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Comparison of changes in locomotor activity with striatal homovanillic acid and 3,4-dihydroxyphenylacetic acid concentrations following the bilateral intranigral injection of dopamine agonist drugs in rats

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Bilateral injection of apomorphine (2·5 μg) into the substantia nigra zona reticulata of rats reduced both locomotor activity and striatal HVA and DOPAC concentrations. Bilateral injection of dopamine (10 μg) did not affect locomotor activity whereas a higher dose of dopamine (50 μg) enhanced locomotor activity. Striatal HVA and DOPAC concentrations were unchanged following injection of dopamine. Bilateral injection of (±)-3PPP (0·1 or 2·5 μg) into the zona reticulata of the substantia nigra did not alter locomotor activity while a higher dose (10 μg) enhanced locomotion. Injection of (±)-3PPP (0·1–10 μg) into the zona reticulata was without effect on striatal HVA or DOPAC concentrations. The bilateral manipulation of nigral dopaminergic neurotransmission alters motor activity and nigrostriatal dopamine turnover in conscious rats. However, the changes in motor activity are not necessarily related to altered nigrostriatal activity, suggesting the involvement of dopamine receptors located at non-dopaminergic sites within the substantia nigra.

Pharmacological manipulation of dopaminergic neurotransmission in the terminal area of dopaminergic projections to the forebrain alters locomotor activity in rodents. Thus, the bilateral injection of dopamine into the nucleus accumbens (Pijnenburg & van Rossum 1973: Costall & Naylor 1975) or striatum (Svensson & Ahlenius 1983) of rats enhances locomotor activity and can induce stereotyped sniffing behaviour.

Dopamine is released not only from the terminals of the nigrostriatal pathway in the forebrain, but also from dendrites of the neurons located in the substantia nigra (Geffen et al 1976). The cell bodies of these neurons are located in the zona compacta of the substantia nigra, whilst the dendrites extend throughout the zona compacta and into the zona reticulata (Bjorklund & Lindvall 1975). Dendritic dopamine release in the cell body region may regulate motor behaviour, however the effects of bilateral intranigral application of dopamine agonists are uncertain. Bilateral injection of high doses of dopamine into the zona reticulata of rats was reported to enhance locomotion (Jackson & Kelly 1983), whereas bilateral intranigral injection of dopamine, or the potent dopamine agonist 2-di-n-propylamino-5,6-dihydroxytetralin, dose-dependently reduced locomotor activity in mice (Bradbury et al 1983), although the exact site of injection was not defined in that study.

It is possible that the different effects on locomotor activity produced by the intranigral application of dopamine agonists may reflect interactions with dopamine receptors located at different anatomical sites within substantia nigra (Phillipson et al 1977). In particular, differences may exist between effects elicited from the zona compacta as opposed to the zona reticulata of the substantia nigra. To investigate further the effects of intranigral application of dopaminergic drugs on motor activity, we have compared the effects of bilateral injection of dopamine, apomorphine and the putative selective dopamine autoreceptor agonist 3-(3-hydroxyphenyl)-*N*,n-propylpiperidine ((±)-3PPP; Hjorth et al 1981) into the zona reticulata, on locomotor activity in rats. As an index of drug action on nigrostriatal dopaminergic neurons, we also measured striatal concentrations of the dopamine metabolites homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC).

MATERIALS AND METHODS

Bilateral cannulation of substantia nigra

Female Wistar rats (151–175 g, Charles River Ltd)

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were anaesthetized using chloral hydrate (300 mg kg^{-1} i.p.; BDH Ltd) and placed in a Stoelting stereotaxic frame. Stainless steel guide cannulae (length 7·0 mm; i.d. 0·8 mm) were then placed onto the surface of the cortex overlying the substantia nigra at the coordinates A 2·0, L 2·0 for zona reticulata, according to the atlas of Konig & Klippel (1963). Cannulae were fixed in place using three stainless steel retaining screws embedded in the skull and acrylic dental cement. Animals were treated with ampicillin trihydrate (0·1 mL, i.p.; Penbritin; Beecham Animal Health) to prevent infection and allowed at least 4 days to recover from the effects of surgery.

Intranigral injection techniques

Intranigral injections were made using a 5 μL Hamilton syringe with Luer needle (o.d. 0·33 mm; i.d. 0·18 mm) inserted via the guide cannulae to a depth of 7·8 mm from the surface of the cortex in lightly hand-restrained conscious animals. Injections were made at a rate of 1 μL min^{-1}, the needle was then left in place a further 0·5 min to limit drug diffusion before being slowly withdrawn.

Animals received bilateral injections of apomorphine hydrochloride (2·5 μg in 0·5 μL 0·9% NaCl (saline); Sigma Chemical Co.) or dopamine hydrochloride (10–50 μg in 0·5 μL saline; Sigma Chemical Co.) or (±)-3PPP hydrochloride (0·1–10 μg in 0·5 μL saline; Astra Pharmaceuticals) into the zona reticulata (A 2·0, L 2·0, V −2·5; Konig & Klippel 1963) of the substantia nigra. Control injections into the zona reticulata consisted of an equal weight of sucrose (0·1–50 μg in 0·5 μL saline; Fisons).

Measurement of locomotor activity

Animals were placed in individual Perspex cages (40 × 26 × 26 cm) each fitted with two lamps (20 cm apart) throwing collimated beams of light onto two photocells (designed and constructed in the Department by Mr H. C. Bertoya). Cages were housed in a darkened room at 21 °C. Every 0·2 s a PET 4002 computer sampled each photocell to detect sequential changes in the light field (either open to closed or closed to open). Locomotor activity was assessed as the number of changes in the two photocells occurring in 5 min time segments which could be summed to give a cage total.

Following a 15 min habituation period in the cages, animals were removed to receive intranigral injections. The animals were then returned to the same cages and locomotor activity was measured for a 30 min period. Each animal received only one injection into each substantia nigra, and the locomotor activity of drug-injected animals was always assessed at the same time as animals receiving the appropriate bilateral intranigral injection of sucrose. The effects of drugs on locomotor activity are presented as the time course of activity during the 5 min before, and then the 30 min period following intranigral injection.

Measurement of striatal HVA and DOPAC concentrations

Striatal concentrations of HVA and DOPAC were determined in tissue from animals which 15 min previously had received bilateral injections of drug or sucrose into the zona reticulata. Animals were killed by cervical dislocation and decapitation and the brains removed. Following dissection, the paired striata from each animal were homogenized in 0·4 M perchloric acid. HVA and DOPAC were then separated from dopamine using Sephadex G10 columns according to Earley & Leonard (1978), and their concentrations estimated by the semi-automated fluorometric methods of Westerink & Korf (1976).

Histology

Following completion of behavioural experiments, the midbrain of each animal was frozen on an ice block at −20 °C. The injection sites were then determined by macroscopic examination of the needle tracts following coronal sectioning of the brain by hand with a scalpel blade. Data from animals in which one or both injection sites were not located symmetrically within the zona reticulata were discarded.

Statistics

The time courses of locomotor activity following bilateral intranigral drug injection were analysed using a two-tailed, two-way analysis of variance with replicates. Spontaneous locomotor activity in the 5 min before intranigral injection and the effects of bilateral intranigral injections of drugs on striatal HVA and DOPAC concentrations were compared using a two-tailed Student's *t*-test.

RESULTS

The effect of control intranigral injections of sucrose on spontaneous locomotor activity and striatal HVA and DOPAC concentrations

The spontaneous locomotor activity of cannulated rats 4 days following surgery was not different to that of rats receiving no prior surgery (Fig. 1). Bilateral

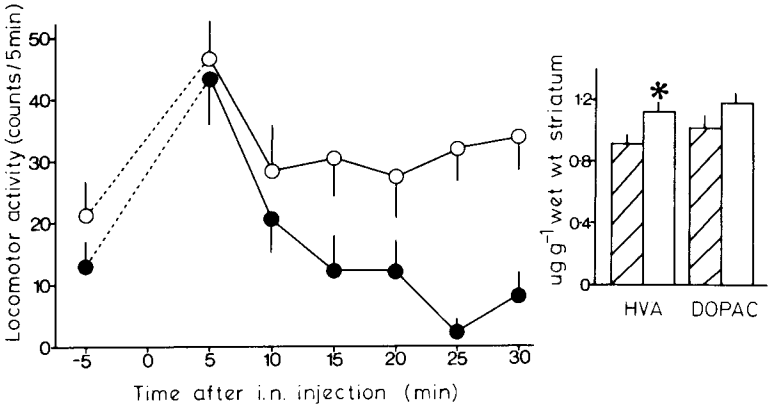

FIG. 1. The effect of bilateral injection of sucrose (2·5 μg) into the substantia nigra zona reticulata of rats on locomotor activity and striatal HVA and DOPAC concentrations. Locomotor activity was assessed in photocell cages for a 30 min period following treatment. Previously animals were placed in the cages for a 15 min habituation period immediately before subsequent treatment and measurement of motor activity. At time 0 animals received either bilateral intranigral (i.n.) injections of sucrose (2·5 μg per nigra, n = 8; —●—) or no intranigral injection or prior surgery (n = 9; —○—). Animals receiving no intranigral injection were hand restrained for the same length of time as those receiving intranigral sucrose (~3 min). Basal locomotor activity in the 5 min period before injection, shown at −5 min, was not significantly different between the groups when compared by Student's *t*-test. Values are means ± 1 s.e.m. Locomotor activity in untreated rats was higher than in those receiving intranigral sucrose, $P < 0{\cdot}01$, calculated by two-tailed, two-way analysis of variance with replicates. Striatal HVA and DOPAC concentrations were determined in separate groups of animals, either 15 min following intranigral sucrose (2·5 μg, n = 10; clear bars) or after no prior treatment (n = 13; hatched bars). The striatal HVA concentration in animals receiving sucrose treatment was higher than in animals receiving no treatment, $^*P < 0{\cdot}05$ calculated by Student's *t*-test.

injection of sucrose (2.5 μg in 0·5 μL saline) into the zona reticulata of the substantia nigra reduced locomotor activity compared with animals receiving no prior surgery or intranigral injections (F (1,90) = 29·5; $P < 0{\cdot}01$) (Fig. 1). The effect of sucrose was not dose-dependent since the locomotor activity in the 30 min following bilateral intranigral injection of 0·1 μg sucrose was not different to that following 50 μg sucrose (F (1,90) = 0·61; $P > 0{\cdot}05$; data not shown).

Bilateral intranigral injection of sucrose (2·5 μg) increased striatal HVA concentrations by 22% when compared with unoperated animals (Fig. 1). In all subsequent experiments control intranigral injections consisted of sucrose (in 0·5 μL 0·9% saline) equal in weight to the dose of drug injected under each treatment.

The effect of bilateral intranigral injection of apomorphine on locomotor activity and striatal HVA and DOPAC concentrations

The bilateral injection of apomorphine hydrochloride (2·5 μg in 0·5 μL saline) into the zona reticulata of the substantia nigra reduced locomotor activity (F (1,48) = 32·4; $P < 0{\cdot}01$). Immediately following bilateral intranigral injection of apomorphine a period (20–30 min) of almost total motor inactivity occurred. During this the animals would readily respond by moving away if touched or prodded. The bilateral injection of apomorphine hydrochloride (2·5 μg in 0·5 μL saline) into the reticular formation and overlying superior colliculus 3–6 mm dorsal to the substantia nigra also reduced locomotor activity compared with animals receiving intranigral injection of sucrose (2·5 μg; F (1,54) = 8·63; $P < 0{\cdot}01$) (Fig. 2). However, this reduction was less marked compared with injections of apomorphine located in the zona reticulata (F 1,54 = 20·1; $P < 0{\cdot}01$).

The bilateral injection of apomorphine hydrochloride (2·5 μg) reduced the striatal HVA and DOPAC concentrations by 25 and 29%, respectively, when compared with animals receiving bilateral injections of sucrose (2·5 μg) (Fig. 2).

The effect of bilateral intranigral injection of dopamine hydrochloride on locomotor activity and striatal HVA and DOPAC concentrations

Bilateral injection of dopamine hydrochloride (10 μg in 0·5 μL saline) into the zona reticulata of the substantia nigra did not alter locomotor activity compared with animals injected with sucrose (10 μg in 0·5 μL saline: F (1,96) = 5·9 ($P > 0{\cdot}05$; Fig. 3A), although a trend towards a decrease was apparent in the dopamine-treated group.

Bilateral injection of a higher dose of dopamine hydrochloride (50 μg in 0 4 μL saline) into the zona

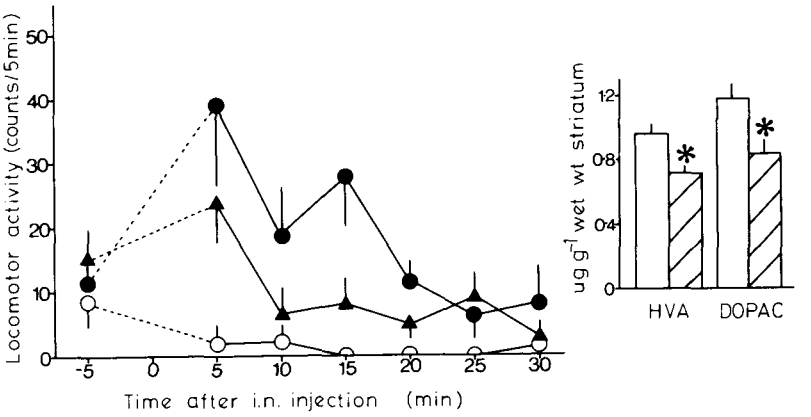

FIG. 2. The effect of bilateral injection of apomorphine hydrochloride (2·5 μg) into the substantia nigra zona reticulata, or 3–6 mm dorsal to the substantia nigra on locomotor activity, and the effect of bilateral intranigral injection of apomorphine (2·5 μg) on striatal HVA and DOPAC concentrations. Following a 15 min habituation period in photocell cages, animals received either bilateral intranigral (i.n.) injection of apomorphine hydrochloride (2·5 μg per nigra n = 5; —○—), bilateral intranigral injection of sucrose (2·5 μg per nigra, n = 5; —●—) or bilateral injection of apomorphine hydrochloride 3–6 mm dorsal to the substantia nigra (2·5 μg per injection, n = 6; —▲—), all at time 0. Basal activity was recorded in the 5 min before injection. Values are means ± 1 s.e.m. Locomotor activity following intranigral injection of apomorphine was lower than in sucrose injected controls, $P < 0·01$, and lower than that obtained when apomorphine was injected 3–6 mm dorsal to the substantia nigra, $P < 0·01$, P values calculated by two-tailed, two-way analysis of variance with replicates. Striatal HVA and DOPAC concentrations were determined in separate groups of animals, 15 min following either intranigral injection of sucrose (2·5 μg per nigra; n = 5; clear bars) or intranigral injection of apomorphine (2·5 μg per nigra; n = 6; hatched bars). Striatal HVA and DOPAC concentrations in animals receiving intranigral injection of apomorphine were lower than those in animals receiving intranigral injection of sucrose, $^*P < 0·05$ by Student's t-test.

reticulata markedly increased locomotor activity (F (1,60) = 32·0; ($P < 0·01$) when compared with animals receiving intranigral injections of sucrose (50 μg in 0·5 μL saline) (Fig. 3B).

Bilateral injection of dopamine hydrochloride (10 and 50 μg) did not alter striatal concentrations of HVA and DOPAC compared with animals injected intranigrally with sucrose (10 and 50 μg) (data not shown).

The effect of bilateral intranigral injection of (±)-3PPP on locomotor activity and striatal HVA and DOPAC concentrations

The bilateral injection of (±)-3PPP (0·1 or 2·5 μg in 0·5 μL saline) into the zona reticulata of the substantia nigra did not alter locomotor activity (0·1 μg (±)-3PPP, F (1,60) = 0·10; 2·5 μg (±)-3PPP, F (1,54) = 0·07; $P > 0·05$) compared with animals receiving bilateral intranigral injections of sucrose (0·1 and 2·5 μg in 0·5 μL saline) (Fig. 3C, D). Bilateral injection of a higher dose of (±)-3PPP (10 μg in 0·5 μL saline) into the zona reticulata enhanced locomotor activity (F (1,60) = 11·2; $P <$ 0·01) compared with animals receiving bilateral intranigral injections of sucrose (10 μg in 0·5 μL saline) (Fig. 3E).

Bilateral injection of (±)-3PPP (0·1, 2·5 or 10 μg in 0·5 μL saline) into the zona reticulata did not affect striatal concentrations of HVA or DOPAC when compared with animals receiving intranigral sucrose (0·1, 2·5 or 10 μg in 0·5 μL saline) (data not shown).

DISCUSSION

The results of this study, summarized in Table 1, show that bilateral intranigral injection of some dopamine agonist drugs in the rat may cause alterations in locomotor activity and/or striatal HVA and DOPAC concentrations. However, the responses obtained differed between the different dopaminergic drugs used in this study. Thus, changes in locomotor activity were not necessarily related to

Table 1. Summary of the effects of bilateral injection of different drugs into substantia nigra zona reticulata on locomotor activity and striatal HVA and DOPAC concentrations. Symbols in the table indicate either an increase (↑), a decrease (↓) or no change (○) in the parameter measured.

Bilateral intranigral drug	Dose (μg per nigra)	Locomotor activity	Striatal HVA	Striatal DOPAC
Apomorphine	2·5	↓	↓	↓
Dopamine	10·0	○	○	○
	50·0	↑	○	○
(±)-3PPP	0·1	○	○	○
	2·5	○	○	○
	10·0	↑	○	○

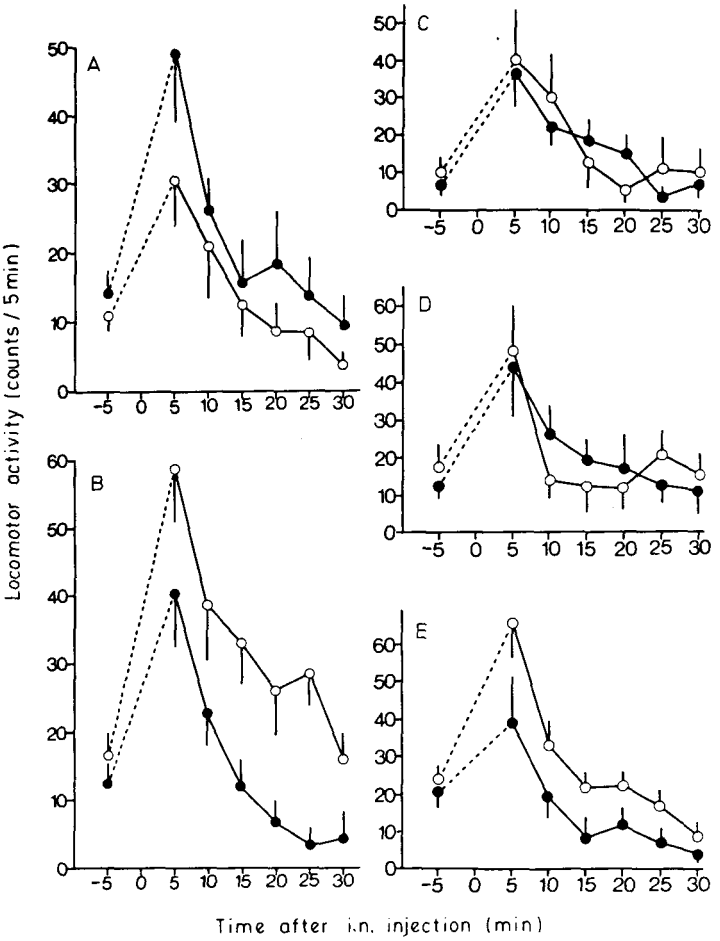

FIG. 3. The effect of bilateral injections of (A) dopamine hydrochloride (10 μg), (B) dopamine hydrochloride (50 μg), (C) (±)-3PPP (0·1 μg), (D) (±)-3PPP (2·5 μg) or (E) (±)-3PPP (10·0 μg) into the substantia nigra zona reticulata of rats on locomotor activity. Following a 15 min habituation period in photocell cages, animals received either bilateral intranigral (i.n.) injection of (A and B) dopamine (10 or 50 μg per nigra, n = 9 and 6 respectively; —○—) or sucrose (10 or 50 μg per nigra, n = 9 respectively; —●—), or bilateral injection of (C, D and E) (±)-3PPP (0·1, 2·5 or 10·0 μg per nigra, n = 6, 6 and 6 respectively: —○—), or sucrose (0·1, 2·5 or 10·0 μg per nigra, n = 6, 5 and 6 respectively; —●—). Basal activity was recorded in the 5 min before injection, values being means ±1 s.e.m. Locomotor activity following intranigral injection of dopamine (50 μg) was higher than observed in sucrose (50 μg) injected control animals, $P < 0{\cdot}01$, whilst activity following (±)-3PPP (10·0 μg) was higher than that observed in sucrose (10·0 μg) injected control animals, $P < 0{\cdot}01$, both by two-tailed, two-way analysis of variance with replicates.

changes in striatal dopamine metabolite concentrations. Furthermore, the reduction in locomotor activity and increase in striatal HVA concentration produced by control injections of sucrose into zona reticulata indicates that the micro-injection procedure can itself disrupt nigral function. For this reason, the effects of all injections of drugs were compared with those of similar injections of equal weights of sucrose, even though these control injections may lead to changes in nigral function upon which dopamine receptor stimulation must be superimposed.

It is possible that the changes in locomotor activity and striatal dopamine metabolite concentrations elicited by the bilateral intranigral application of dopaminergic drugs were mediated by diffusion of drugs to the striatum. However, the localization of these responses to dopamine receptors in the ventral midbrain is indicated by the observation that injections of apomorphine dorsal to the substantia nigra inhibited locomotor activity to a much smaller extent than when injections were placed in the zona reticulata.

Dopamine receptors may lie at a number of

different sites within the substantia nigra. Lesion studies coupled with ligand binding assays and measurement of dopamine-stimulated adenylate cyclase suggest the presence of dopamine receptors on the cell bodies and/or dendrites of dopamine-containing cells (Reisine et al 1979; Quik et al 1979; Murrin et al 1979) and on the terminals of afferent inputs to the substantia nigra from the striatum (Premont et al 1976; Gale et al 1977; Phillipson et al 1977; Spano et al 1977). Further evidence from ligand binding studies (Hall et al 1983) and electrophysiological investigations (Ruffieux & Schultz 1980; Waszczak & Walters 1983) suggests other dopamine receptors lie on the cell bodies of nigral output neurons, particularly those of the nigrothalamic tract.

Dopamine cell body autoreceptors are thought to represent the site at which the local application of dopaminergic drugs inhibit both nigral cell firing (Bunney et al 1973) and striatal dopamine release (Cheramy et al 1977). The reduction in striatal HVA and DOPAC concentrations, indicating decreased dopamine turnover, caused by the bilateral injection of apomorphine into the zona reticulata presumably reflects an action on nigral autoreceptors. This finding is in agreement with previous biochemical studies where intranigral injection of apomorphine (2–10 μg) reduced striatal concentrations of HVA (Wolfarth et al 1978) and 3-methoxytyramine (Maggi et al 1978).

The bilateral injection of apomorphine into the substantia nigra also reduced locomotor activity as previously reported for other dopamine agonists (Bradbury et al 1983). This is also consistent with nigral dopamine autoreceptor stimulation. However, an action of apomorphine on nigral non-dopaminergic neurons cannot be ignored. Indeed, in-vitro apomorphine inhibits the potassium-evoked release of [^{3}H]GABA from nigral slices (Arbilla et al 1981; Kelly et al 1985).

The effects of bilateral injection of dopamine into the zona reticulata on locomotor activity differed from those observed with apomorphine. While a low dose of dopamine (10 μg) tended to reduce locomotor activity, a higher dose (50 μg) enhanced motor activity. Such findings are in general agreement with previous studies where the bilateral intranigral injection of low doses of dopamine (0·31–25 μg) in mice inhibited locomotor activity (Bradbury et al 1983), but higher doses (100 μg) enhanced locomotion in the rat (Jackson & Kelly 1983). One interpretation of such data is that in low doses dopamine exerts a preferential action on autoreceptors, but that it acts on post-synaptic receptors at higher doses (Strombom 1976).

The idea of dopamine acting on dopamine receptors located on non-dopamine containing neurons is supported by the biochemical findings. Thus in the doses used (10–50 μg) dopamine did not alter striatal HVA or DOPAC concentrations, suggesting that nigrostriatal dopamine neurons do not mediate the increased locomotor activity observed following the higher dose. However, it is feasible that small amounts of dopamine, or its metabolites, injected into the substantia nigra may have diffused to the striatum, possibly even masking a decrease in striatal dopamine turnover; also, the fact that intranigral sucrose can increase striatal HVA concentrations may mask a greater effect of dopamine on this parameter. Overall, however, these results suggest that the locomotor stimulation produced by intranigral injection of dopamine involves dopamine receptors located on non-dopaminergic neurons.

It is unclear why apomorphine also did not stimulate locomotor activity when applied intranigrally. Similar findings have previously been reported following the bilateral application of apomorphine to the nucleus accumbens. Whereas low doses of apomorphine (1–100 ng) inhibited locomotor activity (Van Ree & Wolterink 1981), higher doses (1·56–25 μg) never resulted in motor stimulation (Costall et al 1980). The potent motor inhibition and reduction in nigrostriatal dopamine turnover produced by intranigral injection of apomorphine suggests a greater potency and preferential effect of apomorphine to act on nigral dopamine neuronal autoreceptors in the substantia nigra. Electrophysiological studies also indicate this to be the case since apomorphine was more than one hundred times more potent than dopamine in inhibiting nigral dopamine cell firing (Pinnock 1983).

One apparent means of distinguishing between an action of dopamine agonists on nigral dopamine cell body autoreceptors and dopamine receptors located elsewhere would be the use of the autoreceptor agonist (±)-3PPP. However, in contrast to apomorphine, but similar to dopamine, the bilateral injection of (±)-3PPP into the zona reticulata increased locomotor activity and did not alter striatal HVA and DOPAC concentrations. The failure of (±)-3PPP to decrease motor activity or to alter striatal dopamine turnover suggests that (±)-3PPP does not interact with nigral dopamine autoreceptors so as to influence nigro-striatal activity. This conclusion is supported by electrophysiological studies in which the iontophoretic application of (±)-3PPP to dopam-

inergic neurons of the zona compacta only inhibited 50% of cells tested, whereas the similar application of dopamine inhibited all dopaminergic cells examined (Bunney et al 1983). Clearly the effects of (±)-3PPP on intranigral injection are difficult to reconcile with the actions of a dopamine autoreceptor agonist. Indeed, iontophoretic application of (±)-3PPP enhances the activity of non-dopaminergic neurons of the zona reticulata (Bunney et al 1983), perhaps explaining the stimulant effect of a higher dose of (±)-3PPP on locomotor activity.

One other possibility must be considered. The enantiomers of (±)-3PPP differ in their agonist/antagonist profile at pre- and postsynaptic dopamine receptors. The (−)-enantiomer is an autoreceptor agonist and a postsynaptic receptor antagonist, whilst the (+)-enantiomer is an agonist of both autoreceptors and postsynaptic receptors (Hjorth et al 1983). It is possible that the different actions of the enantiomer results in little or no net effect on nigral dopamine function.

In conclusion the bilateral injection of some dopaminergic drugs into the substantia nigra zona reticulata of rats may influence motor activity and/or nigrostriatal dopamine turnover. Apomorphine induced pronounced hypoactivity, with reduction of striatal dopamine metabolites, suggesting an action on nigral dopamine neuronal autoreceptors. In contrast, high doses of dopamine and (±)-3PPP enhanced motor activity, without alteration in striatal dopamine metabolites, suggesting an action on dopamine receptors located on non-dopaminergic nigral neurons.

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