg/kg, s.c.) markedly increased c-fos mRNA expression in the cerebellum, while its effects in the striatum, nucleus accumbens, and frontal cortex were negligible. The effect of 7-OH-DPAT on cerebellar c-fos mRNA expression was dose-dependent and statistically significant at doses of 0.3 mg/kg or more. A preferential dopamine D₂ agonist, bromocriptine (0.01 – 3 mg/kg, s.c.), failed to increase c-fos mRNA expression in the cerebellum. The effect of 7-OH-DPAT was blocked by two dopamine D₂-type-receptor antagonists, haloperidol and perospirone, but not the D₁-type-receptor antagonist SCH23390. Furthermore, dopaminergic denervation by 6-hydroxydopamine did not inhibit but rather potentiated the 7-OH-DPAT-induced c-fos mRNA expression in the cerebellum. These findings suggest that 7-OH-DPAT increases c-fos mRNA expression in the rat cerebellum, probably through postsynaptic dopamine D₃ receptor activation.

Keywords: 7-OH-DPAT, c-fos, Northern blot, Cerebellum, Dopamine D₃ receptor

The dopamine receptors were originally classified as D₁ or D₂ based on their differing affinities for various ligands and linkage to intracellular signaling pathways. Recent advances in molecular biology have revealed additional dopamine receptor subtypes. The D₂ and D₃ receptors, which have homology and similar pharmacological profiles to the D₂ receptor, are considered to belong to the D₂-type-receptor family. The D₃ receptor, which is homologous to the D₁ receptor, belongs to the D₁-type-receptor family (1). Of the different dopamine receptor subtypes, the dopamine D₁ receptor has been of particular interest, because it has a unique anatomical distribution, i.e., its mRNA is located mainly in the limbic brain areas (e.g., nucleus accumbens, island of Calleja and olfactory tubercle), hypothalamus and cerebellum (2 – 4). Pharmacological studies and those using genetically manipulated mice have revealed that the dopamine D₃ receptor regulates locomotor activity, yawning behavior and body temperature (5, 6); however, the biochemical events underlying its physiological role are still to be determined. In addition, although certain cellular events mediated by the dopamine D₃ receptor have been reported in transfected cell lines expressing the recombinant receptor (e.g., inhibition of adenylyl cyclase, increased extracellular acidification, alterations in Ca²⁺ and K⁺ currents, and the induction of c-fos gene expression (7 – 10)), in vivo cellular responses to dopamine D₃ receptor activation have not been demonstrated.

The expression of c-fos, an immediate early gene, is known to be a useful in vivo marker for changes in neuronal activity, and it is widely used in mapping cellular signal transduction in the brain (11). In fact, a variety of stimuli, both biological (e.g., pain, stress and seizure) and pharmacological (e.g., activation and inhibition of various receptor systems) can increase c-fos mRNA expression or Fos-like immunoreactivity in the specific areas of the brain that respond to the stimulus (12, 13). In the present study, to determine whether activation of the dopamine D₃ receptor affects c-fos mRNA expression in the rat brain, we studied the effect of a preferential dopamine D₃ receptor agonist 7-hydroxy-N,N’-di-n-propyl-2-aminotetralin (7-OH-DPAT) (14, 15) on the levels of c-fos mRNA expression in the frontal cortex, nucleus accumbens, striatum and cerebellum.

*Corresponding author. FAX: +81-6-6466-5182
E-mail: isibasi@sumitomopharm.co.jp
#Present address: Center for Tsukuba Advanced Research Alliance, University of Tsukuba, Tennoudai 1-1-1, Tsukuba, Ibaragi 305-0006, Japan
MATERIALS AND METHODS

Animals and drug treatments
Male Sprague-Dawley rats (Charles River Japan, Inc., Yokohama) weighing 170–230 g were injected with vehicle (saline; 5 ml/kg, s.c.), 7-OH-DPAT (0.003–10 mg/kg, s.c.) or bromocriptine (0.01–3 mg/kg, s.c.). Haloperidol (0.3–3 mg/kg), perospirone (1–10 mg/kg) or SCH23390 (1 mg/kg) were administered orally 1 h before the 7-OH-DPAT injection. For the dopaminergic denervation experiments, the animals were injected with 6-hydroxydopamine as described previously (16). In brief, the animals were pretreated with desipramine (25 mg/kg, i.p.) and pargyline (40 mg/kg, i.p.), and then injected with 6-hydroxydopamine (370 μg in 10 μl of saline containing 0.1% ascorbic acid) into the lateral ventricle (coordinate, A: 8.2, L: 1.5, H: 6.5). Sham-operated rats were given the vehicle alone, and the animals were used for experiments 6 days after the injection. Striatal dopamine levels were reported to be decreased by more than 97% by this treatment (17).

The 7-OH-DPAT, haloperidol and perospirone were synthesized in our laboratory. Bromocriptine and SCH23390 were purchased from Sigma (St. Louis, MO, USA) and RBI (Natick, MA, USA), respectively. All other chemicals were obtained from commercial sources. 7-OH-DPAT and bromocriptine were dissolved in saline and 0.3% tartaric acid, respectively. Haloperidol, perospirone and SCH23390 were suspended in 0.5% methylcellulose. All drugs were freshly prepared and administered in a volume of 5 ml/kg.

RNA isolation and Northern blot analysis
The animals were killed by decapitation 1 h after the 7-OH-DPAT injection, and the brain was rapidly removed from the skull. The bilateral striata, nucleus accumbens, frontal cortex and cerebellum were dissected out on an ice-cold Petri dish. Total RNA from the tissue was prepared with the AGPC method (18) and stored at −80°C until analysis.

Twenty micrograms of the total RNA was fractionated by electrophoresis on a 1% agarose formaldehyde gel, blotted onto a nylon membrane (Hybond-H’; Amersham, Little Schalfont, UK), and prehybridized in 5 × standard saline citrate buffer (SSC), 40% formamide, 2 × Denhardt’s solution, 1% sodium dodecyl sulfate (SDS), and 100 μg/ml salmon sperm DNA for 2 h at 42°C. Hybridization was carried out at 42°C using as the probe the 4th exon of the human c-fos gene (Takara Shuzou, Kyoto) labeled with [α-32P]dCTP using the random-priming method. Membranes were washed with 0.2 × SSC in 0.1% SDS for 1 h at 55°C and exposed to Kodak KAR-5 film. The levels of c-fos mRNA expression were evaluated by measuring the optical density of the band on film, using an image analyzer (TIF-256R; Toyoojo, Shizuoka).

Data analyses
The results were expressed as means ± S.E.M. of percentages of the control value (vehicle administration). In the 6-hydroxydopamine experiments, the c-fos mRNA levels of the sham-operated rats, which were treated with vehicle alone, were used as the control. The statistical significance of the differences among drug treatments was determined by one-way analysis of variance (ANOVA) followed by a two-tailed Dunnett multicomparsion test or Student’s t-test, as described in the figure legends.

RESULTS

Effect of 7-OH-DPAT and bromocriptine on c-fos mRNA expression in rat brain
Subcutaneous injection of saline had little influence on c-fos mRNA expression in any region of the brain tested. 7-OH-DPAT (0.003–10 mg/kg, s.c.) markedly increased the cerebellar c-fos mRNA expression in a dose-dependent manner (Figs. 1 and 2). The cerebellar c-fos mRNA levels increased to about twice the control levels at 0.03 mg/kg, and the increase was statistically significant at 0.3 mg/kg or more (Dunnett’s test). The time-course experiment revealed that the action of 7-OH-DPAT (3 mg/kg, s.c.) was transient with a maximum effect at 1 h, and c-fos levels completely recovered to the control levels within 4 h (data not shown). In contrast with the cerebellum, 7-OH-DPAT did not have a significant effect on c-fos mRNA expression in the nucleus accumbens or the frontal cortex, except at the highest dose (10 mg/kg). In the striatum, 7-OH-DPAT slightly decreased the levels of c-fos mRNA expression, at 0.03–0.3 mg/kg (Fig. 2).

A preferential dopamine D2 receptor agonist, bromocriptine, failed to increase c-fos mRNA expression in the cerebellum (Fig. 3). At 0.01–3 mg/kg, s.c., it did not affect the c-fos mRNA levels in the cerebellum or the striatum, and it slightly reduced the c-fos mRNA levels in the frontal cortex.

Effect of dopamine antagonists on 7-OH-DPAT-induced c-fos expression in the cerebellum
We next examined the effect of two dopamine D2-type-receptor antagonists, haloperidol and perospirone (19), and the D2-type receptor antagonist SCH23390 on 7-OH-DPAT-induced c-fos expression in the cerebellum. Pretreatment with haloperidol (0.3–3 mg/kg, p.o.) or perospirone (1–10 mg/kg, p.o.) reduced the cerebellar c-fos mRNA expression induced by 7-OH-DPAT (3 mg/kg, s.c.) in a dose-dependent manner. These drugs, at their highest doses, completely abolished the effects of 7-OH-DPAT (Fig. 4). In contrast, SCH23390 given at 1 mg/kg, p.o.,...
Effects of a dopaminergic lesion by 6-hydroxydopamine on 7-OH-DPAT-induced c-fos expression in the cerebellum

We also investigated the effect of dopaminergic denervation by 6-hydroxydopamine on 7-OH-DPAT-induced c-fos expression (Fig. 5). Pretreatment with 6-hydroxydopamine slightly lowered the cerebellar c-fos mRNA expression in vehicle-treated rats, although this change was not statistically significant (Student’s t-test). In the sham-operated group, 7-OH-DPAT (3 mg/kg, s.c.) increased the cerebellar c-fos mRNA expression level to about five times that in vehicle-treated animals. 6-Hydroxydopamine pre-
Treatment did not inhibit but rather increased the 7-OH-DPAT-induced c-fos mRNA expression level in the cerebellum (Fig. 5). The effect of 7-OH-DPAT in the 6-hydroxydopamine-pretreated rats was about threefold higher than in the sham-operated rats, and it was statistically significant (Student’s t-test).

DISCUSSION

The present study demonstrated that a preferential dopamine D₃ agonist 7-OH-DPAT increased c-fos mRNA expression levels in the cerebellum, which expresses the dopamine D₃ receptor (2, 3). This effect was elicited by relatively low doses of 7-OH-DPAT (0.03 mg/kg and more), which are thought to selectively act at the dopamine D₃ receptor (21). In contrast, a preferential dopamine D₂ agonist, bromocriptine, failed to affect c-fos mRNA expression in the cerebellum. In addition, the dopamine D₂-type antagonists, haloperidol and perospirone, but not the D₁-type antagonist SCH23390, completely abolished the 7-OH-DPAT-induced c-fos expression in the cerebellum. Taken together, these data suggest that 7-OH-DPAT increases c-fos mRNA expression in the rat cerebellum via the dopamine D₃ receptor. Additional support for this
idea comes from our preliminary experiments, in which we observed that the increase in c-fos mRNA expression levels induced by 7-OH-DPAT was greater in lobules 9 and 10 than the remaining part of the cerebellum (data not shown). It is reported that these lobules contain high densities of the dopamine D₃ receptors and almost no D₂ receptors (2, 3, 14).

Dopaminergic denervation by 6-hydroxydopamine did not inhibit but rather enhanced the 7-OH-DPAT-induced c-fos mRNA expression in the cerebellum (Fig. 5). This result suggests that the cerebellar c-fos expression did not require presynaptic dopamine release. Moreover, a previous study reported that the inhibitory effect of an intrastratal infusion of 7-OH-DPAT on striatal acetylcholine release is potentiated by lesioning the nigrostriatal dopaminergic neurons, suggesting that the dopamine D₃ receptor regulating the striatal acetylcholine release is hypersensitized by presynaptic denervation (22). Our results are consistent with these findings and suggest that the cerebellar c-fos expression we observed was mediated by the postsynaptic dopamine D₃ receptor and hypersensitized by the presynaptic denervation.

In the present study, 7-OH-DPAT did not cause any increase in c-fos expression in the striatum, nucleus accumbens, or frontal cortex, although these regions express dopamine D₃ receptor mRNA (3). The reason for this regional difference in the effect of 7-OH-DPAT is still uncertain, but two possibilities may account for it. First, since c-fos mRNA is expressed near the nucleus in the neuronal soma, the postsynaptic dopamine D₃ receptor seems to be responsible for the c-fos mRNA expression. However, the dopamine D₃ receptor in the striatum or nucleus accumbens is not only the postsynaptic receptor, but also the presynaptic receptor, which is located at the nerve terminal of dopaminergic neurons where it acts as an autoreceptor to reduce dopamine release in the innervated areas (23). The activation of the presynaptic D₃ receptor by 7-OH-DPAT could inhibit release of endogenous dopamine from the nerve terminal and thereby reduce the stimulation of the postsynaptic D₃ receptor, even if 7-OH-DPAT is a direct postsynaptic agonist. In fact, 7-OH-DPAT at a relatively low dose (0.03–0.3 mg/kg) slightly, but significantly decreased the c-fos mRNA level in the striatum (Fig. 2), which might result from the reduction of striatal dopamine release (23, 24). Secondly, it is possible that there is a regional difference in the intracellular effector system coupled to the dopamine D₃ receptors. As mentioned above, the dopamine D₃ receptor potentially couples to several kinds of intracellular effector systems in transfected cell lines (15). If the neurons in some brain regions do not possess the intracellular mechanisms that are associated with c-fos expression, 7-OH-DPAT would fail to increase c-fos expression in these areas.

It is reported that the other preferential D₃ agonist cis-8-hydroxy-3-(n-propyl)1,2,3a,4,5,9b-hexahydro-1H-benz[e]indole (cis-8-OH-PBZI) induced Fos expression in rat medial prefrontal cortex and shell regions of the nucleus accumbens, contrary to the present study (25). However, compared to 7-OH-DPAT, cis-8-OH-PBZI reportedly shows relatively higher affinity for the D₃ receptor that is involved in the induction of Fos expression in the cortex (26, 27). In addition, the authors used immunohistochemical methods by using anti-Fos antiserum, which potentially detects not only the c-fos gene product, but also the other fos-related antigens. Because of difference of such experimental conditions, further studies are required to elucidate the details.

The functional role of the dopaminergic system in the cerebellum is still unknown. However, recent histological studies demonstrated the presence of dopaminergic innervation in the cerebellum, in that, dopamine-containing fibers originating from the ventral tegmental areas project to each cell layer of the cerebellar lobule (28). In addition, the D₃ receptors as well as the D₂ receptor has also been demonstrated in the cerebellum (29), and the psychomotor stimulant amphetamine has been shown to alter discharge of the cerebellar Purkinje neurons (30). Interestingly, Klitnickenick et al. reported that amphetamine and cocaine, which act as dopaminomimetics, increase c-fos expression in the cerebellum at the same doses that induce hyperactivity in rats (31), suggesting that the cerebellum is a

Fig. 5. The effect of dopaminergic denervation on 7-OH-DPAT-induced c-fos mRNA expression in the cerebellum. For dopaminergic denervation, the animals were pretreated with 6-hydroxydopamine (370 μg/10 μl, i.e.v.) 6 days before the drug treatment. The c-fos mRNA levels are expressed as percentages of the value induced by vehicle in the sham-operated rats. **P<0.01, ***P<0.001: Significantly different from the respective vehicle control (Student’s t-test, n = 4). N.S.: Not significant.
substrate for the motor-stimulant effects of amphetamine and cocaine. Although the implications of the increased c-fos expression in response to 7-OH-DPAT are presently uncertain, our study supports the view that the cerebellum may be one of the target of dopaminergic agents and play a role in part in expressing their psychomotor effects.

In conclusion, the present study showed that a preferential dopamine D3 agonist, 7-OH-DPAT, but not the preferential dopamine D2 agonist bromocriptine, induced c-fos mRNA expression in the rat cerebellum. This effect was completely abolished by pretreatment with a dopamine D2-type-receptor antagonist and was elevated by dopaminergic denervation. Although further studies using selective D3 antagonists will be required to clarify the role of the D3 receptor in the cerebellum, the results presented here will contribute to research on the in vivo function of the dopamine D3 receptor and the in vivo drug interaction with D3 receptor.

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