*Mol. Cells*, Vol. 10, No. 5, pp. 546–551

Molecules and Cells



# c-Fos Expression by Dopaminergic Receptor Activation in Rat Hippocampal Neurons

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*(Received on June 5, 2000)*

**While dopamine is likely to modulate hippocampal synaptic plasticity, there has been little information about how dopamine affects synaptic transmission in the hippocampus. The expression of IEGs including c-*fos* has been associated with late phase LTP in the CA1 region of the hippocampus. The induction of c-*fos* by dopaminergic receptor activation in the rat hippocampus was investigated by using semiquantitative RT-PCR and immunocytochemistry. The hippocampal slices which were not treated with dopamine showed little expression of c-*fos* mRNA. However, the induction of c-*fos* mRNA was detected as early as 5 min after dopamine treatment, peaked at 60 min, and remained elevated 5 h after treatment. Temporal profiles of increases in c-*fos* mRNA by R(+)-SKF-38393 (50 μM) and forskolin (50 μM) were similar to that of dopamine. An increase in [cAMP] was observed in dopamine-, SKF-, or forskolin-treated hippocampal slices. By immunocytochemical studies, control hippocampal cells showed little expression of c-Fos immunoreactivity. However, when cells were treated with dopamine, an increase in the expression of c-Fos immunoreactivity was observed after treatment for 2 h. The treatment of hippocampal neurons with R(+)-SKF38393 (50 μM) or forskolin (50 μM) also induced a significant increase in c-Fos expression. These results indicate that the dopamine D1 receptor-mediated cAMP dependant pathway is associated with the expression of c-Fos in the hippocampal neurons. These data are consistent with the possible role of endogenous dopamine on synaptic plasticity via the regulation of gene expression. Furthermore, these results imply that dopamine might control the process of memory storage in the hippocampus through gene expression.**

**Keywords:** c-Fos; Dopamine; D1; Hippocampus; Rat; Synaptic Plasticity.

## Introduction

The hippocampus plays an important role in learning and memory (Huang *et al*., 1996; Nguyen *et al*., 1994). The hippocampal CA1 region receives a dopaminergic input from the ventral tegment and has all five types of dopamine receptors (Hersi *et al*., 1995). Immunocytochemical localization of D1 and D5 receptors reveals heavy staining along the pyramidal cells and the stratum radiatum (Huang *et al*., 1992). An increase in the hippocampal dopaminergic function improves learning in animals (Bernabeu *et al*., 1997). Studies on the Schaffer collateral input to the CA1 region show that dopamine enhances long-term potentiation (Huang *et al*., 1995) and inhibits depotentiation (Otmakhova and Lisman, 1998). The fact that dopamine receptors are concentrated in the dendritic region of CA1 suggests that there might be dopaminergic modulation of the synaptic inputs to the CA1 pyramidal neurons responsible for synaptic plasticity (Frey *et al*., 1993; Otmakhova and Lisman, 1996).

Several lines of evidence suggest that dopamine is likely to modulate synaptic plasticity (Hersi *et al*., 1995). The mesolimbic dopaminergic system lies at the core of the brain reward mechanism involved in electrical self-stimulation, place conditioning, intracranial drug self-application, and natural reinforcement. The role of the mesolimbic dopaminergic system in the reinforcement of learning suggests that dopamine should be able to modulate activity dependent synaptic plasticity (Wang and McGinty, 1996). Dopamine hyperfunction has been previously implicated in schizophrenia, but there has been little information about how dopamine affects synaptic transmission in the hippocampus. The only previous connection between dopamine and hippocampal function were the reports

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Abbreviations: ACSF, artificial cerebrospinal fluid; IEGs, immediate early genes; LTP, long-term potentiation.

that dopamine could affect LTP in CA1 (Frey *et al.*, 1991) and inhibit depotentiation (Chen *et al.*, 1995). In the hippocampus, it was demonstrated that blockage of either the D1 or D2 receptor decreases the magnitude of the late phase LTP (Frey *et al.*, 1991). This late phase appears to involve the effects of cAMP on protein synthesis (Frey *et al.*, 1993). Perfusion of the hippocampal slices with high concentrations (50–100 μM) of D1 agonists without any tetanus can itself imitate the late phase LTP, an effect that is blocked by inhibitors of protein synthesis (Huang and Kandel, 1995).

D1 receptors have been shown to be required for the dopamine-dependent activation of IEG expression both in the intact rat striatum *in vivo* and dissociated primary striatal cultures (Liu *et al.*, 1995). D1 receptors are positively coupled to adenylyl cyclase, thus activating the cAMP pathway. D1 receptor agonists induce expression of c-*fos* immunoreactivity as well as AP-1 transcription factors composed of c-Fos and c-Jun/JunB in rat striatal neurons (Huang and Walters, 1996). The expression of IEGs including c-*fos* has been associated with late phase LTP in the CA1 region of the hippocampus (Kaczmarek, 1992). While the functional significance of IEG expression is unclear, it is suggested that IEGs may act as transcription factors that would facilitate expression of the late genes which lead to long-term neuronal changes such as late phase LTP (Matthies *et al.*, 1990; Xia *et al.*, 1996).

The functional significance of hippocampal D1 receptor localization is largely unknown, although previous studies have shown that D1 receptors may play a role in hippocampal synaptic plasticity (Huang and Kandel, 1995; Otmakhova and Lisman, 1996). To explore the possible involvement of IEGs in the activation of transcription factors after D1 receptor activation in the hippocampal neurons, we have addressed the following questions: (1) Can a specific D1 agonist stimulate c-*fos* mRNA and c-Fos expression? (2) If so, is it related to an increase in [cAMP]? (3) Can these effect be reversed by D1 antagonists? We applied semiquantitative RT-PCR and immunohistochemical methods to determine temporal profiles of c-*fos* mRNA expression in the rat hippocampus after dopaminergic receptor activation. Our results suggest that hippocampal D1 receptors are coupled to the activation of transcription factor genes, including c-*fos*.

## Materials and Methods

Male (4-week old) or pregnant female Sprague-Dawley rats were purchased from Sam Yuk Laboratory Animals (Osan, Kyunggido, Korea). The animals were housed in groups of 3 in the Hanyang University College of Medicine Animal Care Facility.

**Preparation of hippocampal slices and drug treatments** Male Sparuge-Dawley rats (8–10 weeks) were anesthetized by ether and then their hippocampi were immediately dissected. Slices (400 μm) were cut on a manual tissue chopper and were immediately incubated in oxygenated artificial cerebrospinal fluid (ACSF; 124 mM NaCl, 4.4 mM KCl, 25 mM $NaHCO_3$, 1 mM $KH_2PO_4$, 2.3 mM $CaCl_2$, 1.3 mM $MgSO_4$, 10 mM glucose) at 37°C for an indicated time period. To treat with dopamine (5 μM), R(+)-SKF38393 (50 μM), or forskolin (50 μM), R(+)-SCH23390 (50 μM), each drug was added to slices at the indicated time for a fixed period at 37°C.

### Semiquantitative RT-PCR

**Reverse transcription** In order to measure the amount of c-*fos* mRNA induced by drug treatment, semiquantitative RT-PCR was used. Total cellular RNA was isolated by the single-step method using RNAzol B (Biotex, Houston, TX). One microliter of oligo dT15 (20 pmol) was added to RNA solution (5 μg total RNA/10 μl DEPC-water), boiled for 5 min at 95°C and then immediately cooled. The mixture was mixed with reverse transcriptase buffer (50 mM Tris-HCl, pH 8.3, 50 mM KCl, 10 mM $MgCl_2$, 0.5 mM spermidine, 10 mM DTT), 20 μM deoxylnucleotide triphosphate (dNTP), 20 units RNasin (Promega), 5 units avian myeloblastosis virus (AMV) reverse transcriptase (Promega), distilled water was then added to make a total volume of 20 μl, and reacted for 1 h at 42°C.

**PCR** The β-actin gene was used as a control in measuring the amount of amplified c-*fos* gene for which c-*fos* cDNA and β-*actin* cDNA were amplified in a tube. The primers (forward and backward primers, respectively) used for PCR of β-actin mRNA were 5′-TTGTAACCAACTGGGACGATATGG-3′ and 5′-GAACTTGATCTTCATGGTGCTAGG-3′; for c-*fos* mRNA they were 5′-GGTCATCGGGGATCTTGC-3′ and 5′-GGGCTCTCCTGTCAAC-3′. One pair of c-*fos* primers (20 pmole) and one pair of β-actin primers (1 μl) was mixed with a reaction mixture containing 5 μl cDNA, 10 mM Tris-HCl, pH 8.3, 40 mM KCl, 105 mM $MgCl_2$, 1 mM DTT, 500 mg/ml bovine serum albumin, 50 μM dNTP, 2.5 units of *Taq* polymerase (Takara) and distilled water to make final volume of 50 μl. PCR was performed in a thermal cycler (Stratagene) starting with denaturation for 5 min at 94°C, and then repeated for 30 cycles of denaturation (94°C, 1 min), annealing (60°C, 1 min), elongation (72°C, 1 min) for 30 cycles, and finally extended for 7 min at 72°C. The amplified PCR products were observed on a 1.5% agarose gel containing ethidium bromide (EtBr). The intensity of the PCR products was quantitated by a computer-assisted densitometer, TINA 2.0c (Fuji BAS, Japan). The relative amount of *c-fos* mRNA was calculated by the ratio c-*fos* PCR product/β-actin product.

**Primary hippocampal neuronal cell culture** Hippocampi were dissected out under a stereomicroscope from postnatal day one (P1) Sprague-Dawley rats. The tissue was suspended in 15 ml of dissection solution with the following supplements per l of Hank's: 8 mM HEPES, pH 7.2, 10 mM $MgCl_2$, 5% glucose. The tissue was dissected mechanically with an Eppendorf tip (1 ml) in 15 ml of dissection solution. The tissue

was incubated at 37°C for 10 min in trypsin solution (0.1%) containing 1 mM EDTA. The reaction was stopped by a trypsin inhibitor and the tissue was briefly centrifuged at $200 \times g$ for 3 min. The tissue was washed in serum-free neurobasal medium (GIBCO cat. #21103-049), following the addition of 10% fetal bovine serum and 0.5 mM glutamine. The tissue was then triturated through a Pasteur pipette. Cells were plated at a density of $1 \times 10^6$ per dish onto glass coverslips coated with poly-L-lysine (25 μg/ml) and laminin (10 μg/ml). From the second day in culture, the medium was switched to serum-free neurobasal medium containing 0.5 mM glutamine and a 1 × B27 supplement to inhibit the proliferation of non-neuronal cells. Cultures were maintained for up to 5 weeks in a humidified incubator with 95% $O_2$ and 5% $CO_2$ at 37°C.

**c-Fos immunoreactivity in hippocampal cultured neurons** c-Fos was immunostained using methods cited in Craig *et al*. (1993). Hippocampal cells (400 μm) were fixed for 15 min at 37°C in 4% paraformaldehye/4% sucrose in phosphate-buffered saline (PBS; 4.3 mM $NaH_2PO_4$, 1.4 mM $KH_2PO_4$, 137 mM NaCl, 2.7 mM KCl, pH 7.4), washed in PBS (10 min, 3×), permeabilized in 0.25% Triton X-100/in PBS for 5 min, and washed with PBS. Nonspecific binding was blocked by incubation of cells in 10% normal goat serum/in PBS for 1 h at 37°C. The cells were incubated with rabbit polyclonal anti-c-*fos* antiserum (Santa Cruz Biotechnology) diluted 1:250 in 10% normal goat serum/in PBS for 36 h at 4°C. After washing in PBS for 30 min (3×), cells were incubated in Cy3 conjugated goat anti-rabbit secondary antibody (1:250; Jackson Immunoresearch) for 2–3 h at RT. After extensive washing in PBS, cells were viewed on a Biorad confocal microscope mounted on a Zeiss Axiovert microscope under a magnification of 400.

**cAMP radioimmunoassay** Hippocampal slices were treated with several drugs, as described in **Materials and Methods**, and at the end of each treatment slices were collected and ice-cold trichloroacetic acid (TCA) was added. The pooled slices were homogenized in a tube, and centrifuged at $2{,}500 \times g$ for 15 min. The clear supernatant was removed to a new tube, shaken with water-saturated ether and the organic phase was aspirated off. This process was repeated three times to remove TCA from the tissue extract. The extract was evaporated to dryness at 70–80°C. After dryness the particulate was reconstituted in sodium acetate buffer to measure cAMP using a radioimmunoassay kit (NEB). Each sample was run in duplicate and the averaged values from separate experiments were pooled.

## Results

We attempted to identify whether c-Fos protein is selectively induced in response to transient or prolonged administration of dopamine onto hippocampal slices. The action of dopamine on hippocampal neurons is thought to be mediated by D1/D5 receptors located on pyramidal neurons and dopamine D1 receptors are positively coupled to adenylate cyclase. Therefore, we also used a D1 selective agonist, SKF 38393, and an adenylate activator, forskolin. As a first step in determining the increase in c-*fos* mRNA induced by the drug, we performed semiquantitative RT-PCR. Coamplification with internal standards allowed us to semiquantitatively measure c-*fos* mRNA levels in small hippocampal slice samples. For each time point, the net value of β-actin and the c-*fos* cDNA band was quantified by densitometry. The relative distribution of c-*fos* mRNA was determined as a ratio of c-*fos* to β-actin. The time-dependent change of c-*fos* mRNA expression was expressed as a % of the control (see Figs. 1 and 2). We treated hippocampal slices with dopamine or its agonists in the same concentration that was used for the induction of synaptic potentiation or LTP elsewhere (Huang and Kandel, 1995). For *in vitro* LTP recordings, hippocampal slices are usually allowed to recover for about 2 h after dissection prior to stimulation. Since the expression of c-*fos* mRNA might be increased by incubation alone in the absence of drug treatment, the potential effect of incubation periods (in the absence of the drug) on c-*fos* mRNA expression was determined and used as a control. In these experiments the control slices were those perfused with artificial cerebrospinal fluid (ACSF) only for 5 h in the absence of drugs. For other time points, for example, '30 min' samples indicate those that were first treated with a drug for 30 min and then switched to drug-free ACSF for up to 5 h. The results showed that little expression of c-*fos* mRNA in the control. After treatment of cells with dopamine (50 μM) or SKF38393 (50 μM), the expression of c-*fos* mRNA was remarkably increased during the first 30 min and then persisted (Figs. 1A and 1B). However, there was a decrease in the expression of c-*fos* mRNA after 5 h treatment with dopamine relative to that seen with SKF38393 at the same time point. SCH23390 (50 μM), a D1 antagonist, had no significant effects on the induction of c-*fos* mRNA (Fig. 1). The increase in c-*fos* mRNA by SKF38393 was not blocked by a 30 min prior application of SCH23390 (Figs. 1A and 1B).

Next we applied forskolin and Sp-cAMPS, an adenylate cyclase activator and cAMP analog, respectively, onto hippocampal slices to see if a direct increase in [cAMP] can cause the expression of c-*fos* mRNA. There was a significant increase in the expression within 60 min treatment either with forskolin (50 μM) or Sp-cAMPS (20 μM) and the increased level persisted for up to 5 h (Figs. 2A and 2B). In contrast 1,9-dideoxyforskolin (100 μM), which is a pseudo-analog of forskolin, did not induce the expression of c-*fos* mRNA (Figs. 2A and 2B). D1 agonists are known to be positively coupled to adenylate cyclase. Therefore, we investigated if the intracellular concentration of cAMP is increased after the drug treatments. A radioimmunoassay was used to measure the [cAMP]. Figure 3 shows that [cAMP] was actually increased by dopamine, forskolin or SKF38393 ($n = 5$, $p < 0.05$). The increase in [cAMP] by either dopamine or SKF38393 was efficiently blocked by

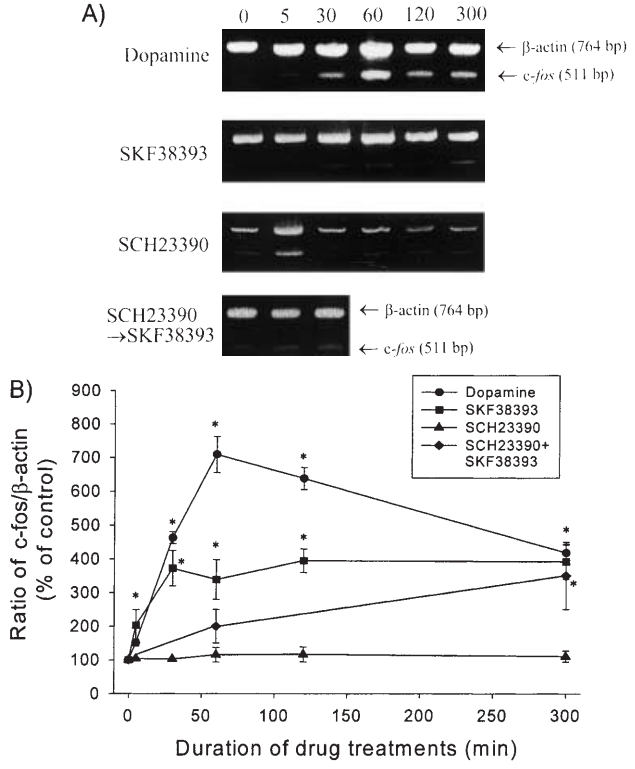


**Fig. 1.** Temporal profile of increases in β-actin and c-*fos* mRNA by semiquantitative RT-PCR in the rat hippocampus for 0 (control), 5, 30, 60, 120, and 300 min under dopamine (50 μM), SKF38393 (50 μM) and SCH23390 (50 μM) treatments. In the case of SCH23390 + SKF38393, SCH23390 was applied 30 min prior to SKF38393. **A.** A representative RT-PCR. **B.** A plot of the (**A**) Mean ± SEM represents the percentages of control levels. *$p < 0.05$, significantly different from control values as determined by a Student's *t*-test ($n = 4$–6 per group).

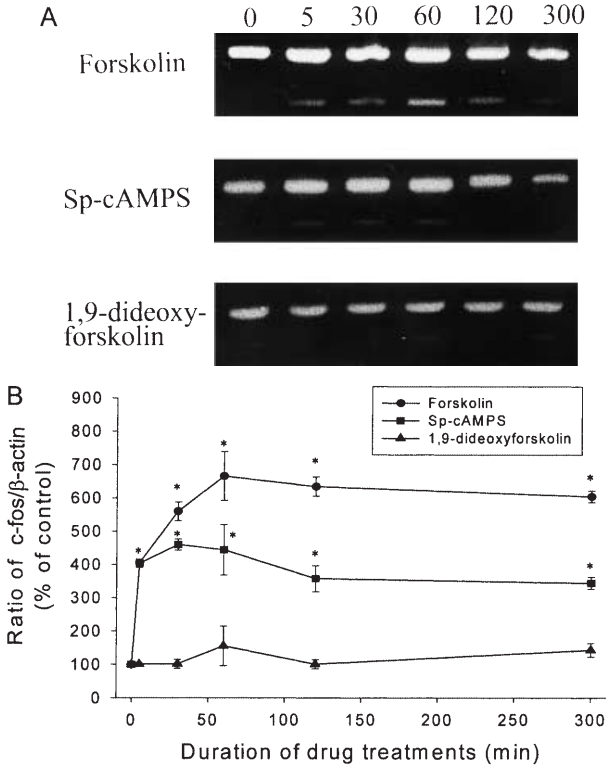


**Fig. 2.** Temporal profile of increases in β-actin and c-*fos* mRNA by semiquantitative RT-PCR in the rat hippocampus for 0 (control), 5, 30, 60, 120, and 300 min under forskolin (50 μM), Sp-cAMPS (20 μM) and 1,9-dideoxyforskolin (100 μM) treatments. **A.** A representative RT-PCR. **B.** A plot of the (**A**) Mean ± SEM represents the percentages of control levels. *$p < 0.05$, significantly different from control values as determined by a Student's *t*-test ($n = 4$–6 per group).

SCH23390. Therefore, these results indicate that activation of the D1 receptor are coupled to an increase in [cAMP].

To examine the consequence of the drug induction of c-*fos* mRNA on the protein level, we performed immunocytochemistry on the cultured primary hippocampal neuronal cells by using anti-c-Fos antibody. As shown in Fig. 4, c-Fos immunoreactivity was little induced in control cells but was remarkably induced within 120 min of treatment with dopamine (50 μM), SKF38393 (50 μM), or forskolin (50 μM) (Fig. 4A, 4B, and 4C). The amount of c-Fos immunoreactivity was increased with a higher concentration (data not shown). In this experiment the basal level of c-Fos immunoreactivity was detected in accordance with the slight detection of c-*fos* mRNA as shown in the results by RT-PCR (Fig. 4).

Taken together, these results suggest that the increase in c-*fos* mRNA and protein by dopamine, D1 agonists or forskolin involve the cAMP-mediated pathway. But the results that SCH23390 did not block the effects of SKF38393 on the c-*fos* mRNA and protein expression suggest that D1 receptor activation might involve a cAMP-independent pathway to induce c-Fos expression.

## Discussion

On the basis of previous findings that dopamine can modulate hippocampal synaptic plasticity, we tried to extend the role of the dopaminergic mechanism in gene expression of the hippocampal neurons.

Elucidation of the role of dopamine in the hippocampus is relevant to schizophrenia and other dopamine-dependent brain disorders. Several lines of physiological evidence provide some support for a role of dopamine in synaptic modification, particularly in long-term depression in the striatum (Calabresi *et al.*, 1992) and hippocampus (Chen *et al.*, 1995). Importantly this late synaptic enhancement occurs without strong synaptic stimulation suggesting that this form of potentiation is not activity dependent or synapse-specific. It was reported that dopamine reduces both

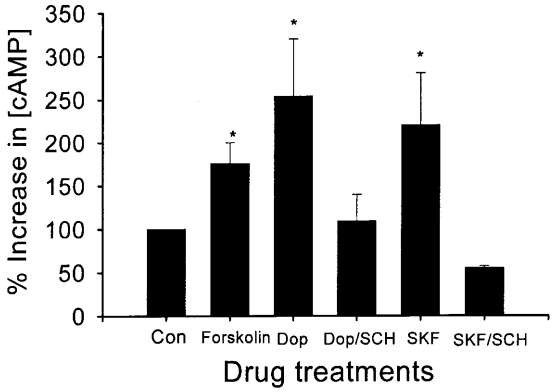


**Fig. 3.** Measurements of [cAMP] after drug treatments in hippocampal slices using $^{125}$I-cAMP. [cAMP] was increased by dopamine (50 μM), forskolin (50 μM) or SKF38393 (50 μM). The increase in [cAMP] by either dopamine or SKF38393 was efficiently blocked by SCH23390 (50 μM). Mean ± SEM represents the percentages of control levels. *$p < 0.05$, significantly different from control values as determined by a Student's *t*-test ($n = 5$ per group).

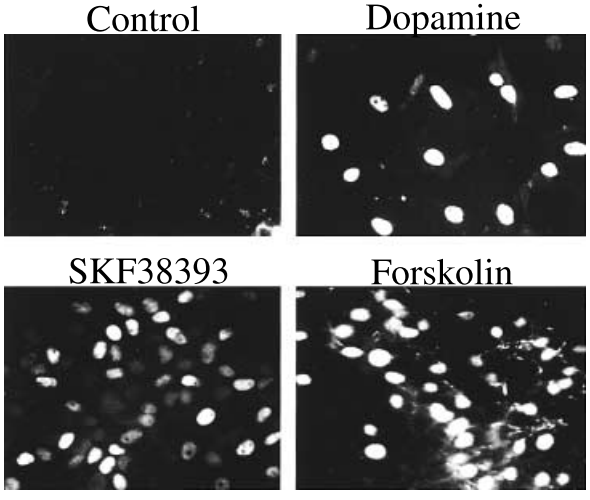


**Fig. 4.** Immunocytochemistry of cultured hippocampal neurons with anti-c-Fos. Dopamine (50 μM) robustly induced c-Fos expression relative to SKF38393 (50 μM) and forskolin (50 μM). c-Fos immunoreactivities are seen in the nuclei of hippocampal neurons (×400).

the NMDA and AMPA components of transmission at the perforant pathway (Otmakhova and Lisman, 1998). By inhibiting this pathway, dopamine hyperfunction and/or NMDA hypofunction abnormalities may occur in CA1. The dopamine hyperfunction and NMDA hypofunction would isolate CA1 from specific sensory information coming from the entorhinal cortex via the perforant pathway. Both dopaminergic hyperfunction and NMDA hypofunction are thought to underlie schizophrenia. Combining these results, dopamine hyperfunction might increase random memory information and disrupt the ability to inhibit incorrect associations, which are known to occur in schizophrenia.

c-Fos expression represents adaptive responses of the nervous system at the genetic level to environmental stimuli (Wang and McGinty, 1996). In striatal neurons, drugs that stimulate dopamine and glutamate receptors have been shown to induce the expression of c-Fos and to induce binding of the protein to AP-1 sites on DNA (Schwarzchild *et al.*, 1997). However, only glutamate, but not dopamine and forskolin, induces transcription of a AP-1-driven fusion gene (Schwarzchild *et al.*, 1997). In the present study, we only investigated the expression of c-Fos. Therefore, it should in future be followed up to see if dopamine receptor activation can lead to the binding of c-Fos to AP-1 sites and the transcription of a AP-1-driven fusion gene in hippocampal neurons.

Manipulations of D1- or D2-dopamine receptors have differential and selective effects on the striatonigral output pathways of the striatum. Combined stimulation of these receptors produces synergistic responses (Keefe and Gerfen, 1995). In the present study using hippocampal slices, however, we did not observe the synergistic or antagonistic effects of SCH23390 on the activity of SKF38393 both in c-*fos* mRNA and protein expression. Instead the increase in [cAMP] by SKF38393 was reduced by SCH23390. While there is no clue for this discrepancy between c-Fos expression and an increase in [cAMP] mediated by SCH23390, it is possible that D1 and D2 receptors could modulate transmission at different sites and through complex processes in c-Fos expression. Both the affinity and efficacy of SKF38393 are substantially lower compared to dopamine D1 action. SKF38393, a highly selective partial D1 agonist, has only a 45–70% efficacy of dopamine in stimulating adenylate cyclase (Wang and McGinty, 1996). This might be the reason for the reduced ability of SKF38393 to stimulate c-Fos expression in hippocampal neurons (Fig. 4). The effect of dopamine and SKF38393 on the increase in [cAMP] is reversed by SCH23390. However, SKF38393 was more efficiently and completely blocked by SCH23390 than dopamine was, indicating that the increase in [cAMP] is occurring solely via D1 receptors. According to previous electrophysiological results, the D1 agonist, 6-chloro-PB, and forskolin produced an enhancement of LTP (20–25%) (Otmakhova and Lisman *et al.*, 1996). The D1 agonist effect was completely blocked by the D1 antagonist SCH23390. These results suggest that dopamine produces a synapse-specific enhancement of early LTP through D1 receptors and of cAMP in the CA1 region of the hippocampus. Our results that SCH23390 did block the effects of SKF38393 on the increase in [cAMP] but not the expression of c-*fos* mRNA and protein suggest that D1 receptor activation might involve a cAMP-independent pathway to induce c-Fos expression.

In conclusion, we show several lines of evidence that dopamine could be involved in the process of memory

storage in the hippocampus through gene expression. These data are consistent with the possible role of endogeneous dopamine on synaptic plasticity via the regulation of gene expression.

**Acknowledgements** This work was supported by a Hanyang University New Faculty Grant and a Basic Medical Science Grant of the Korea Research Foundation awarded to H. Son.

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