

Carbamazepine Suppresses Methamphetamine-Induced Fos Expression in a Regionally Specific Manner in the Rat Brain

Possible Neural Substrates Responsible for Antimanic Effects of Mood Stabilizers

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Carbamazepine (CBZ) has been widely used for treatment of manic states. Because amphetamine produces effects in humans similar to those of idiopathic mania, acute methamphetamine administration could serve as a model of this condition. To elucidate the neurobiological substrates responsible for the antimanic effects of carbamazepine, this study investigated the effects of chronic carbamazepine administration on regional Fos protein expression induced by a single dose of methamphetamine (2mg/kg). Chronic treatment with CBZ (0.25% in food for 7 days, followed by

0.5% for 7 days; final mean serum carbamazepine concentration: $4.09 \pm 0.34 \mu\text{g/ml}$) significantly attenuated the number of Fos-like immunoreactivity-positive nuclei induced by methamphetamine administration in the core of the nucleus accumbens and the caudate/putamen. The results indicate these brain regions are involved in the antimanic effects of carbamazepine.

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Carbamazepine is a widely used tricyclic anticonvulsant drug. It shares a common clinical profile with lithium for its acute and prophylactic therapeutic effects in bipolar affective disorder (Emilien et al. 1996; Post and Ballenger 1990). Although a wide variety of biochemi-

cal and neurophysiological effects (including stabilizing the sodium and potassium channel, reducing calcium fluxes, antagonizing peripheral-type benzodiazepine receptors, up-regulating GABA_B receptors, and acting as an adenosine antagonist or agonist) have been described for this drug, the precise mechanism of its mood-stabilizing effects remains unknown (Post et al. 1994). Moreover, the neuroanatomic substrates responsible for the antimanic effects of carbamazepine have not yet been identified.

Because such psychostimulants as d-amphetamine and cocaine produce effects in humans that are very similar to the symptoms of idiopathic mania (Brauer and de Wit 1996, 1997; Smith and Davis 1977), it has been proposed that administration of these agents may serve as a model of this condition (Robbins and Sa-

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hakian 1980). Quantification of changes in the expression of the immediate early gene *c-fos* has proved to be a very useful method of mapping the distribution of neurons that are activated by physiological or pharmacological stimuli (Dragunow and Faull 1989; Morgan and Curran 1991; Sagar et al. 1988). In our previous study (Lee et al. 1999), we investigated the neurobiological substrates involved in the antimanic effects of lithium in a methamphetamine-manic model using Fos mapping. Chronic lithium administration significantly reduced the number of Fos-like immunoreactivity (Fos-LI)-positive nuclei induced by methamphetamine administration in the prefrontal cortex, the nucleus accumbens, the caudate/putamen, and the amygdala.

In the previous study, it was hypothesized that these regions were possible neural targets for the antimanic efficacy of lithium. The next step was to identify the specific antimanic target region. The objective of the present study was to investigate the neural substrate involved in the therapeutic efficacy of another mood stabilizer in order to search for a possible common neural pathway for the antimanic effects of mood stabilizers. The effects of chronic carbamazepine treatment on the methamphetamine-induced regional expression of Fos protein in the rat brain were, therefore, examined.

MATERIALS AND METHODS

Subjects

Male Wistar rats (Clea, Japan, initial weight, 220–260 g) were used for this study. They were housed two per cage and maintained under a controlled 12–12 h light–dark cycle (lights on at 07:00 AM) and at a constant temperature (28°C), with water and food ad libitum. To minimize stress-induced Fos expression, the rats were adapted to handling during the first week.

Chronic Carbamazepine Administration

Diets containing either 0.25% or 0.5% (w/w) CBZ were prepared. CBZ-treated rats ($n = 14$) were fed the low-dose diet for one week, then the high-dose diet for the following week. Control rats ($n = 14$) were fed the same diet without additional CBZ for 2 weeks. This feeding regimen was used to produce serum CBZ levels approaching the human therapeutic range while minimizing weight loss (Elphick 1989; Weiss et al. 1987).

Methamphetamine Challenge

After CBZ administration for 2 weeks, the rats were divided into two subgroups. One received a single meth-

amphetamine injection (2 mg/kg, subcutaneously [SC] in saline), the other received a saline injection (0.9% NaCl, SC). Thus, there were four groups of rats altogether, with 7 animals per group: control diet + saline, control diet + methamphetamine, CBZ diet + saline, and CBZ diet + methamphetamine.

Immunohistochemistry

Two hours after injection, the rats received an overdose of sodium pentobarbital and were then perfused. Blood samples for determination of the CBZ concentration were obtained by heart puncture. The rats were perfused through the ascending aorta with 200 ml saline followed by 250 ml 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). The brains were removed immediately after perfusion and soaked in the same fixative. After a 24-h postfixative period, coronal sections (30 μ m) were cut from each brain using a Microslicer (DSK, Kyoto, Japan). The procedure used for the immunohistochemistry was as described elsewhere (Hamura et al. 1997). Briefly, the sections were incubated in a primary antiserum (1:2500 dilution in phosphate-buffered saline (PBS, pH 7.4) containing 0.3% Triton X-100, 0.05% sodium azide, and 2% normal rabbit serum) for 72 h at 4°C. The primary antibody was a polyclonal antibody against residues 2–16 of the N-terminal region of the Fos protein, raised in sheep (OA-11-824; Genosys, USA). The sections were incubated next in a solution of biotinylated rabbit antisheep secondary antibody (Vector Laboratories, USA; 1:400 dilution in PBS containing 0.3% Triton X-100) for 75 min, then in PBS containing 0.2% avidin-biotinylated horseradish peroxidase complex (Vector Laboratories) for 75 min. Immunoreactivity was visualized using a glucose oxidase-diaminobenzidine-nickel method (Shu et al. 1988). The sections were mounted on chrome-alum-gelatin-coated slides, allowed to dry overnight, counterstained with neutral red, and then coverslipped. Because the antibody recognizes Fos and related antigens, the staining is referred to as Fos-LI.

Quantification

In pilot studies, sections from different areas of the brain were examined to determine the regions of interest for the quantitative analysis. For each side of the brain, Fos-LI-positive nuclei were counted in six sequential sections from each of 21 brain areas located according to the coordinates of Paxinos and Watson (1986), and each site was investigated bilaterally, resulting in a total of 12 determinations per brain region. The average of these 12 determinations was used for the statistical analysis. The antero posterior (AP) coordinates

relative to the bregma and associated structures were as follows: AP +2.7: cingulate cortex area 3, agranular insular cortex (layers 2 and 3), agranular insular cortex (layer 5) and claustrum; AP +1.6: shell and core of the nucleus accumbens, piriform cortex and rostral part of the medial and central caudate/putamen; AP +0.7: ventral lateral septum nucleus and caudal part of the medial and central caudate/putamen; AP -0.27: lateral division of the bed nucleus stria terminalis (BSTLD); AP -3.1: lateral part of the central amygdaloid nucleus and anterior part of the basolateral amygdaloid nucleus; AP -3.6: CA1, CA2, CA3, and dentate gyrus of the hippocampal formation, medial and lateral parts of the lateral habenula (Figure 1). For the most part, immunoreactivity was quantified by counting the number of Fos-LI-positive nuclei within a $380 \times 380 \mu\text{m}^2$ grid placed over each area at $\times 95$ magnification; however, in the BSTLD, the field was $190 \times 380 \mu\text{m}^2$, and in the hippo-

campal formation, all Fos-LI-positive neurons were counted. Fos-LI-positive nuclei counting was performed in a double blind fashion. The serum CBZ concentration was measured by EIA-autoanalyzer (Hitachi, Japan).

Statistical Analysis

A one-way analysis of variance (ANOVA) was performed on the number of Fos-LI-positive neurons within 21 regions. Because there were no significant differences between the control diet + saline and the CBZ diet + saline group, the data from these groups were combined to form a single control group. Another one-way ANOVA was then performed between the control diet + methamphetamine, the CBZ diet + methamphetamine, and the combined control group. Post hoc individual comparisons were done using Scheffe's test.

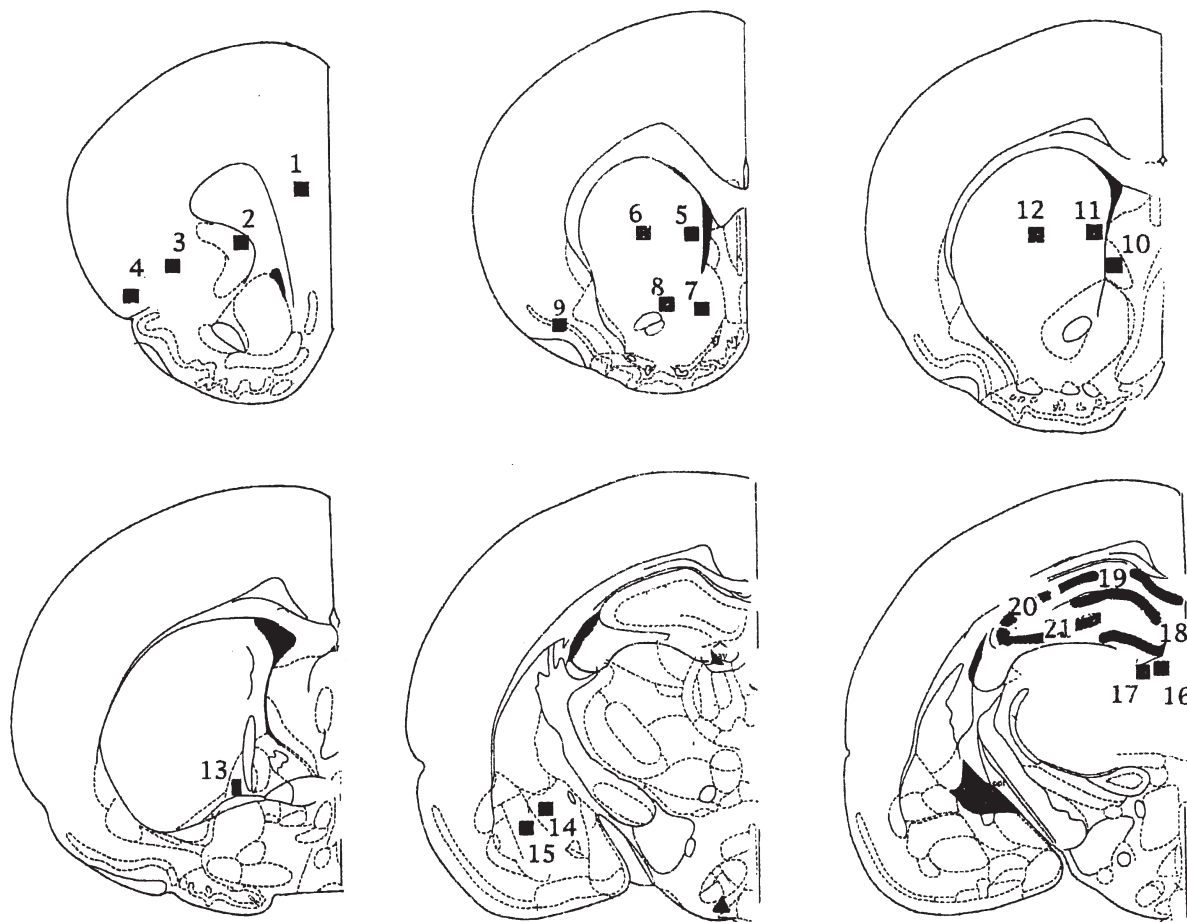


Figure 1. Drawings of representative sections used for the quantification of Fos-LI-positive neurons in the cingulate cortex area 3 (1), claustrum (2), agranular insular cortex layer 5 (3), layers 2 and 3 (4), rostral part of the medial (5) and central (6) caudate/putamen, shell (7) and core (8) of the nucleus accumbens, piriform cortex (9), ventral lateral septum (10), caudal part of the medial (11) and central (12) caudate/putamen, lateral division of the bed nucleus stria terminalis (13), lateral part of the central amygdaloid nucleus (14), anterior part of the basolateral amygdaloid nucleus (15), medial (16) and lateral (17) parts of the lateral habenula, dentate gyrus (18), and CA1 (19), CA2 (20) and CA3 (21) of the hippocampal formation. Drawings are from Paxinos and Watson (1986).

The significance level was set at $p < .05$. A one-way ANOVA followed by Scheffé's test ($p < .05$) also was done to compare body weight between groups.

RESULTS

Carbamazepine Levels and Body Weight

The mean (\pm SEM) serum CBZ level was 4.09 ± 0.34 $\mu\text{g/ml}$, which corresponds closely to the range of therapeutic serum concentrations of 4–12 $\mu\text{g/ml}$ (Post 1987). Mean (\pm SEM) body weights after 14 days of treatment were as follows: the control diet + saline group, 303 ± 4.6 g; the control diet + methamphetamine group, 300 ± 4.2 g; the CBZ diet + saline group, 277 ± 3.6 g; the CBZ diet + methamphetamine group, 274 ± 3.3 g. Body weights of the CBZ diet groups were significantly less than the control diet group.

Effects of Chronic CBZ Treatment on Methamphetamine-Induced Fos-LI

There were significant intergroup differences between both the control diet + methamphetamine and the CBZ diet + methamphetamine, and the combined control groups (control diet + saline and CBZ diet + saline) in 18 of the 21 regions studied. No significant differences were found in the ventral lateral septum nucleus, the dentate gyrus, or CA2 (Table 1). Post hoc comparisons showed that, compared to the control group, the methamphetamine challenge had significantly induced Fos-LI-positive neurons in the same 18 regions. These regions were the cingulate cortex area 3, the claustrum, the agranular insular cortex (layer 5), the agranular insular cortex (layers 2 and 3), the piriform cortex, the shell and core of the nucleus accumbens, the rostral and caudal parts of the medial and central caudate/putamen, the BSTLD, the lateral part of the central amygdaloid nucleus, the anterior part of the basolateral amygdaloid nucleus, CA1 and CA3 of the hippocampal formation, and the medial and lateral parts of the lateral habenula. Compared with the control diet + methamphetamine group, the CBZ diet + methamphetamine group had markedly fewer methamphetamine-induced Fos-LI-positive neurons in several regions, but the difference reached significance only in the core of the nucleus accumbens and the caudate/putamen (Figure 2).

DISCUSSION

The major finding of this study is that chronic CBZ treatment significantly reduced the number of methamphetamine-induced Fos-LI-positive neurons in the core of the nucleus accumbens and the caudate/putamen. In contrast, our previous study (Lee et al. 1999) showed

that lithium treatment significantly reduced the number of these neurons in the prefrontal cortex and the central amygdaloid nucleus, as well as in the nucleus accumbens and the caudate/putamen. Thus, the core of the nucleus accumbens and the caudate/putamen are common target regions in which both CBZ and lithium treatments suppress methamphetamine-induced Fos expression. In these regions, chronic lithium administration significantly attenuates the number of methamphetamine-induced Fos-LI-positive neurons by approximately 40–65% (Lee et al. 1999), and chronic CBZ administration significantly attenuates it by approximately 32–39% (Table 1). The caudate/putamen (especially the medial section) and the nucleus accumbens are closely related to emotion and serve as output organs of reward to the motor system (Fibiger and Phillips 1986; Mogenson et al. 1980; Robbins and Everitt 1996). Therefore, it is conceivable that these regions are the target of the antimanic effects of mood stabilizers. Areas in which chronic CBZ treatment reduced MAP-induced Fos expression but did not reach statistical difference include the claustrum, the BSTLD, the shell of the nucleus accumbens, and the central amygdaloid nucleus.

The nucleus accumbens is regarded as a ventral striatal area consisting of core and shell, and the caudate/putamen is regarded as a dorsal striatal area. The nucleus accumbens is integrated into the neural circuitry of both the motor and mesolimbic systems (Heimer et al. 1991; Zahm and Brog 1992). The shell, whose output is divided among the ventral pallidum, the extended amygdala, and the hypothalamus, is considered to be involved in the mesolimbic system. On the other hand, the core, whose output is projected to the basal ganglia regions such as the nigro-striatal system, affects the cortical processing of motor activity (Heimer et al. 1991; Zahm and Brog 1992). The present study shows that the core is more involved in the antimanic effect of CBZ in the nucleus accumbens than the shell.

Amphetamine and methamphetamine facilitate the release and inhibit the re-uptake of dopamine and norepinephrine (Kuczenski and Segal 1994). Both the nucleus accumbens and the caudate/putamen are densely innervated by the mesolimbic dopaminergic system. In contrast, although the BSTD, the lateral septum, the prefrontal cortex, and the amygdaloid nucleus are also innervated by the limbic dopaminergic system, Fos-LI expression in these regions was not significantly changed by chronic CBZ treatment. Therefore, factors other than regulation of dopamine may also be involved.

Several studies have indicated that therapeutic concentrations of CBZ administered either acutely and chronically increase the extracellular levels of dopamine and its metabolites in rat striatum slices similar to that with amphetamine or methamphetamine (Barros et

Table 1. Effect of Chronic Carbamazepine Treatment on the Number of Fos-LI Induced by Methamphetamine in Different Brain Regions

Area	Control group N = 14	Control diet + MAP N = 7	Carbamazepine diet + MAP N = 7	F value
Cingulate cortex area 3	11.1 ± 1.0	30.3 ± 2.6 *	25.0 ± 2.2	[2, 25] = 36.5, <i>p</i> < .0001
Clastrum	7.8 ± 1.4	35.6 ± 2.8 *	26.6 ± 2.9	[2, 25] = 35.2, <i>p</i> < .0001
Aguranular insular cortex				
Layers 2 and 3	3.2 ± 0.7	13.6 ± 1.3 *	15.1 ± 2.6	[2, 25] = 24.8, <i>p</i> < .0001
Layer 5	4.1 ± 0.7	17.3 ± 1.9 *	14.5 ± 1.8	[2, 25] = 32.3, <i>p</i> < .0001
Piriform cortex	17.3 ± 4.2	31.6 ± 4.1 *	28.9 ± 2.8	[2, 25] = 13.3, <i>p</i> < .0001
Accumbens				
Core	2.9 ± 0.5	25.6 ± 2.1 *	17.3 ± 2.4 [†]	[2, 25] = 67.0, <i>p</i> < .0001
Shell	6.1 ± 1.1	21.9 ± 2.9 *	15.7 ± 2.3	[2, 25] = 19.3, <i>p</i> < .0001
Rostral part of caudate/putamen				
Central	0.4 ± 0.2	16.3 ± 2.4 *	10.6 ± 1.3 [†]	[2, 25] = 50.8, <i>p</i> < .0001
Medial	2.7 ± 0.5	34.3 ± 2.1 *	21.0 ± 2.0 [†]	[2, 25] = 152.8, <i>p</i> < .0001
Caudal part of caudate/putamen				
Central	0.3 ± 0.2	23.0 ± 0.9 *	20.3 ± 1.4	[2, 25] = 310.7, <i>p</i> < .0001
Medial	3.1 ± 0.5	68.0 ± 3.8 *	43.9 ± 2.3 [†]	[2, 25] = 285.1, <i>p</i> < .0001
Ventral lateral septum	9.4 ± 1.6	15.3 ± 4.0	9.6 ± 1.8	[2, 25] = 2.2, <i>p</i> < .12
BSTLD	7.1 ± 0.6	34.0 ± 4.0 *	25.6 ± 2.7	[2, 25] = 45.4, <i>p</i> < .0001
Amygdala				
Central nucleus, lateral	7.2 ± 2.3	77.9 ± 5.2 *	69.9 ± 3.0	[2, 25] = 158.8, <i>p</i> < .0001
Basolateral nucleus, anterior	4.5 ± 0.5	12.9 ± 1.1 *	11.0 ± 1.4	[2, 25] = 27.0, <i>p</i> < .0001
Lateral habenula nucleus				
Lateral	4.6 ± 0.8	12.0 ± 1.5 *	9.7 ± 1.6	[2, 25] = 11.1, <i>p</i> < .0003
Medial	2.7 ± 0.6	7.3 ± 1.2 *	6.1 ± 0.9	[2, 25] = 9.8, <i>p</i> < .0007
Hippocampal formation				
Dentate gyrus	7.9 ± 1.4	13.1 ± 1.2	16.4 ± 2.1	[2, 25] = 0.6, <i>p</i> < .56
CA1	3.0 ± 1.0	13.0 ± 2.3 *	16.1 ± 3.9	[2, 25] = 11.6, <i>p</i> < .0003
CA2	0.2 ± 0.2	1.0 ± 0.2	1.0 ± 0.4	[2, 25] = 2.9, <i>p</i> < .07
CA3	4.4 ± 0.8	13.7 ± 2.7 *	14.7 ± 2.8	[2, 25] = 11.2, <i>p</i> < .0003

Values are mean (±S.E.M.) of the number of Fos-LI positive neurons in each groups of animals.

At most sites, immunoreactivity was quantified by counting nuclei showing Fos-LI within a 380 × 380 μm² grid placed over each area at × 95 magnification. In the BSTLD the field was 190 × 380 μm², and in the hippocampal formation all neurons showing Fos-LI were counted.

F values reported in one-way ANOVA factored on three groups.

* Significantly different from the Control group, *p* < .05.

[†] Significantly different from the Control diet + MAP group, *p* < .05.

al. 1986; Okada et al. 1997a, 1997b). In contrast, high-dose CBZ treatment decreases dopamine levels and synthesis (Okada et al. 1997a; Waldmeier et al. 1984). Baptista et al. (1993) have reported no change in the extracellular basal level of dopamine in the nucleus accumbens (measured by microdialysis) following therapeutic concentrations of chronic CBZ treatment. In summary, CBZ treatment at the dose used in this study would not seem to attenuate methamphetamine-induced dopamine release. Thus, molecular substrates downstream of the dopamine receptor become more likely targets of CBZ.

In the caudate/putamen and the nucleus accumbens, several lines of evidence have shown that amphetamine-induced Fos expression is mediated mainly by dopamine D1 receptors (Graybiel et al. 1990; Robertson et al. 1989). Methamphetamine increases synaptic dopamine release, after which dopamine acts through D1 and D2 receptor subtypes, which are differentially linked to c-AMP stimulatory and inhibitory effects, re-

spectively (Stoof and Keabian 1981). Methamphetamine-induced Fos expression is mediated by an increase of c-AMP. It is still not known whether chronic CBZ treatment directly affects dopamine receptor affinity and binding to the D1 receptor or whether it affects the related second messenger systems. Further study on the second messenger systems that are regionally and specifically expressed in the caudate/putamen and the nucleus accumbens is required.

Another possible mechanism of CBZ is to act as an adenosine receptor ligand and regulate dopamine receptors indirectly. Although there are contradictory reports of CBZ acting as either A₁ adenosine agonists and A₂ adenosine antagonists or A₁ adenosine antagonists and A₂ adenosine agonists (Daval et al. 1989; Elphick et al. 1990; Fujiwara et al. 1986; Marangos et al. 1985, 1987; Okada et al. 1997b), recent results have shown that CBZ in therapeutic concentrations acts as an antagonist to A₁ adenosine receptors in the striatum (Daval et al. 1989; Marangos et al. 1985, 1987; Okada et al. 1997b) and as

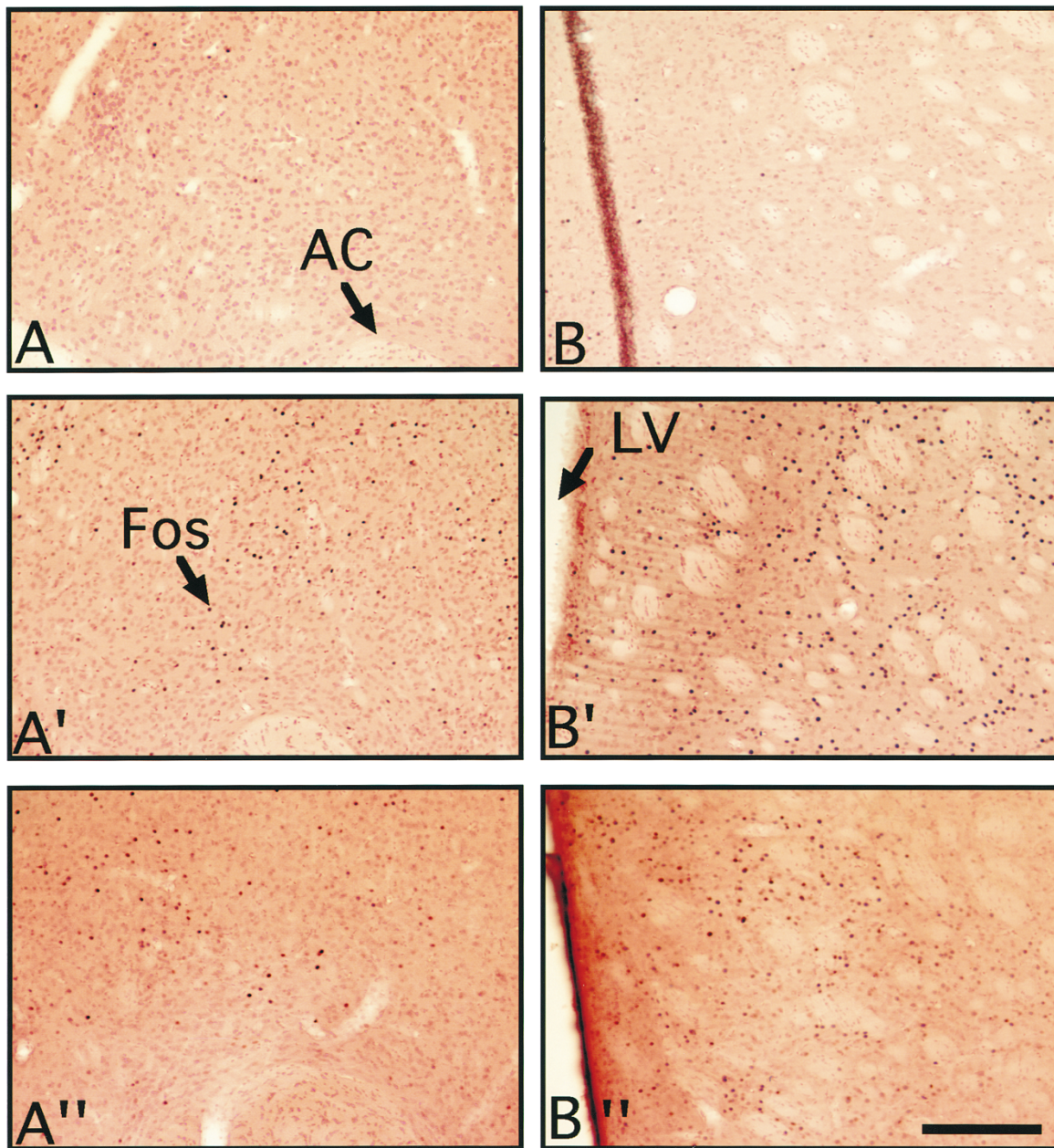


Figure 2. Photomicrographs showing methamphetamine-induced Fos-LI-positive nuclei in various brain areas: medial part of the caudate/putamen [(A), control group; (A'), control diet + MAP; (A''), CBZ diet + MAP] and core [(B), control group; (B'), control diet + MAP; (B''), CBZ diet + MAP] of the nucleus accumbens. The number of Fos-LI neurons in the CBZ diet + MAP group was significantly decreased in comparison with those of the control diet + MAP group. MAP represents methamphetamine. LV, lateral ventricle; AC, anterior commissure. Magnification is $\times 95$. Bar = 200 μm .

an agonist to A_2 adenosine receptors in the striatum (Elphick et al. 1990; Okada et al. 1997b). A_2 adenosine receptors have been further subdivided into high-affinity A_{2a} adenosine receptors and low-affinity A_{2b} adenosine receptors (Collis and Hourani 1993). A_1 receptors (Fastbom et al. 1987; Goodman and Synder 1982) and A_{2b} receptors (Dixon et al. 1996; Feoktistov and Biaggioni 1997) are widely distributed in the rat brain, but A_{2a} adenosine receptors are localized in the striatum, the nu-

cleus accumbens, and the olfactory tubercle (Jarvis and Williams 1989; Parkinson and Fredholm 1990). Le Moine et al. (1992) have examined the interaction between D_1 agonists and A_{2a} antagonists on *c-fos* mRNA in the striatal neurons. Their results have indicated that the administration of the A_{2a} antagonist with a D_1 agonist potentiated the D_1 -induced increase in *c-fos* expression in D_1 -containing neurons in the striatum. Moreover Turgeon et al. (1996) have reported that A_{2a}

agonists significantly attenuated amphetamine-induced Fos expression in the striatum and the nucleus accumbens but that A₁ agonists did not change Fos expression in these regions. Therefore, it can be hypothesized that CBZ treatment attenuates amphetamine-induced Fos expression via an A_{2a} receptor agonistic mechanism. Supporting this hypothesis, A_{2a} receptor agonists induce strong motor-depressant effects when injected into the nucleus accumbens (Barraco et al. 1993).

In the present study, the body weights of the CBZ diet groups were significantly less than those of the control diet group. If the effects of the weight loss caused decrease of the methamphetamine-induced Fos expression, this attenuation would occur not only in caudate/putamen but also in other areas. Therefore, the possibility that weight loss plays a part in this attenuation is minimal.

In conclusion, chronic CBZ treatment significantly reduces the number of methamphetamine-induced Fos-LI-positive neurons in the nucleus accumbens and the caudate/putamen. This and the results of our previous study on the chronic effect of lithium, suggest that these regions represent the neural substrates involved in the antimanic effects of mood stabilizers. One possible mechanism of CBZ in these areas may be an agonistic effect on A_{2a} adenosine receptors. Because the roles of D1 receptor affinity and binding and its related second messenger systems are still not known, further study is needed to elucidate the precise mechanism of the antimanic effects of chronic CBZ treatment on the nucleus accumbens and the caudate/putamen.

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