Stimulation of acetylcholine or dopamine receptors in the nucleus accumbens differentially alters dopamine release in the striatum of freely moving rats

Noriaki Koshikawa [a,*], Yukihiro Yoshida [b], Makiko Kitamura [a], Tadashi Saigusa [a], Masafumi Kobayashi [a], Alexander R. Cools [c]

[a] Department of Pharmacology, Nihon University School of Dentistry, 1-8-13, Kanda-Surugadai, Chiyoda-ku, Tokyo 101, Japan
[b] Department of Dental Anaesthesiology, Nihon University School of Dentistry, 1-8-13, Kanda-Surugadai, Chiyoda-ku, Tokyo 101, Japan
[c] Department of Psychoneuropharmacology, University of Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, Netherlands

Abstract

The present study examined whether unilateral stimulation of acetylcholine or dopamine receptors in the nucleus accumbens induces an asymmetry in dopamine transmission in the ventrolateral striatum. For this purpose, a microdialysis technique was used to measure dopamine release in both sides of the ventrolateral striatum following unilateral injections of carbachol (5 μg/0.5 μl) or a mixture of dopamine D_1 and dopamine D_2 receptor agonists (1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-diol 5 μg + quinpirole 10 μg/0.5 μl) into the nucleus accumbens. The results show that carbachol injection increased dopamine release in the ipsilateral striatum without changing dopamine release in the contralateral striatum, whereas the dopamine D_1/D_2 receptor agonist mixture injected unilaterally into the nucleus accumbens produced an increase followed by a decrease in dopamine release in the ipsilateral striatum, but only a decrease in dopamine release in the contralateral striatum. The biochemical effects of the cholinergic treatment greatly outlasted the drug-induced contralateral turning, whereas the biochemical effects of the dopaminergic treatment showed a good correlation with the drug-induced contralateral turning. The present study provides biochemical evidence that unilateral stimulation of acetylcholine or dopamine receptors in the nucleus accumbens elicits an asymmetry in dopaminergic activity in the ventrolateral striatum. The present study also provides biochemical evidence that two distinct neural substrates are involved in the effects of cholinergic and dopaminergic manipulation of the nucleus accumbens.

Keywords: Nucleus accumbens stimulation; Dopamine receptor; Acetylcholine receptor; Ventrolateral striatum; Dopamine release; Turning behavior

1. Introduction

Asymmetry between the left and right nucleus accumbens results in unilateral turning in freely moving rats (Pijnenburg et al., 1973; Colle and Wise, 1991; Messier et al., 1991a, b; McKenzie et al., 1991). Such an asymmetry can be produced by unilateral stimulation of either acetylcholine or dopamine D_1 and D_2 receptors (Saigusa et al., 1993, 1995). The effects of these treatments are both similar and dissimilar. So, both treatments produce contralateral turning which is inhibited by blockade of

dopamine D_1 and D_2 receptors in the ipsilateral, but not contralateral, ventrolateral striatum (Saigusa et al., 1993, 1995). This, together with the fact that the nucleus accumbens projects directly and indirectly (via the ventral pallidum) to the dopaminergic A_9 cell area (Groenewegen et al., 1991; Wouterlood et al., 1992; Zahm and Heimer, 1993) which, in turn, projects to the ipsilateral and contralateral striatum (Fass and Butcher, 1981), opens the possibility that unilateral stimulation of acetylcholine or dopamine receptors in the nucleus accumbens activates both the process of locomotion (known to be mediated by the nucleus accumbens) and the process of postural asymmetry (known to be mediated by the striatum) (Koshikawa, 1994).

However, unilateral stimulation of acetylcholine recep-

* Corresponding author. Fax: 81-3-3219-8136.

tors in the nucleus accumbens produces a stepping pattern that differs completely from that elicited by unilateral stimulation of dopamine receptors in this nucleus (Saigusa et al., 1995). Moreover, intra-accumbens administration of anticholinergics could not pharmacologically inhibit the turning elicited by dopamine receptor stimulation and intra-accumbens administration of dopamine receptor antagonists could not pharmacologically inhibit the turning elicited by acetylcholine receptor stimulation (Saigusa et al., 1995). These data suggest that two different neurobiological substrates are involved in the contralateral turning elicited by unilateral stimulation of acetylcholine and dopamine receptors in the nucleus accumbens (Saigusa et al., 1995).

Therefore, the goal of the present study was to analyse whether unilateral stimulation of dopamine or acetylcholine receptors in the nucleus accumbens differentially affects the release of dopamine in the ipsilateral and contralateral ventrolateral striatum. For this purpose, the microdialysis technique was used to measure dopamine release in both sides of the ventrolateral striatum following unilateral injections of a mixture of dopamine D_1 and D_2 receptor agonists (SKF 38393 5 μg + quinpirole 10 $\mu g/0.5$ μl) or carbachol (5 $\mu g/0.5$ μl) into the nucleus accumbens.

2. Materials and methods

2.1. Animals and surgery

Male Wistar rats weighing 200-250 g were used throughout the experiments. They were housed in a temperature-controlled environment and under a light (07:00-19:00 h)/dark (19:00-07:00 h) cycle with free access to food and water. Behavioural testing was performed between 13:00 h and 17:00 h. For stereotactic implantation of cannulas, the rats were anaesthetized intraperitoneally with sodium pentobarbitone (50 mg/kg) and placed in a stereotactic apparatus. A guide cannula (0.5 mm o.d., 0.3 mm i.d.) for intracerebral injection was implanted into the nucleus accumbens (ant. 10.6 mm, vert. 3.2 mm, lat. 1.7 mm) and another guide cannula (0.5 mm o.d., 0.4 mm i.d.) for a dialysis probe was implanted into either the ipsilateral or contralateral ventrolateral striatum in relation to the nucleus accumbens guide cannula (ant. 8.6 mm, vert. 3.5 mm, lat 4.0 mm) according to the atlas of Paxinos and Watson (1986) and secured to the skull with stainless screws and dental acrylic cement. The nucleus accumbens cannula was angled 20° from the mid-sagittal plane to avoid the ventricular system. Damage to the target site was minimized by implanting the tips of the guide cannulas just above the desired site. A wire stylet was placed in the guide cannula to prevent occlusion. The rats were then allowed to recover for a minimum of 7 days. The animals were used only once.

2.2. Intracerebral microinjection and drugs

The drugs used were carbachol (Sigma), a non-selective acetylcholine receptor agonist; SKF 38393 hydrochloride (($\pm$)-1-phenyl-2,3,4,5-tetrahydro-1 H-3-benzazepine-7,8-diol hydrochloride, Research Biochemicals International), a dopamine D_1 receptor agonist; and quinpirole hydrochloride (LY 171555, Research Biochemicals International), a dopamine D_2/D_3 receptor agonist. All drugs were dissolved in saline immediately before use. For unilateral intracerebral microinjections, the rats were held manually while the stylets were removed and the injection needles (31 gauge) were lowered through the guide cannulas so that they protruded 1.9 mm beyond the tip. The needles were connected to Hamilton syringes, and the drugs were given slowly in a volume of 0.5 μl over 30 s, after which the needles were left in place for a further 30 s. The extent of diffusion, estimated from the spread of the same volume of dye (thionin), was less than 1 mm in diameter. The doses of the drugs have previously been found to be highly effective in eliciting contralateral turning (Saigusa et al., 1993, 1995).

2.3. Dialysis and neurochemical measurements

The dialysis probe technique assessed in the present study has been described and validated in previous studies of our group (Takada et al., 1993; Tomiyama et al., 1993). Below, a short description is given. The stainless steel insert was removed from the guide cannula immediately before the experiment and replaced with a dialysis probe (2 mm length, 0.22 mm o.d., 50000 mol. wt. 'cut-off') so that only the dialysis tubing protruded from the tip. The rat was then placed in a circular chamber (40 cm diameter) with 30-cm high Perspex sides, and the inlet and outlet tubes were connected to a swivel attached to a counterbalanced beam.

The probe was perfused at a rate of 2.0 $\mu l/min$ with modified Ringer solution (NaCl 147 mM, KCl 4 mM, $CaCl_2$ 1.2 mM, $MgCl_2$ 1.1 mM; pH 7.4), and the outflow was connected by Teflon tubing to an HPLC system (EICOM, Kyoto, Japan). Perfusate samples were taken every 25 min for quantification of dopamine. Drugs were not given via the microinjection cannula until the baseline concentration of dopamine had stabilized (at least 4 h after probe insertion). Baseline levels were the mean of the last three samples before drug injection. The probes had an in vitro recovery of 10-12% for dopamine, but the reported concentrations (pg/50 μl of dialysate) were not adjusted for recovery in vivo because these estimations are inaccurate (Benveniste et al., 1989; Benveniste and Hüttemeier, 1990; Lindefors et al., 1989). Contralateral turnings (defined as complete 360° turns) were counted visually by a trained observer who had no prior knowledge of the drug treatment. Observations were made during consecutive

5-min periods for 120 min, starting immediately after the injection.

Dopamine was separated on an Eicompak CA-5ODS column (particle size, 5 μm; 4.6 × 150 mm; EICOM) using phosphate buffer (0.1 M) containing octane-sulfonic acid (3.2 mM), EDTA (1.5 μM) and methanol (20%, pH 6.0) as the mobile phase at flow rate of 1.0 ml/min. The compounds were quantified by electrochemical detection using a glassy carbon working electrode set at +400 mV against an Ag/AgCl reference electrode, giving a detection limit for dopamine of about 0.5 pg/sample.

2.4. Histology

At the end of the experiments, the rats were deeply anaesthetized with sodium pentobarbitone and perfused transcardially with 10% formalin. The brains were removed, sectioned (50 μm) and stained with Nissl to visualize the site of the injection and the microdialysis probe. Only data from rats in which both the injection and the dialysis probe were correctly placed in the nucleus accumbens and the ipsilateral or contralateral ventrolateral part of the striatum, respectively, were analysed (Fig. 1).

2.5. Data analysis

All dopamine concentrations are expressed as percentages of baseline levels and data were analysed using a one-way analysis of variance (ANOVA) followed by a post hoc Newman-Keuls test, where appropriate. For behavioural studies, values are expressed as means ± S.E.M. and were analysed using a two-way ANOVA (group × time) followed by a post hoc Newman-Keuls test, where appropriate. Effects were considered statistically significant when $P < 0.05$.

3. Results

3.1. Basal release of dopamine

Basal concentration of dopamine in striatal dialysates was 13.2 ± 2.8 pg/25 min (mean ± S.E.M.; $n = 12$). Saline did not affect the concentration of dopamine in the dialysates for at least 4 h after its injection into the nucleus accumbens (Fig. 2B and Fig. 3B). This holds true for rats in which the striatal dialysis probe was placed either
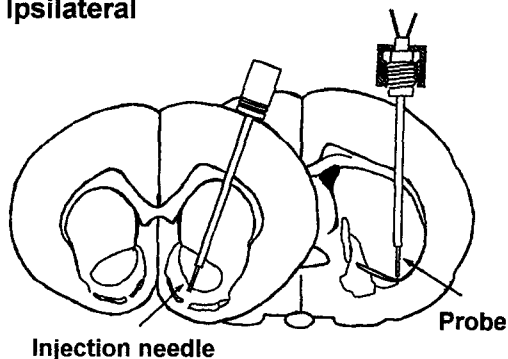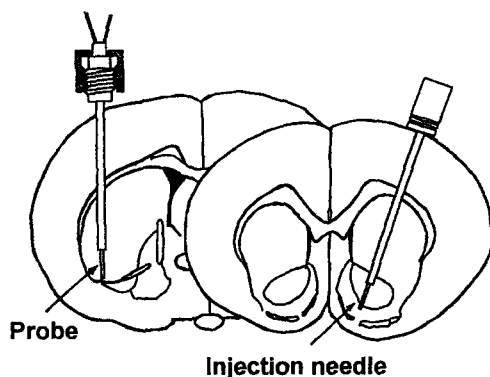

Fig. 1. Schematic illustration and representative photomicrographs showing drug injection sites within the nucleus accumbens and location of the microdialysis probes in the ipsilateral (A) or contralateral (B) ventrolateral striatum. The planes are modified to a series of 2 or 3 sections for each brain area from the atlas of Paxinos and Watson (1986).
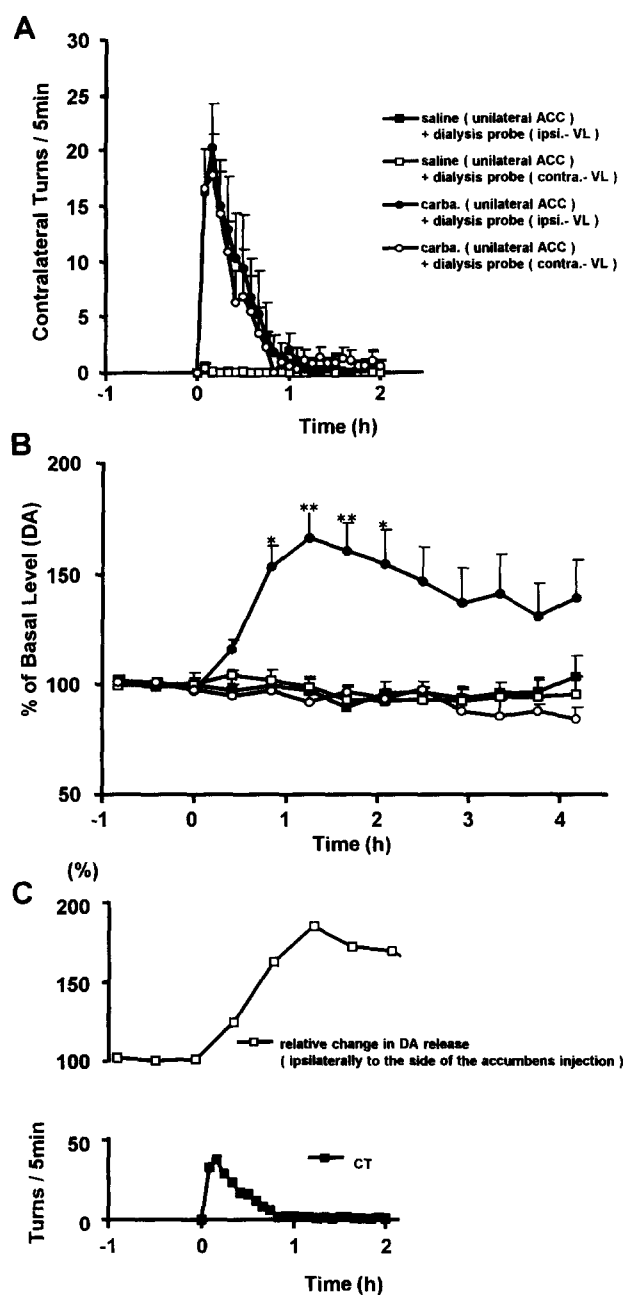
Fig. 2. (A) Effects of unilateral injection of carbachol 5 μg/0.5 μl (circle) or saline (square) into the nucleus accumbens (ACC) in rats with microdialysis probes in the ipsilateral (filled) or contralateral (open) ventrolateral striatum (VL) on production of contraversive turning. The data are expressed as the mean number of turns occurring in 5-min observation periods ($n = 6–9$). Vertical bars indicate S.E.M. (B) Effects of unilateral injection of carbachol 5 μg/0.5 μl or saline into the nucleus accumbens on dopamine (DA) release in the ipsilateral or contralateral ventrolateral striatum. Basal level (pg/25 min, mean ± S.E.M., $n = 29$) was 10.1 ± 1.4. Data are means ± S.E.M. (bars) values from 6–9 rats. * $P < 0.05$; ** $P < 0.01$ compared with value just before administration of carbachol by Newman-Keuls test. (C) Time relationship between contraversive turning (CT, ■) and the change in DA release (□) in the ipsilateral ventrolateral striatum relative to that in the contralateral side induced by unilateral injections of carbachol (5 μg/0.5 μl) into the nucleus accumbens.

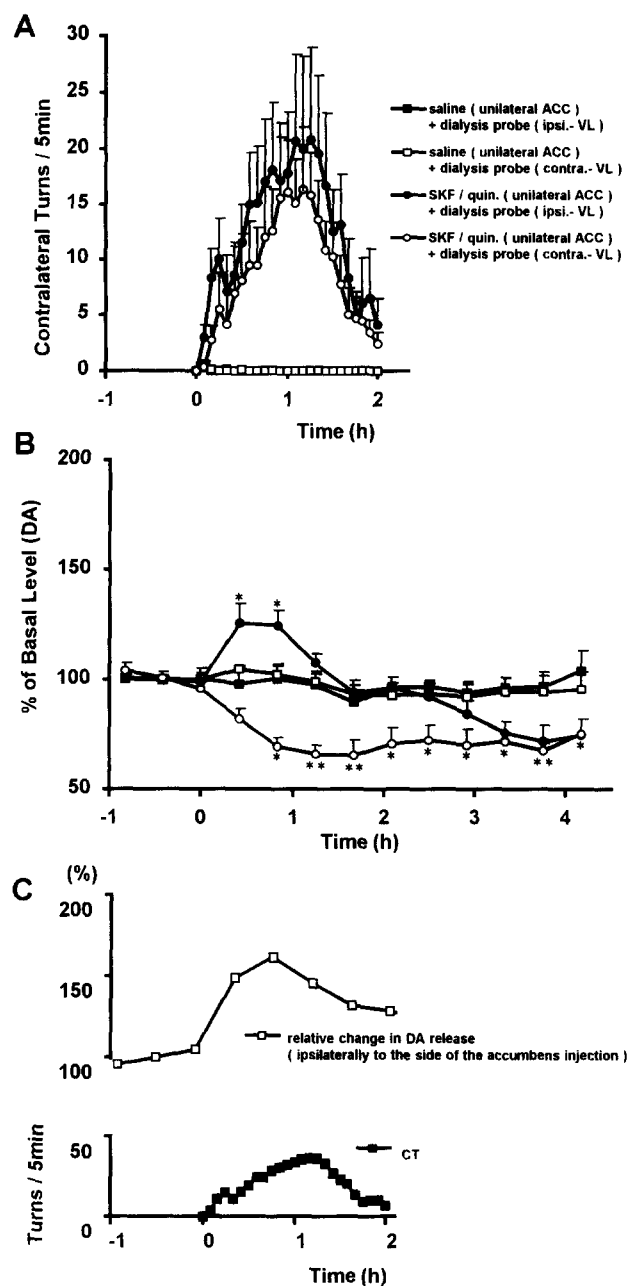Fig. 3. (A) Effects of unilateral injection of SKF 38393 5 μg and quinpirole 10 μg/0.5 μl mixture (circle) or saline (square) into the nucleus accumbens (ACC) in rats with microdialysis probes in the ipsilateral (filled) or contralateral (open) ventrolateral striatum (VL) on production of contraversive turning. The data are expressed as the mean number of turns occurring in 5-min observation periods ($n = 6–8$). Vertical bars indicate S.E.M. (B) Effects of unilateral injection of a mixture of SKF 38393 5 μg and quinpirole 10 μg/0.5 μl or saline into the nucleus accumbens on dopamine (DA) release in the ipsilateral or contralateral ventrolateral striatum. Basal level (pg/25 min, mean ± S.E.M., $n = 26$) was 13.6 ± 2.4. Data are means ± S.E.M. (bars) values from 6–8 rats. * $P < 0.05$; ** $P < 0.01$ compared with value just before administration of the mixture by Newman-Keuls test. (C) Time relationship between contraversive turning (CT, ■) and the change in DA release (□) in the ipsilateral ventrolateral striatum relative to that in the contralateral side induced by unilateral injections of a mixture of SKF 38393 5 μg and quinpirole 10 μg/0.5 μl into the nucleus accumbens.

ipsilaterally or contralaterally to the unilateral injection of saline into the nucleus accumbens.

3.2. Effects of unilateral injection of carbachol on the release of dopamine and production of turning

Carbachol (5 μg/0.5 μl) injected unilaterally into the nucleus accumbens induced wide, contralateral turnings for a period of about 50 min ($P < 0.01$ versus respective saline controls, Newman-Keuls test); the number of turnings reached a maximum 5 min after the injection and then decreased to zero about 50 min after the injection (Fig. 2A). The treatment increased dopamine release in the ipsilateral striatum throughout the whole measurement period. This release reached a maximum about 75 min after the injection and then slowly decreased, although it did not reach baseline levels at the end of the measurement period (250 min). The treatment did not affect dopamine release in the contralateral striatum (Fig. 2B).

3.3. Effects of unilateral injection of SKF 38393 and quinpirole mixture on the release of dopamine and production of turning

The mixture of dopamine D_1/D_2 receptor agonists (SKF 38393 5 μg + quinpirole 10 μg/0.5 μl) injected unilaterally into the nucleus accumbens induced tight head-to-tail, contralateral turnings for a period of about 120 min ($P < 0.01$ versus respective saline controls, Newman-Keuls test); the number of turnings reached a maximum 60 min after the injection and then decreased to zero about 120 min after the injection (Fig. 3A). The treatment increased (25%) dopamine release in the ipsilateral striatum from 25 min to about 100 min after the injection and then decreased (15%) it on that side till the end of the experiment (250 min after the injection). In contrast, the treatment decreased dopamine release in the contralateral striatum throughout the measurement period (Fig. 3B).

4. Discussion

Previous studies in which an identical dialysis technique was used (Takada et al., 1993; Tomiyama et al., 1993) have shown that the baseline dopamine concentration measured in the dialysate of striatally perfused rats which received their implantation at least 7 days earlier, is largely dependent on neuronal activity as more than 80% of the dopamine release has been found to be tetrodotoxin-sensitive and Ca^{2+}-dependent. The results of the present study show that stimulation of acetylcholine or dopamine receptors in the nucleus accumbens produced significant changes in this dopamine release in the ventrolateral striatum. The finding that the two treatments had differential effects on the dopamine release in the ipsilateral and contralateral striatum together with the finding that saline injections into

the nucleus accumbens (controls) did not affect the dopamine release in the left or right striatum clearly indicates that the drug-induced changes in dopamine release were not artifacts of the technique utilized for estimating the release of dopamine.

Although future studies are required to prove that the drug-induced changes found in the present study are also tetrodotoxin-sensitive and/or Ca^{2+}-dependent, it is unlikely that these changes were independent of alterations in neuronal activity. Apart from the highly speculative idea that different brain structures may transmit messages to each other via glial cells or neuroendocrine processes, there is hard evidence that the nucleus accumbens both directly and indirectly via the ventral pallidum projects to the A_9 cell area (Groenewegen et al., 1991; Wouterlood et al., 1992; Zahm and Heimer, 1993) which, in turn, innervates the ipsilateral and contralateral striatum (Fass and Butcher, 1981). Given this and related anatomical connections (see below), it is therefore suggested that the drug-induced changes in the ventrolateral striatum were due to alterations in neuronal activity.

The present study clearly shows that the chosen treatments, which directly alter neurotransmission in the nucleus accumbens, a structure known to be involved in the process of locomotion (Pijnenburg and Van Rossum, 1973), also caused clearcut changes in the striatum, a structure known to be involved in postural asymmetry (Kelly and Moore, 1976; Moore and Kelly, 1977; Pycock and Marsden, 1978; Pycock, 1980). The finding that both the cholinergic and the dopaminergic treatment of the nucleus accumbens produced the greatest increase in dopamine release in the striatum ipsilateral to the drug injection site in the nucleus accumbens provides an unequivocal explanation for the observation that both treatments resulted in contralateral turning, since rats with a functional imbalance between the left and right striatum are known to turn away from the side with the higher dopamine activity (Ungerstedt, 1971). Still, the carbachol-treated rats stopped their contralateral turning long before the increased dopamine release returned to baseline levels. This lack of correlation between the biochemical and the behavioural effects of a particular drug treatment has often been seen (Di Chiara and Imperato, 1988). This phenomenon is not understood. This finding rules out the possibility that the increase in dopamine release was simply the consequence of the behaviour shown: dopamine release remained high despite the lack of turning in the carbachol-treated rats. One can only speculate about the functional meaning of the persistent increase in dopamine release. Apart from the theoretical possibility that it might have been due to non-neuronal processes, it is possible that carbachol injected into the nucleus accumbens activated an additional neuronal system in the nucleus accumbens, which could have obscured the behavioural expression of the increased dopamine release in the striatum. Future studies are required to solve this problem. The finding that the dopaminergic treatment

of the nucleus accumbens produced an overall imbalance in dopamine release between the left and right striatum that correlated nicely with the contralateral turning (Fig. 3C; see also below), however, reveals that unilateral striatal dopamine is required to be released in direct relation to the direction of turning. Taking these data together, it is concluded that the asymmetrical dopamine release in the striatum is indeed the signal to adopt an asymmetrical posture. This together with the fact that the cholinergic or dopaminergic treatment of the nucleus accumbens provides the signal to move forwards (Pijnenburg and Van Rossum, 1973; Cools, 1977) explains why all rats displayed contralateral turning after unilateral injections of cholinergic or dopaminergic agonists into the nucleus accumbens.

The effects of the cholinergic treatment of the nucleus accumbens on the dopamine release in the striatum were limited to one side of the brain, viz. the side of the accumbens injection, implying that a direct or indirect projection from the nucleus accumbens to the ipsilateral striatum is sufficient for mediating these biochemical effects. In contrast, the effects of the dopaminergic treatment of the nucleus accumbens on the dopamine release in the striatum extended to both sides of the brain, implying that a direct or indirect projection from the nucleus accumbens to both the left and the right striatum is required for mediating these biochemical effects. Although the nature of these connections remains to be determined, there are at least three candidates in this respect: (a) the pathway which connects the nucleus accumbens via the A_{10} cells in the ventral tegmental region with the ventrolateral striatum (Loughlin and Fallon, 1982; Heimer et al., 1991; Zahm and Heimer, 1993), (b) the pathway which connects the nucleus accumbens via the A_9 cells in the substantia nigra pars compacta with the ventrolateral striatum (Fass and Butcher, 1981; Groenewegen et al., 1991; Wouterlood et al., 1992; Zahm and Heimer, 1993), and (c) the pathway which connects the nucleus accumbens via pallido-nigral fibres with the ventrolateral striatum (Zahm and Heimer, 1990, 1993). Future studies are required to determine whether these pathways are indeed differentially involved in the effects found in the present study. Anyhow, the above-mentioned data provide biochemical evidence that at least two distinct pathways are required in order to mediate the effects of the cholinergic and dopaminergic treatment (Koshikawa, 1994; Saigusa et al., 1995). The effects of the cholinergic treatment of the nucleus accumbens on dopamine release in the striatum differed from those of the dopaminergic treatment of the nucleus accumbens in two additional aspects. First, the effects of the cholinergic treatment were much greater and longer-lasting than those of the dopaminergic treatment. And, second, analysis of the time relationship between the biochemical and behavioural effects shows that the cholinergic treatment did not produce biochemical changes which correlated with the contralateral turning, whereas the dopaminergic treatment did (Fig. 2C and Fig. 3C). These additional differences in dopamine release between the cholinergic and dopaminergic treatment of the nucleus accumbens strengthen the above-mentioned hypothesis that two distinct neurobiological substrates and/or mechanisms are involved in the phenomena found.

In summary, the present study provides biochemical evidence that stimulation of acetylcholine or dopamine receptors in the nucleus accumbens differentially alters dopamine release in the ventrolateral part of the striatum.

Acknowledgements

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