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The effects of dentate granule cell destruction on behavioral activity and Fos protein expression induced by systemic MDMA in rats

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Abstract

In this study, we examined the effect of the s.c. administration of (±) 3,4-methylenedioxymethamphetamine (MDMA) or saline on locomotor activity and Fos expression following the bilateral destruction of hippocampal dentate granule cells by colchicine in rats. The lesioned animals, when administered s.c. saline, showed a significantly greater increase in locomotor activity compared to the intact animals, and revealed a marginally significant level of increased locomotor activity compared to the sham-lesioned animals. In addition, when the lesioned animals were given s.c. saline or MDMA, there was a significant increase in Fos expression in the nucleus accumbens core, but not in the medial prefrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, piriform cortex, dorsal striatum, or nucleus accumbens shell, compared to the intact and sham-lesioned animals. Overall, these results suggest that the nucleus accumbens core may be involved in the enhancement of locomotor activity induced by the injection of saline alone (stress loading) or MDMA following bilateral destruction of hippocampal dentate granule cells by colchicine.

Keywords: Dentate granule cells; Nucleus accumbens; Colchicine; (±) 3,4-Methylenedioxymethamphetamine; Locomotor activity; Fos protein

1. Introduction

The hippocampus, a structural part of the limbic system, receives its primary afferent inputs from the polymodal association areas of the entorhinal cortex (Emerich and Walsh, 1990). The hippocampus sends outputs to the nucleus accumbens (Groenewegen et al., 1987), dorsal striatum (Groenewegen et al., 1987), septum (Stevens and Cotman, 1991) and neocortical areas (Jay et al., 1989; White et al., 1990; Jay and Witter, 1991), which have been implicated in the initiation and modulation of locomotor activity, rotational movement, and stereotyped behavior induced by the indirect dopamine agonists, methamphetamine and amphetamine (Pijnenburg and Van Rossum, 1973; Kelly et al., 1975; Carboni et al., 1989; Colle and Wise, 1991; Antoniou and Kafetzopoulos, 1992). Aspiration-induced bilateral lesions of the hippocampus (Whishaw and Mittleman, 1991; Mittleman et al., 1993) or intrahippocampal injection of either ibotenic acid (Lipska et al., 1992) or kainic acid+colchicine (Wilkinson et al., 1993; Schaub et al., 1997) have been shown to greatly augment amphetamine-induced locomotor activity in rats. Furthermore, selective and bilateral destruction of the dentate granule cells by colchicine, followed by the bilateral microinjection of amphetamine into the nucleus accumbens, have been shown to produce a significant increase in locomotor activity (Emerich and Walsh, 1990). This finding suggests the existence of functional interactions between dentate granule cells and the nucleus accumbens; these interactions are most likely expressed as perturbations in locomotor activity. We have recently shown that the bilateral destruction of hippocampal dentate granule cells by colchicine in rats significantly enhances

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methamphetamine-induced locomotor activity (Tani et al., 2001).

(±) 3,4-Methylenedioxymethamphetamine (MDMA) is a frequently abused amphetamine analog that produces mild stimulation and a sense of well-being in humans (Green et al., 1995; Schwartz and Miller, 1997; Bankson and Cunningham, 2001). A number of in vitro and in vivo studies have shown that MDMA produces a significant increase in extracellular 5-hydroxytryptamine (5-HT) levels by inducing carrier-mediated release and by blocking re-uptake (Schmidt et al., 1987; Fitzgerald and Reid, 1990; Berger et al., 1992; White et al., 1996). MDMA also increases extracellular levels of dopamine and noradrenaline (Fitzgerald and Reid, 1990; Obradovic et al., 1996; White et al., 1996), albeit to a lesser extent than those of 5-HT. The systemic administration of MDMA increases extracellular levels of 5-HT in the nucleus accumbens, medial prefrontal cortex, hippocampus, and other brain regions of rats (for a review, see White et al., 1996), suggesting that these regions may play a critical role in mediating the MDMA-induced locomotor hyperactivity in rats. In rats, MDMA-induces hyperactivity consisting primarily of increased forward locomotion (Gold et al., 1988; Callaway et al., 1990), which may be dependent on the 5-HT-releasing properties of this drug (Wong et al., 1975; Fuller and Wong, 1977; Callaway et al., 1990, 1991; Bankson and Cunningham, 2001).

To date, no studies have examined the response of animals to MDMA following bilateral destruction of the granule cells in the hippocampus. Therefore, in the present study, we examined the effect of the bilateral destruction of rat hippocampal dentate granule cells using colchicine on the behavioral response to s.c. administered saline or MDMA. We also qualitatively assessed the expression of Fos protein in several brain regions, including the medial prefrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, piriform cortex, dorsal striatum, nucleus accumbens core, and nucleus accumbens shell, as MDMA administration has been reported to significantly induce Fos expression in all of these regions (Hashimoto et al., 1997; Stephenson et al., 1999).

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rat weighting 200–220 g (Japan SLC, Japan) were used in all experiments. The animals were housed 3–4 per cage in a temperature- and humidity-controlled colony room that was maintained on a 12-h light/dark cycle with lights on at 6:00 AM. Animals had ad libitum access to food and water. Experiments were performed in accordance with the principles of laboratory animal care (NIH publication No.85-23, revised 1985).

Lesioning of the dentate granule cells has been described in detail elsewhere (Tani et al., 2001). Briefly, animals were positioned in a stereotaxic apparatus under pentobarbital anesthesia (50 mg/kg, i.p.), followed by bilateral injections of 0.5 μl of 5 μg/μl colchicine into both the dorsal and ventral hippocampi over a period of 5 min using a microinjection pump (EP-60, EICOM, Japan). The stereotaxic coordinates were obtained from the atlas of Paxinos and Watson (3.3 mm posterior, 1.6 mm lateral, 3.7 mm ventral for the dorsal site; 5.3 mm posterior, 4.5 mm lateral, 5.6 mm ventral for the ventral site). The cannulae were left in place for an additional 2 min after the end of the infusion. For sham-lesions, bilateral injections of 0.5 μl of saline into the dorsal and ventral hippocampi were made.

Histological examination indicated that intrahippocampal colchicine caused an almost complete destruction of the granule cells. In contrast, the microinjection of intrahippocampal saline caused no overt morphological changes. Gliosis was present along the insertion track of the needle used for colchicine or saline injection. No overt difference was noted in the density and distribution of the gliosis between the saline- and colchicine-treated animals.

2.2. Locomotor activity

Locomotor activity was measured using an animal movement analyzing system (SCANETSV-10, MATYS, Toyama, Japan). The system consisted of a rectangular enclosure (480×300 mm^2). The side walls (60 mm height) of the enclosure were equipped with 144 pairs of photosensors located at 5 mm intervals at a height of 30 mm from the bottom edge. A rectangular, transparent plastic cage, with an internal floor area of 440×260 mm^2 and a height of 400 mm, was set on the SCANETSV-10 such that the photosensors were 30 mm above the floor of the cage. An animal was placed in the observation cage 1 h before drug treatment. Following treatment, a pair of photosensors was scanned every 0.1 s to detect animal movement. An intersection of two paired-photosensors (10 mm apart) in the enclosure was counted as one unit of locomotor activity. Data collected for 90 min were used for analysis.

Naive animals were randomly selected for the following three groups: A = intact animals, i.e., not lesioned animals ($n = 24$); B = intrahippocampal bilateral sham-lesioned animals (saline administration, $n = 34$), and C = animals with intrahippocampal bilateral lesions resulting from treatment with colchicine ($n = 32$). MDMA was dissolved in saline to render 1 ml/kg volume of injection. The animals in each group received either 1 ml/kg s.c. of saline or 2, 5, or 10 mg/kg s.c. of

MDMA (dissolved in saline). Following the measurement of locomotor activity, animals were sacrificed and Fos protein expression was determined.

2.3. Fos protein immunohistochemistry

Animals were deeply anesthetized with pentobarbital. Subsequently, animals were transcardially perfused with 100 ml of 0.15 M NaCl, followed by 500 ml of ice-cold 4% paraformaldehyde in 0.1 M phosphate-buffer (pH 7.4). The brains were removed, post-fixed overnight at 4 °C in the same fixative for 24 h, coronally sectioned at a thickness of 70 μm using a vibratome (Leica VT1000S, Leica, Germany), and placed in ice-cold 0.01 M phosphate-buffered saline (pH 7.4). Free-floating sections were placed in 0.01 M phosphate-buffered saline containing 2% normal goat serum, 0.2% Triton X-100, and 0.1% bovine serum albumin for 1 h at room temperature. Sections were incubated for 36–48 h at 4 °C in a primary antibody (Fos AB-2 rabbit polyclonal antibody, Oncogene Science, Cambridge, MA) diluted 1:1000. Sections were then washed twice in phosphate-buffer saline, incubated for 1 h in a second antibody (biotinylated goat anti-rabbit IgG adsorbed against rat serum), and incubated in an avidin-horseradish peroxidase solution prepared from the Vectastain® elite ABC kit (Vector Laboratories Inc., Burlingame, CA) for 1 h at room temperature. Sections were washed twice in ice-cold phosphate-buffered saline (pH 7.4) and the antibody reaction was developed with 3,3′-diaminobenzidine (0.015%) and 0.001% hydrogen peroxidase in 50 mM Tris–HCl (pH 7.4). After several rinses in phosphate-buffered saline (pH 7.4), the stained sections were mounted on gelatinized slides, dehydrated, and coverslipped with Permount® (Fisher Scientific Co., Fair Lawn, NJ).

The number of Fos-positive cells within a 0.35 mm^2 area was counted using Macintosh-based image analysis software (NIH Image). The anatomical identifications of sections were made according to the atlas of Paxinos and Watson. The regions (AP coordinates) analyzed were the medial prefrontal cortex (3.2 mm anterior), dorsolateral prefrontal cortex (3.2 mm anterior), anterior cingulate cortex (1.7 mm anterior), piriform cortex (1.7 mm anterior), dorsal striatum (1.7 mm anterior), nucleus accumbens core (1.7 mm anterior), and the nucleus accumbens shell (1.7 mm anterior). We counted the number of Fos-positive cells in the right and left regions of interest. Consequently, the denominator of d.f. was twice the number of rats subjected to treatment.

2.4. Statistical analysis

The main dependent variables were the amount of locomotor activity and the number of Fos immunoreactive cells. Two-way ANOVA was conducted to test the effects of 'Lesion' (A, B, and C groups) and 'Drug' (saline and MDMA at doses of 2, 5, and 10 mg/kg) on these dependent variables. When a significant interaction between lesions and drugs was revealed, we subsequently repeated a separate one-way ANOVA for the drug group (i.e. saline vs. 2, 5, or 10 mg/kg MDMA) to determine whether or not any distinct patterns of the dependent variables across the three levels of the lesioned groups would emerge between the drug-treated groups. According to the results of the second one-way ANOVA, we carried out post hoc pair comparisons using Bonferroni's test. All values are expressed as the mean ± S.E.M. Analyses were carried out with the SPSS package for Windows, version 7.5 (SPSS Inc., Chicago, Illinois).

3. Results

3.1. Effect of intrahippocampal administration of saline and colchicine on the locomotor response to s.c. saline and MDMA (Fig. 1)

There was no significant difference in the baseline locomotor activity among the A, B, and C groups prior to saline or MDMA administration (data not shown). Two-way ANOVA showed a significant interaction between the Lesion and Drug groups in the number of locomotions ($F = 6.90$, d.f. $= 6.78$, $P = < 0.001$). One-way ANOVA revealed a significant difference among the three Lesion groups after saline injection ($F = 6.26$, d.f. $= 2.19$, $P < 0.01$), 2 mg/kg MDMA ($F = 9.37$, d.f. $= 2.21$ $P < 0.01$), 5 mg/kg MDMA ($F = 34.6$, d.f. $= 2.20$, $P < 0.001$), and 10 mg/kg MDMA ($F = 21.27$, d.f. $= 2.18$, $P < 0.001$). The C group showed a significantly larger number of locomotions after saline injection than did the A ($P = 0.01$) group, and the comparison between groups C and B also revealed a marginally significant difference ($P = 0.055$). There was no significant difference between the A and B groups ($P = 1.00$). When 2, 5, or 10 mg/kg MDMA was given, there was no significant difference in the locomotor activity between the A and B groups ($P = 1.00$ for each of the MDMA doses). However, MDMA caused a significantly higher value in the C group than in either the A or the B group ($P <$ 0.01 vs. the A and B groups, for 2 mg/kg; $P < 0.001$ vs. the A and B groups, for 5 mg/kg; $P < 0.001$ vs. the A and B groups, for 10 mg/kg).

3.2. Effects of intrahippocampal administration of saline and colchicine on Fos protein expression in response to s.c. saline and MDMA (Figs. 2 and 3)

The administration of saline or MDMA-induced the expression of Fos protein in all of the brain regions examined, i.e., in the medial prefrontal cortex, dorso-

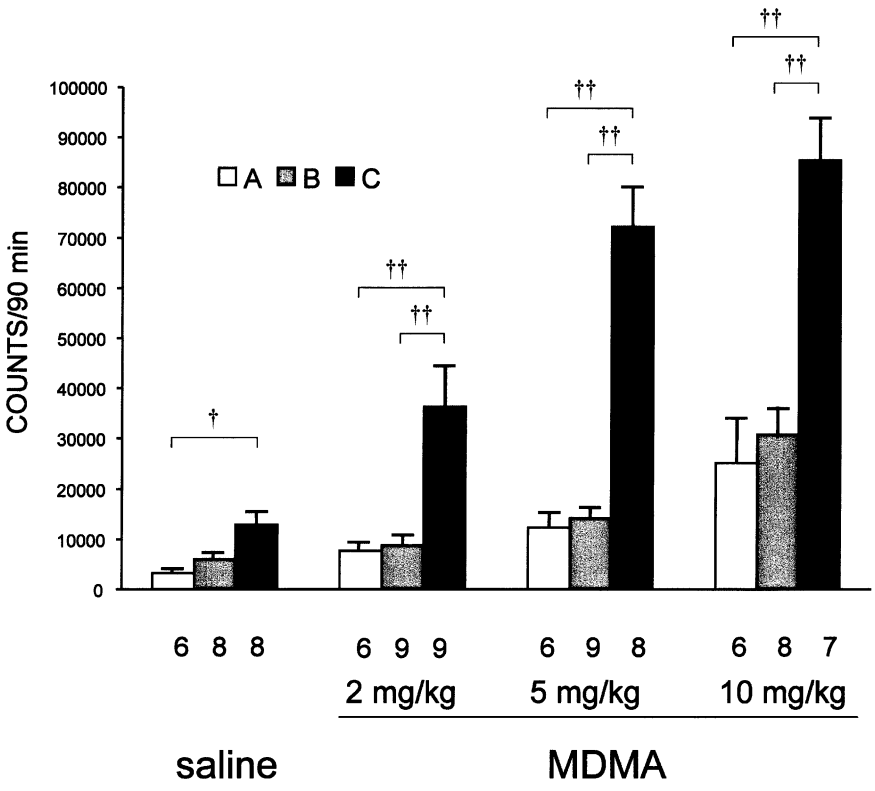

Fig. 1. Locomotor activity following the s.c. administration of saline or MDMA in A, intact (□); B, sham-lesioned (▨); and C, colchicine-lesioned (■) group animals. All values represent the mean ± S.E.M. The symbol (†) denotes a $P < 0.05$ difference between the A and the C groups or between the B and the C groups. The symbol (††) denotes a $P < 0.01$ difference between the A and the C groups or between the B and the C groups.

lateral prefrontal cortex, anterior cingulate cortex, piriform cortex, dorsal striatum, nucleus accumbens core, and the nucleus accumbens shell. Two-way ANOVA revealed a significant Lesion X Drug interaction in the number of Fos-positive cells only in the nucleus accumbens core ($F = 2.56$, d.f. $= 6.168$, $P = 0.021$). In the nucleus accumbens core, one-way ANOVA revealed a significant difference across the three Lesion groups following saline injection ($F = 9.40$, d.f. $= 2.41$, $P = 0.001$) or 2 mg/kg MDMA ($F = 24.50$, d.f. $= 2.45$, $P < 0.001$), 5 mg/kg MDMA ($F = 13.40$, d.f. $= 2.43$, $P < 0.001$), or 10 mg/kg MDMA ($F = 5.32$, d.f. $= 2.39$, $P = 0.009$). Subsequent post hoc pair comparisons were carried out using Bonferroni's test to compare the Lesion groups, focusing on the nucleus accumbens core; these comparisons indicated that the number of Fos-positive cells was significantly greater in the C group compared to the A and B groups following saline administration ($P = 0.002$ vs. the A and B groups), 2 mg/kg MDMA ($P < 0.001$ vs. the A and B groups), 5 mg/kg MDMA ($P < 0.001$ vs. the A and B groups), and 10 mg/kg MDMA ($P < 0.05$ vs. the A and B groups). There was no significant difference observed in the response to either saline or MDMA between the A and B groups ($P = 1.00$ for saline; $P = 1.00$ for 2 mg/kg MDMA; $P = 1.00$ for 5 mg/kg MDMA; $P = 1.00$ for 10 mg/kg MDMA).

4. Discussion

The results of the present study confirm the findings of previous studies demonstrating an increase in locomotor activity after the injection of MDMA (Gold et al., 1988, 1989a; Callaway et al., 1990; Callaway and Geyer, 1992b). Our results also show that MDMA-induced locomotor activity is significantly enhanced by the bilateral destruction of granule cells in the hippocampal dentate gyrus. This finding suggests that the bilateral destruction of granule cells enhances the locomotor activity induced by MDMA.

Both the intact and the sham-lesioned animals, when given systemic MDMA, showed a similar dose-dependent increase in the number of Fos-positive cells in all the regions examined, i.e., the medial prefrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, piriform cortex, dorsal striatum, nucleus accumbens core, and the nucleus accumbens shell. These findings are compatible with a previous result showing the robust emergence of Fos-positive cells in several brain areas of rats receiving systemic MDMA (Stephenson et al., 1999). In the present study, the lesioned animals also showed a dose-dependent increase in Fos expression in all of the examined regions after receiving systemic MDMA. Interestingly, MDMA administration led to a significant increase in the number of Fos-positive cells

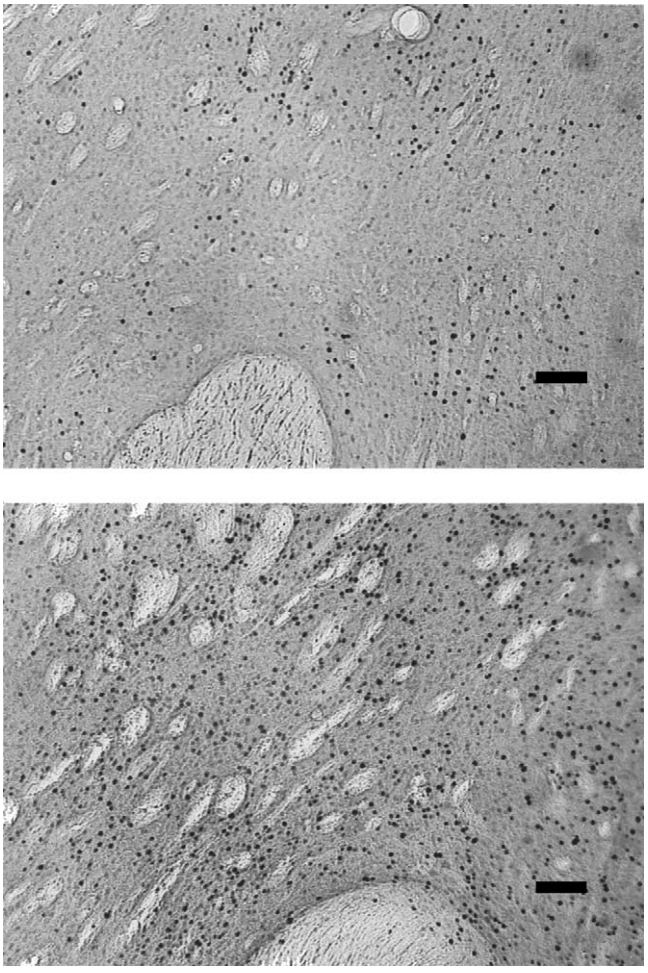

Fig. 2. The induction of Fos protein in the nucleus accumbens core after saline (top) or MDMA (bottom) injection, each from the C group. The calibration bar represents 100 μm.

only in the nucleus accumbens core of the lesioned animals, when this treatment was compared among the lesioned, sham-lesioned, and intact animals. In the past, a locomotor response due to systemic MDMA was attenuated by lesioning of the nucleus accumbens in rats (Gold et al., 1989b), whereas MDMA injection into the nucleus accumbens produced locomotor hyperactivity in rats (Callaway and Geyer, 1992a). Taken together with these previous findings, the present results suggest that the destruction of dentate granule cells modifies the function of the nucleus accumbens core, leading to an enhancement of locomotor activity induced by MDMA injection. However, in order to determine whether or not the nucleus accumbens is essential when the dentate granule cells are lesioned, further studies will be needed that involve either the lesioning of the nucleus accumbens or MDMA injection directly into that structure.

In a previous study, we destroyed hippocampal dentate granule cells by the same method that was employed here, followed by the systemic administration of 2 mg/kg methamphetamine (Tani et al., 2001). When we compared the locomotor activity induced by 10 mg/kg MDMA (the maximum dose tested in this study) and 2 mg/kg methamphetamine, the amount of activity induced by MDMA was less than that induced by methamphetamine (85 408.7 ± 8338.2 for MDMA and 103 382.3 ± 3340.1 counts/90 min for methamphetamine). Furthermore, as mentioned previously, an injection of 2 mg/kg methamphetamine led to an increase in the number of Fos-positive cells in widespread brain areas innervated by dopaminergic inputs (Tani et al., 2001); in contrast, 10 mg/kg MDMA did so only in the nucleus accumbens core. Therefore, it is possible that the dentate granule cell destruction differentially modified the effects of the two psychostimulants, MDMA and methamphetamine, and that recruitment of other brain regions, in addition to that of the nucleus accumbens core, may be necessary for further augmentation of locomotor activity.

The major hippocampal afferents are the entorhinohippocampal pathway, the excitatory commissural/associational system, and the septal projection (Amaral and Witter, 1995). These afferents terminate in a laminated fashion on target neurons in the dentate gyrus and cornu ammonis. Inside the hippocampus, fiber systems specifically and reciprocally connect the dentate granule cells with CA3, CA3 with CA1, and CA1 with the subiculum (Amaral et al., 1991; Amaral and Witter, 1995; Bausch and McNamara, 2000). Due to the sequential nature of the hippocampus, information travels from the granule cells to the subiculum. Therefore, dentate granule cell destruction may disrupt or modify the function of the efferent system from the hippocampus, which is mediated by the subiculum. On the other hand, acutely applied MDMA increases extracellular levels of 5-HT and dopamine in the nucleus accumbens (White et al., 1994; Yamamoto and Spanos, 1994), although its local application has an inhibitory effect on the excitability of most neurons within the nucleus accumbens (White et al., 1994). This MDMA-induced inhibition appears to be mediated by both 5-HT and dopamine, since it is mimicked by these monoamines and can be attenuated by depleting DA and 5-HT or by applying receptor antagonists (White et al., 1994; Obradovic et al., 1996). Since the subiculum sends a large glutamergic output to the nucleus accumbens (DeFrance et al., 1980; Christie et al., 1987; White et al., 1996), and since this glutamergic pathway may modulate 5-HT and dopamine release in the nucleus accumbens (Imperato et al., 1990; Shimizu et al., 1990; Cartmell et al., 2000; Grace, 2000; Tao and Auerbach, 2000; Floresco et al., 2001), the destruction of granule cells might have resulted in the enhancement of 5-HT and dopamine function in the present study. In addition, the enhanced release of 5-HT, which may have been caused by the dentate granule cell destruction, might have activated post-synaptic 5-HT receptors located on the GABA interneurons,

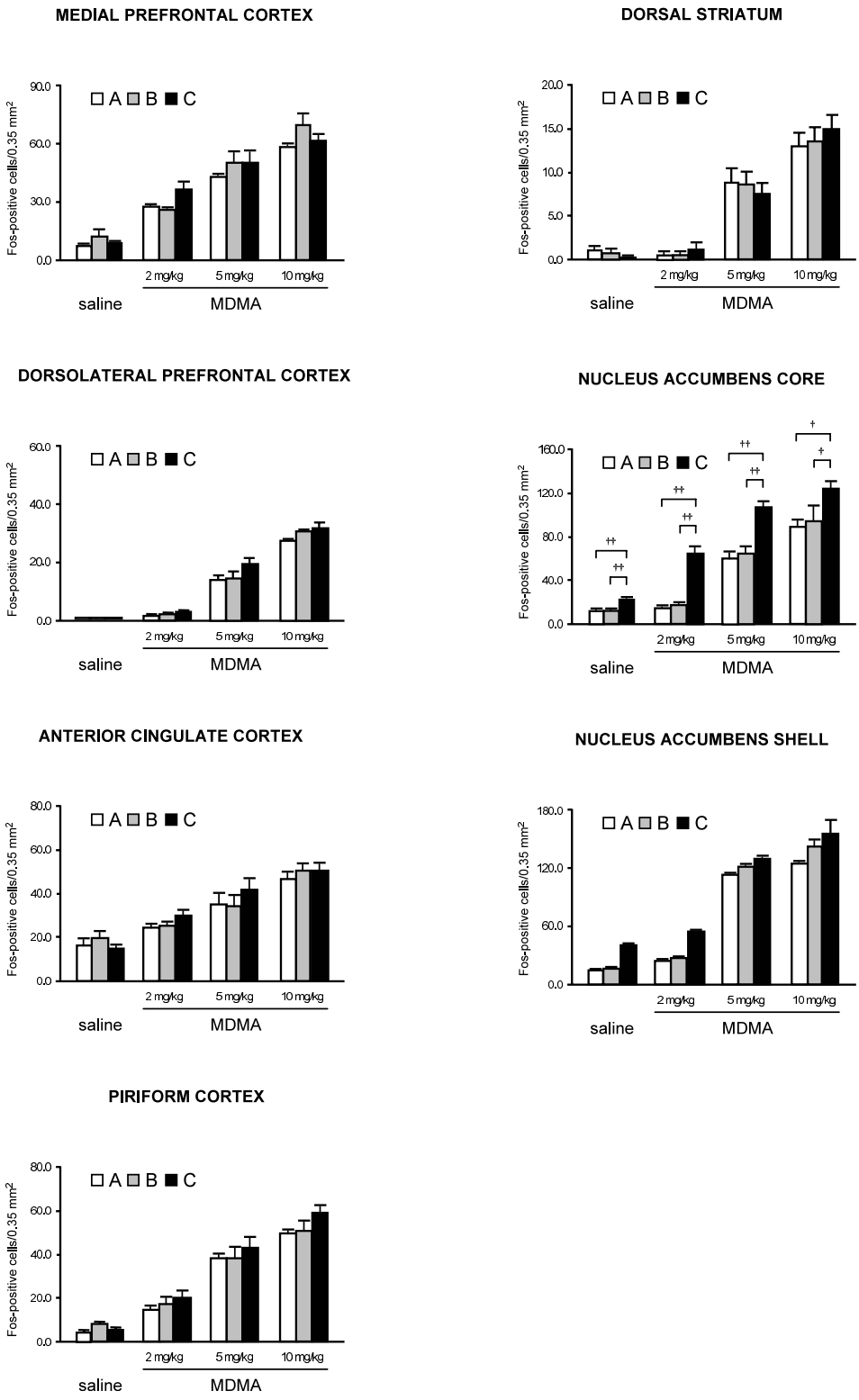

Fig. 3. The number of Fos-positive cells in the medial prefrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, piriform cortex, dorsal striatum, nucleus accumbens core, and nucleus accumbens shell following the s.c. injection of saline or 5 mg/kg of MDMA in A, intact (□); B, sham-lesioned (▨); and C, colchicine-lesioned (■) animals. All values represent the mean ± S.E.M. The symbol (†) denotes a $P < 0.05$ difference between the A and the C groups or between the B and the C groups. The symbol (††) denotes a $P < 0.01$ difference between the A and the C groups or between the B and the C groups.

resulting in a decrease in GABAergic transmission (Sprague et al., 1998), by which the excessive 5-HT release then may have taken.

The granule cell destruction significantly enhanced locomotor activity in this study. The lesioned animals performed a much larger number of locomotions after saline injection compared to the intact and sham-lesioned animals, although the difference between the lesioned and sham-lesioned animals was only marginally significant ($P < 0.055$). Furthermore, the granule cell destruction increased the number of Fos-positive cells in the nucleus accumbens core after saline treatment alone. Such an elevation was not observed in the nucleus accumbens shell. Caine et al. (2001) have reported that in rats, projections from the dorsal subiculum to the accumbens core and from the ventral subiculum to the accumbens shell exert distinct influences on behavioral responses, which are then amplified by psychomotor stimulant drugs such as amphetamine and cocaine. In that study, animals with lesions of the dorsal subiculum showed hyperlocomotor activity, whereas those with lesions of the ventral subiculum exhibited an attenuated locomotor response. Therefore, it is likely that dentate gyrus destruction per se interferes with the pathway from the dorsal subiculum to the nucleus accumbens core; this would be one plausible explanation for the enhancement of locomotor activity due to stress loading, such as that provided by saline injection alone.

In conclusion, the results of this study indicate that the dentate granule cell destruction induced by local injection of colchicine augments locomotor activity after systemic MDMA or saline injection. In addition, after granule cell destruction, a significant enhancement of Fos induction was observed to occur selectively in the nucleus accumbens core after saline or MDMA administration. These results suggest that the nucleus accumbens core is involved in the enhancement of locomotor activity induced by the injection of saline (stress loading) or by MDMA injection following the destruction of dentate granule cells. Further studies are required to clarify the mechanisms of action of these phenomena, particularly regarding the functional interactions between the hippocampus and the nucleus accumbens.

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