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European Journal of Pharmacology 442 (2002) 73–79

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The medial prefrontal cortex mediates 3-methoxytyramine-induced behavioural changes in rat

Taizo Nakazato*

Department of Physiology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received 13 August 2001; received in revised form 27 February 2002; accepted 1 March 2002

Abstract

L-3,4-Dihydroxyphenylalanine (L-DOPA) remains a common treatment for Parkinson's disease; however, side effects (i.e., dyskinesia and hallucinations) also remain problematic. We recently reported that the dopamine metabolite 3-methoxytyramine causes stereotypy in rats via dopamine receptors, raising the possibility that 3-methoxytyramine is involved in the adverse side effects of chronic L-DOPA treatment. Thus, the present study examined the sites of 3-methoxytyramine action in the rat brain. After intracerebroventricular administration of 3-methoxytyramine, significantly more neurones expressed c-Fos in mesocortico-limbic dopamine areas including frontal cortex, medial prefrontal cortex, parietal cortex, piriform cortex, the nucleus accumbens shell, and ventral tegmental area. 3-Methoxytyramine injection into the medial prefrontal cortex specifically resulted in behavioural changes characteristic of those elicited by the more general intracerebroventricular injection of 3-methoxytyramine. This suggests that the medial prefrontal cortex mediates the 3-methoxytyramine-induced behavioural changes and that a reduction of its action there may alleviate the adverse effects of chronic L-DOPA treatment.

Keywords: c-Fos; Parkinson's disease; Dyskinesia; L-DOPA (L-3,4-dihydroxyphenylalanine); Dopamine receptor agonist

1. Introduction

In Parkinson's disease, there is a progressive loss of dopamine neurones in the substantia nigra and its related areas, resulting in progressive extrapyramidal dysfunction. L-3,4-Dihydroxyphenylalanine (L-DOPA) has been widely used as a treatment for the disease; however, adverse side effects, such as dyskinesia (uncontrollable movement) and hallucinations, continue to be a serious problem with long-term use (Barbeau, 1969; Diamond et al., 1987). Dopamine receptor supersensitivity to dopamine has been thought to underlie chronic-L-DOPA-induced dyskinesia (Klawans et al., 1975; Lee et al., 1978); however, our previous study showed that L-DOPA itself may also be related to the adverse effects of chronic L-DOPA treatment (Nakazato and Akiyama, 1989). Moreover, we recently showed that the dopamine metabolite 3-methoxytyramine also causes increased behavioural activity in rats, and that this effect is blocked by a dopamine D_1/D_5 receptor antagonist, suggesting that it is mediated via dopamine D_1/D_5 receptors (Nakazato and Akiyama, 2002). Dopamine is metabolised to 3,4-dihydroxyphenylacetic acid (DOPAC) and 3-methoxytyramine. Both of these metabolites can be further metabolised to homovanillic acid (HVA). In a previous study, we demonstrated that neither DOPAC nor HVA causes significant behavioural activity and that dopamine-denervated rats exhibit a supersensitive response to 3-methoxytyramine. Thus, we proposed that 3-methoxytyramine may be related to the adverse side effects of chronic L-DOPA treatment in Parkinson patients. It is also likely that 3-methoxytyramine has therapeutic antiparkinsonian effects, as do dopamine and L-DOPA. The mechanism underlying 3-methoxytyramine-induced behaviour, however, has not yet been well characterised.

In the present study, we first localised the possible target sites of exogenous 3-methoxytyramine by examining immediate early gene (c-Fos) expression in the rat brain following intracerebroventricular administration of 3-methoxytyramine. Because c-Fos expression is induced by increased activity of neurones, the areas exhibiting increased c-Fos expression may not necessarily reflect the areas directly stimulated by 3-methoxytyramine (Dragunow et al., 1990; Paul et al., 1992; Robertson et al., 1989). Therefore, to determine which c-Fos-positive area was related to 3-

* Tel.: +81-3-5802-1027; fax: +81-3-3813-4954.
E-mail address: nakazato@med.juntendo.ac.jp (T. Nakazato).

0014-2999/02/$ - see front matter
PII: S0014-2999(02)01495-4

methoxytyramine-induced behavioural changes, 3-methoxytyramine was locally injected into each area that both (1) received dense dopaminergic projections and (2) exhibited highly significant increases in the number of c-Fos-positive neurones, and behavioural activity was examined. Moreover, the possibility also exists that the inhibition of an area may be important to the resultant behaviour, but because c-Fos expression only reflects increases in activity, a functionally important area may not be c-Fos-positive. Therefore, 3-methoxytyramine was injected into a possibly relevant c-Fos-negative area (striatum) as well as into areas that exhibited marked, but not statistically significant, increases in c-Fos-positive neurones (occipital and temporal cortices).

2. Materials and methods

2.1. Preparation of animals

Male Wistar rats (350 to 400 g, $n=31$ total) were anaesthetised with pentobarbital (50 mg/kg, i.p.) and held stationary in a stereotaxic apparatus. For rats used for immunohistochemistry ($n=12$), a stainless-steel cannula (0.6 mm in diameter) for drug administration was placed unilaterally in the lateral ventricle (coordinates: 0.8 mm posterior and − 1.5 mm lateral to bregma; 3.0 mm ventral to the dura mater). The cannula was equipped with an inner cannula (0.3 mm outer diameter). For local administration of drug, a cannula was placed stereotaxically in the ipsilateral medial prefrontal cortex ($n=5$; coordinates: 2.8 mm anterior and 0.5 mm lateral to bregma; 2.5 mm ventral to the dorsal surface of the cerebral cortex), frontal cortex ($n=4$; 1.0; 2.0; 1.0), parietal cortex ($n=2$; 2.5; 4.5; 1.0), temporal cortex ($n=2$; − 4.8; 6.5; 1.5), occipital cortex ($n=2$; − 5.5; 4.0; 1.0), striatum ($n=2$; 0.5; 3.0; 5.5), and nucleus accumbens shell ($n=2$; 2.0; 1.5; 6.5; Paxinos and Watson, 1982). These rats were used to examine the behavioural effects of 3-methoxytyramine. Animals were allowed to recover for at least 4 weeks postsurgery before use.

Table 1
Behavioural rating scale

Score	Definition
0	Asleep, lying down with eyes closed.
1	Lying down with eyes open, little movement.
2	Lying down with head up, slow periodic sniffing.
3	Getting up with periodic sniffing.
4	Some rearing with sniffing and slow head swinging, some turning.
5	Frequent rearing with prominent sniffing, head swinging, and turning.
6	Continuous rearing with faster head swinging or frequent turning.

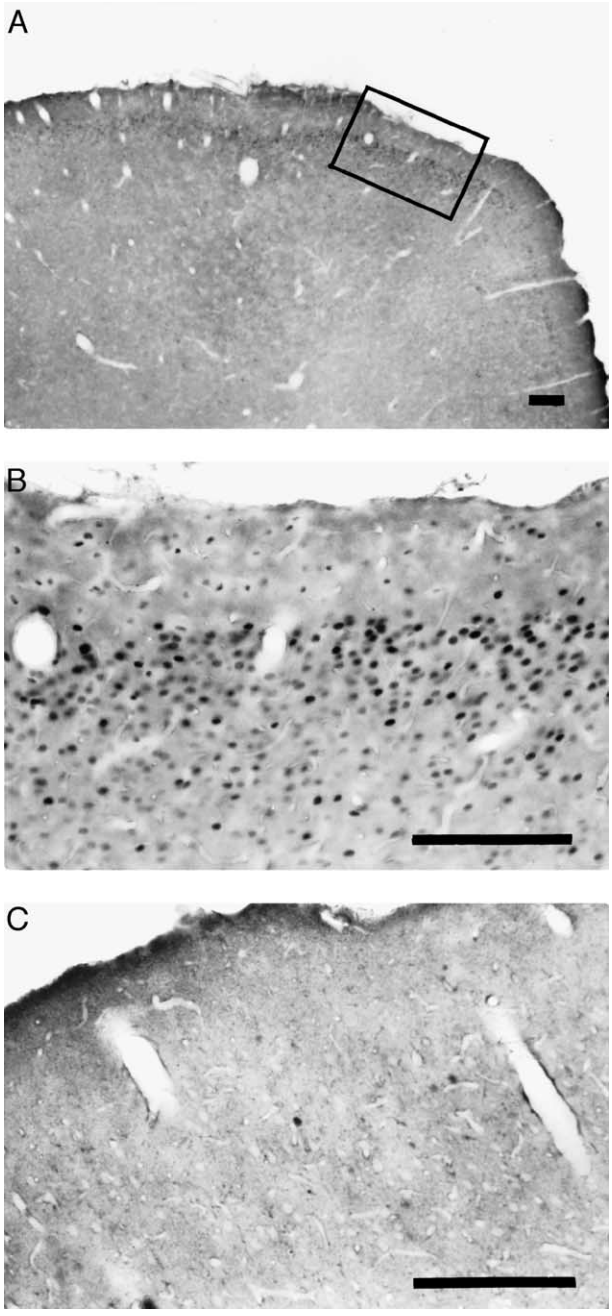

Fig. 1. Micrographs showing c-Fos-positive neurones in the frontal cortex. 3-Methoxytyramine (200 μg in 40 μl, 30 min) was administered intracerebroventricularly. (A) Many c-Fos-positive neurones were observed in the left frontal cortex. (B) Higher magnification of the area in the square in (A). c-Fos-positive neurones were observed primarily in layers II–III. (C) There were fewer c-Fos-positive neurones in controls. Scale bar = 100 μm.

2.2. Drug administration

For immunohistochemical examination, 3-methoxytyramine was administered intracerebroventricularly over a period of 30 min at a dose of 200 μg dissolved in 40 μl of Ringer's solution. For behavioural observations, 3-

methoxytyramine was administered locally over a period of 30 min into the medial prefrontal cortex at doses of 0.1, 1, 10, 40, and 80 μg ($n = 5$) and into other areas at doses of 40 and 80 μg ($n = 14$) dissolved in 7.5 μl Ringer's solution. Six injections were administered to each rat receiving medial prefrontal injections; one injection given once a week for 6 weeks, starting with the lowest dose and progressing to the highest dose in each rat, then ending with Ringer's-only control. Injections into other areas were administered bi-weekly to a separate group of rats; each rat received a total

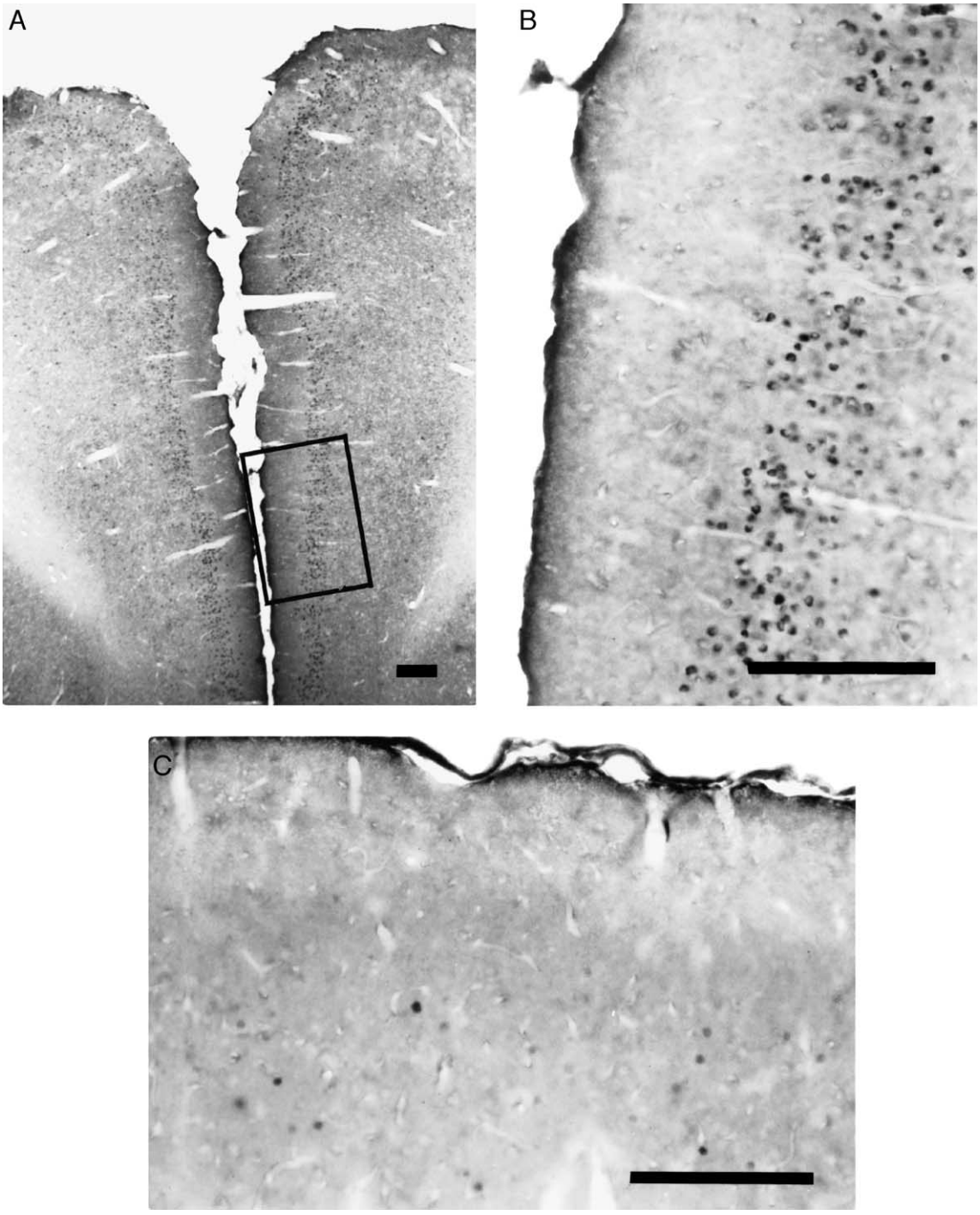

Fig. 2. Micrographs showing c-Fos-positive neurones in the medial prefrontal and temporal cortices. 3-Methoxytyramine (200 μg in 40 μl, 30 min) was administered intracerebroventricularly. (A) There was a significant increase in the number of c-Fos-positive neurones in the right medial prefrontal cortex. (B) Higher magnification of the area in the square in (A). c-Fos-positive neurones were observed primarily in layers II–III. (C) c-Fos-positive neurones in the temporal cortex. There was not a significant increase in the number of c-Fos-positive neurones in this area. Scale bar = 100 μm.

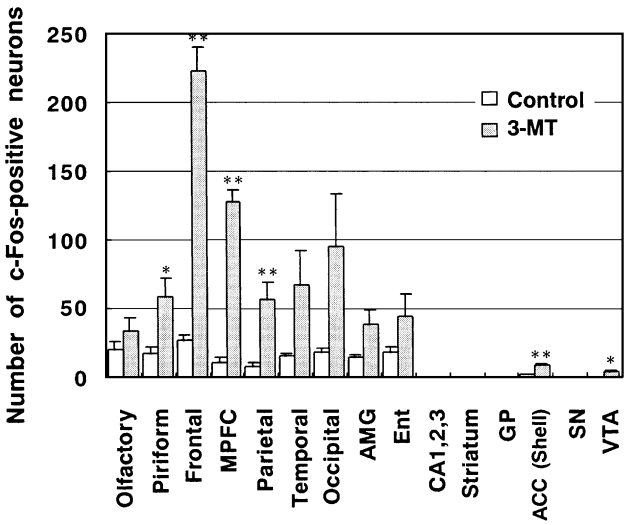

Fig. 3. Number of c-Fos-positive neurones in various brain areas (mean ± S.E.M.; $n=7$; dotted columns) after intracerebroventricular injection of 3-methoxytyramine (200 μg in 40 μl, 30 min). The numbers of c-Fos-positive neurones in 0.2 × 0.2-mm squares were counted. * $P<0.01$; * * $P<0.001$ compared with vehicle injection (mean ± S.E.M.; $n=5$; open columns). ACC, accumbens (shell); AMG, amygdaloid nucleus; ENT, entorhinal cortex; MPFC, medial prefrontal cortex; SN, substantia nigra; VTA, ventral tegmental area.

of three injections, the first being the low dose, the second at the higher dose, then a Ringer's-only control.

2.3. Immunohistochemical examination

Two hours after intracerebroventricular administration of 3-methoxytyramine (200 μg/40 μl), the animals were anaesthetised with pentobarbital (15 mg/kg) and perfused intracardially with 4% paraformaldehyde solution, and the brain was removed. After a postfixation period of 24 h, the brain was transferred to a solution of 20% sucrose in 0.1 M phosphate-buffered saline (PBS). On the following day, the brain was rapidly frozen. The brain was sectioned at 30 μm, and the sections were incubated for 20 min in PBS containing 0.25% Triton-X and 1% H_2O_2 (Miwa et al., 1998; Nishi, 1997). To visualise c-Fos, sections were preincubated in 5% normal goat serum and incubated for 72 h with primary antibody, a rabbit polyclonal anti-c-Fos antibody (Oncogene Research Products, Cambridge, MA) that was diluted 1:3000. Then, sections were incubated for 3 h with secondary antibody, using avidin–biotin–peroxidase complex (VECTASTAIN *Elite* ABC Kit; Vectar Laboratories, CA, USA), and developed with 0.03% diaminobenzidine and 0.02% nickel ammonium sulphate. The numbers of c-Fos-positive neurones were determined in 0.2 × 0.2-mm squares. The c-Fos-positive neurones in several squares placed randomly within each structure examined were counted, and the average calculated for each structure. Data were analysed statistically using a paired Student's *t*-test. Differences were considered statistically significant with *P* values less than or equal to 0.05.

2.4. Behavioural observations

Each rat was placed in a 30 × 22 × 24-cm box and its behaviour was recorded on videotape for 120 min. Behavioural activity was scored using a rating scale developed by Creese and Iversen (1973) with slight modification, as shown in Table 1. Behaviour was scored every 30 s, and the scores were averaged and rounded to the nearest whole number. Data were analysed statistically using analysis of variance (ANOVA) with two within-subjects factors (time and dose) followed by a post-hoc test (Dunnet's test) comparing 10 and 80 μg 3-methoxytyramine with vehicle for each time point.

The experiments were performed according to the Principles of Animal Experiments at Juntendo University.

3. Results

3.1. Immunohistochemical examination

After 3-methoxytyramine administration in the left lateral ventricle, many c-Fos-positive neurones were observed in the frontal cortex (Fig. 1A,B). After control injections, few c-Fos-positive neurones were observed (Fig. 1C). There was also a significant increase in c-Fos-positive neurones in the medial prefrontal cortex (Fig. 2A,B). There were no significant differences between the right and left cortices. In these areas, c-Fos-positive neurones were distributed primarily in layers II–III and to a lesser extent in layers IV–VI. An increase in c-Fos-positive neurones was also observed in the parietal and piriform cortices, although to a lesser degree

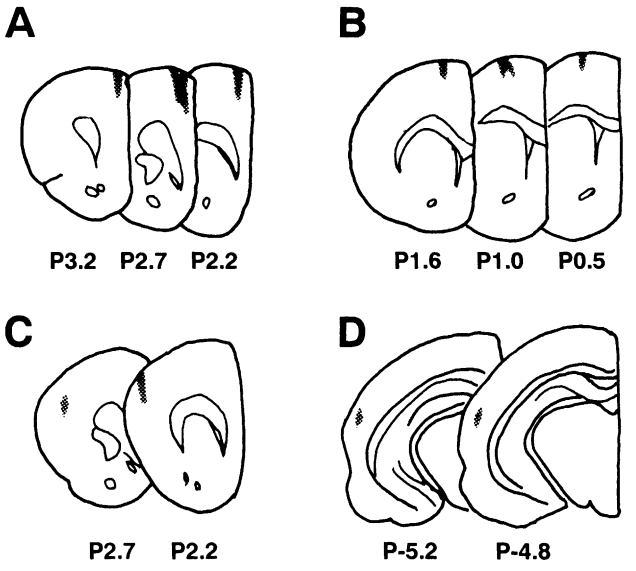

Fig. 4. Illustrations of the local injection areas in the medial prefrontal (A), frontal (B), parietal (C), and temporal (D) cortices. Shaded areas indicate the injection sites. Numerals after "P" indicate the distance (mm) anterior (positive numbers) and posterior (negative numbers) from bregma (Paxinos and Watson, 1982).

compared with the frontal and medial prefrontal cortices (Fig. 3). There was not a significant increase in the number of c-Fos-positive neurones observed in the temporal or occipital cortex (Fig. 2C). In the shell of the nucleus accumbens and the ventral tegmental area, a small but significant increase in the number of c-Fos-positive neurones was observed compared with the number after vehicle injection (Fig. 3).

3.2. Behavioural examination

3-Methoxytyramine (40, 80 μg) was administered locally into the striatum, nucleus accumbens shell, medial prefrontal cortex, and frontal, parietal, temporal, and occipital cortices (Fig. 4). Local injection into each of these structures (except the medial prefrontal cortex) induced maximal behavioural scores of only 0 or 1. Behavioural activity increased significantly only after the injection of 3-methoxytyramine into the medial prefrontal cortex. Moreover, after medial prefrontal cortex injections, the rats exhibited increased locomotion, rotation behaviour (without directional preference), stereotypy (primarily prolonged sniffing), and catalepsy-like posture (getting up and staying in the same position without movement) like that previously observed with intracerebroventricular injections of 3-methoxytyramine (Nakazato and Akiyama, 2002). Behavioural activ ity increased approximately 10 min after the start of the injection and reached a peak immediately after the end of the injection (Fig. 5A). The catalepsy-like posture was observed only after the highest dose of 3-methoxytyramine (80 μg) and occurred between 15 and 30 min after the start of injection. At lower doses (10 μg), behavioural activity increased only slightly. As the dose of 3-methoxytyramine was increased from 0.1 to 80 μg in the medial prefrontal cortex, there was a dose-dependent increase in the maximal behavioural rating score (Fig. 5B).

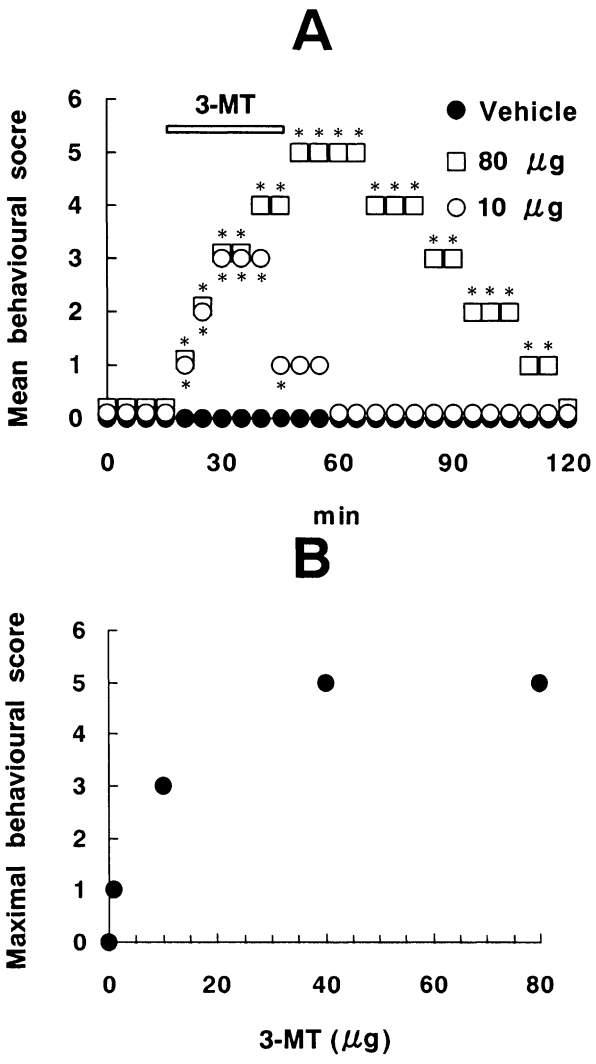

Fig. 5. Mean behavioural score induced by local application of 3-methoxytyramine in the medial prefrontal cortex. (A) Ten micrograms (○) and 80 μg (□) 3-methoxytyramine were administered locally in the medial prefrontal cortex of each rat ($n=5$) during the time indicated by the open bar, and behaviour was observed for 120 min. Mean scores were rounded to the nearest whole number. * $P<0.01$ compared with vehicle injection ($n=5$; ●). (B) Dose-dependent changes induced by local injection of Ringer's solution only and 3-methoxytyramine (0.1, 1, 10, 40, and 80 μg) into the medial prefrontal cortex in the same rat; one dose given each week for 6 weeks. Data points represent the maximal behavioural score after each injection.

4. Discussion

The results of the present study show that intracerebroventricular injection of 3-methoxytyramine caused an increase in behavioural activity and stereotypy, indicating that this dopamine metabolite may have a role in the dyskinesia associated with chronic L-DOPA treatment in Parkinson patients. Moreover, it appears that this behavioural change was mediated by the medial prefrontal cortex, because more specific, local injection of 3-methoxytyramine did not cause behavioural changes except when the injection was into the medial prefrontal cortex.

4.1. Effective brain area

After intracerebroventricular injection of 3-methoxytyramine, the greatest increases in numbers of c-Fos-positive neurones were observed in the frontal, medial prefrontal, parietal, and piriform cortices, and small but significant increases in numbers were observed in the shell of the nucleus accumbens and the ventral tegmental area. Dopamine afferents originate in the last structure (mesocortico-limbic dopamine system), suggesting that exogenous 3-methoxytyramine activated this dopamine system. To investigate the primary area involved in the behavioural effects observed previously after more general intracerebroventricular injections of 3-methoxytyramine (Nakazato and Akiyama, 2002), 3-methoxytyramine was injected locally into the areas that both (1) received dopamine afferents and (2) exhibited highly significant increases in numbers of c-Fos-positive neurones. Only injections into the medial prefrontal cortex

caused significant behavioural changes, suggesting that the medial prefrontal cortex mediated the behavioural changes observed after the more general 3-methoxytyramine injections and that activation of the frontal and parietal cortices was not directly involved.

The striatum was c-Fos negative in the present study. c-Fos-negative areas, however, are not necessarily unrelated to 3-methoxytyramine-induced behavioural changes. There are reports (Dragunow et al., 1990; Robertson et al., 1989) that L-DOPA does not cause c-Fos expression in the rat striatum without a prior lesion of the dopamine system. In contrast, L-DOPA does cause a behavioural change in unlesioned animals. In the present study, in addition to the striatum being c-Fos negative, behavioural changes were not induced by local injection of 3-methoxytyramine into the striatum, indicating that the striatum may not be directly involved in 3-methoxytyramine-induced behavioural changes. Similarly, no behavioural changes were observed after local injections into structures that exhibited marked (but not statistically significant) increases in c-Fos-positive neurones after intracerebroventricular injection of 3-methoxytyramine (i.e., occipital and temporal cortices).

4.2. Dopamine receptor subtypes

It is still unclear which of the dopamine receptor subtypes is involved. The results of our previous study (Nakazato and Akiyama, 2002) showed that the behavioural effects of 3-methoxytyramine are blocked by a dopamine-D_1/D_5-receptor antagonist, suggesting that 3-methoxytyramine-induced behavioural changes are mediated via dopamine D_1/D_5 receptors. This is supported by anatomical evidence showing that dopamine D_1 receptors are more densely distributed than dopamine D_2 receptors in rat cerebral cortical areas, including the medial prefrontal cortex (Dubois et al., 1986; Richfield et al., 1989; Wamsley et al., 1989). In this way, the c-Fos expression observed in the present study paralleled dopamine-D_1-receptor distribution. On the other hand, in the present study, c-Fos-positive neurones were distributed predominantly in cortical layers II–III, and to a lesser extent in layers IV–VI. Although previous immunohistochemical evidence shows that dopamine D_1 receptors are denser in cortical layers IV–VI than in layers II–III in the rat (Davidoff and Benes, 1998; Dawson et al., 1986), more recent immunocytochemical evidence (Ciliax et al., 2000) shows that dopamine D_5 receptors are located predominantly in cortical layers II–III. This supports the possibility that 3-methoxytyramine-induced behaviour is mediated via dopamine D_5 receptors. Steiner and Kitai (2000), however, have also reported recently that dopamine D_1 receptors are distributed prominently in cortical layers II–III. This evidence also raises the possibility that dopamine D_1 receptors are involved. Taken together, these data indicate that 3-methoxytyramine-induced behaviour is mediated by dopamine D_1 and/or D_5 receptors.

4.3. Clinical implications

In the present study, 3-methoxytyramine injection induced c-Fos expression in mesocortico-limbic areas, and injection of 3-methoxytyramine into the medial prefrontal cortex caused an increase in behavioural activity. The medial prefrontal cortex is involved in many cognitive processes, such as learning (De Bruin et al., 1997; Sawaguchi and Goldman-Rakic, 1991; Yee, 2000), motivation, exploratory behaviour (Mitchell and Laiacona, 1998), and hallucinations (Kubota et al., 1999). Moreover, it has been reported (Carter and Pycock, 1980; Hebert and Gerhardt, 1998; Speciale et al., 1986) that the medial prefrontal cortex is involved in stereotypical behaviour and locomotion. Assuming that the tissue levels of 3-methoxytyramine in patients treated with L-DOPA are sufficient to activate dopamine receptors, it is conceivable that 3-methoxytyramine has a role in both the antiparkinsonian effects and the side effects of chronic L-DOPA treatment. Thus, 3-methoxytyramine may add to the effects of L-DOPA and dopamine. Initially, 3-methoxytyramine may alleviate some of the symptoms of Parkinson's disease by increasing mobility. Then, as dopamine receptors become supersensitive, 3-methoxytyramine likely contributes to the adverse side effects of chronic L-DOPA treatment, particularly dyskinesia. Previous studies suggest that 3-methoxytyramine may be primarily related to end-of-dose dyskinesia (Nakazato and Akiyama, 2002), L-DOPA to onset-of-dose dyskinesia (Nakazato and Akiyama, 1989), and dopamine to peak-of-dose dyskinesia. Further characterisation of the effects of L-DOPA, dopamine, 3-methoxytyramine, and the other L-DOPA metabolites may aid in the development of new therapeutic strategies for Parkinson's disease patients.

Acknowledgements

This study was supported in part by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and by grants for Project Research from Juntendo University School of Medicine. I am grateful to Dr. Katsunori Nishi of the Tokyo Metropolitan Institute of Neuroscience for his valuable advice. I also thank Professor Okihide Hikosaka of the Department of Physiology, Juntendo University for his helpful discussion.

References

Barbeau, A., 1969. L-DOPA therapy in Parkinson's disease: a critical review of nine years experience. Can. Med. Assoc. J. 101, 791–800.

Carter, C.J., Pycock, C.J., 1980. Behavioural and biochemical effects of dopamine and noradrenaline depletion within the medial prefrontal cortex of the rat. Brain Res. 192, 163–176.

Ciliax, B.J., Nash, N., Heilman, C., Sunhara, R., Hartney, A., Tiberi, M., Rye, D.B., Caron, M.G., Niznik, H.B., Levey, A.I., 2000. Dopamine D_5 receptor immunolocalization in rat and monkey brain. Synapse 37, 125–145.

Creese, I., Iversen, S.D., 1973. Blockade of amphetamine induced motor stimulation and stereotypy in the adult rat following neonatal treatment with 6-hydroxydopamine. Brain Res. 55, 369–382.

Davidoff, S.T., Benes, F., 1998. High-resolution scatchard analysis shows D_1 receptor binding on pyramidal and nonpyramidal neurons. Synapse 28, 83–90.

Dawson, T.M., Gehlert, D.R., McCabe, R.T., Barnett, A., Wamsley, J.K., 1986. D-1 dopamine receptors in the rat brain: a quantitative autoradiographic analysis. J. Neurosci. 6, 2352–2365.

De Bruin, J.P.C., Swinkels, W.A.M., De Brabander, J.M., 1997. Response learning of rats in a Morris water maze: involvement of the medial prefrontal cortex. Behav. Brain Res. 85, 47–55.

Diamond, S.G., Markham, C.H., Hoehn, M.M., McDowell, F.H., Muenter, M.D., 1987. Multi-center study of Parkinson mortality with early versus later dopa treatment. Ann. Neurol. 22, 8–12.

Dragunow, M., Robertson, G.S., Faull, R.L.M., Robertson, H.A., Jansen, K., 1990. D_2 dopamine receptor antagonists induce Fos and related proteins in rat striatal neurons. Neuroscience 37, 287–294.

Dubois, A., Savasta, M., Curet, O., Scatton, B., 1986. Autoradiographic distribution of the D_1 agonist [^{3}H]SKF 38393, in the rat brain and spinal cord. Comparison with the distribution of D_2 dopamine receptors. Neuroscience 19, 125–137.

Hebert, M.A., Gerhardt, G.A., 1998. Normal and drug-induced locomotor behavior in aging: comparison to evoked DA release and tissue content in Fischer 344 rats. Brain Res. 797, 42–54.

Klawans, H.L., Margolin, D.I., Dana, N., Crosset, P., 1975. Supersensitivity of d-amphetamine-and apomorphine-induced stereotyped behavior induced by chronic d-amphetamine administration. J. Neurol. Sci. 25, 283–289.

Kubota, T., Hirota, K., Yoshida, H., Takahashi, S., Anzawa, N., Ohkawa, H., Kushikawa, T., Matsuki, A., 1999. Effects of sedatives on noradrenaline release from the medial prefrontal cortex in rats. Psychopharmacology 146, 335–338.

Lee, T., Seeman, P., Rajput, A., Fareley, I., Horneykiewicz, O., 1978. Receptor basis for dopaminergic supersensitivity in Parkinson's disease. Nature 273, 59–61.

Mitchell, J.B., Laiacona, J., 1998. The medial frontal cortex and temporal memory: tests using spontaneous exploratory behaviour in the rat. Brain Res. 97, 107–113.

Miwa, H., Fuwa, T., Nishi, K., Mizuno, Y., 1998. Effect of the globus pallidus lesion on the induction of c-Fos by dopaminergic drugs in the striatum possibly via pallidostriatal feedback loops. Neurosci. Lett. 240, 167–170.

Nakazato, T., Akiyama, A., 1989. Effects of exogenous L-DOPA on behavior in the rat: an in vivo voltammetric study. Brain Res. 490, 332–338.

Nakazato, T., Akiyama, A., 2002. Behavioral activity and stereotypy in rats induced by L-DOPA metabolites: a possible role in the adverse effects of L-DOPA treatment of Parkinson's disease. Brain Res. 930, 134–142.

Nishi, K., 1997. Expression of c-Jun in dopaminergic neurons of the substantia nigra in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice. Brain Res. 771, 133–141.

Paul, M.L., Graybiel, A.M., David, J.C., Robertson, H.A., 1992. D_1-like and D_2-like dopamine receptors synergistically activate rotation and c-Fos expression in the dopamine-depleted striatum in a rat model of Parkinson's disease. J. Neurosci. 12, 3729–3742.

Paxinos, G., Watson, C., 1982. The Rat Brain in Stereotaxic Coordinates Academic Press, New York, NY.

Richfield, E.K., Young, A.B., Penney, J.B., 1989. Comparative distributions of dopamine D-1 and D-2 receptors in the cerebral cortex of rats, cats, and monkeys. J. Comp. Neurol. 286, 409–426.

Robertson, G.S., Herrera, D.G., Dragunow, M., Robertson, H.A., 1989. L-DOPA activates c-Fos in the striatum ipsilateral to a 6-hydroxydopamine lesion of the substantia nigra. Eur. J. Pharmacol. 159, 99–100.

Sawaguchi, T., Goldman-Rakic, P.S., 1991. D_1 dopamine receptors in prefrontal cortex: involvement in working memory. Science 251, 947–950.

Speciale, S.G., Miller, J.D., McMillen, B.A., German, D.C., 1986. Activation of specific central dopamine pathway: locomotion and footshock. Brain Res. Bull. 16, 33–38.

Steiner, H., Kitai, S.T., 2000. Regulation of rat cortex function by D_1 dopamine receptors in the striatum. J. Neurosci. 20, 5449–5460.

Wamsley, J.K., Gehlert, D.R., Filloux, F.M., Dawson, T.M., 1989. Comparison of distribution of D-1 and D-2 receptors in the rat brain. J. Chem. Neuroanat. 2, 119–137.

Yee, B.K., 2000. Cytotoxic lesion of the medial prefrontal cortex abolishes the partial reinforcement extinction effect, attenuates prepulse inhibition of the acoustic startle reflex and induced transient hyperlocomotion, while sparing spontaneous object recognition. Neuroscience 95, 675–689.