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Behavioural topography in the striatum: differential effects of quinpirole and D-amphetamine microinjections

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Abstract

Behavioural evidence has accumulated that supports the hypothesis that specific territories of the striatum contribute differentially to the control of motor behaviours. The present experiments compare the behavioural effects of microinjections of amphetamine (20 μg/0.5 μl) with those elicited by the D_2-class dopamine receptor agonist quinpirole (3 μg/0.5 μl) following direct microinjection into three anatomically distinct sectors of the striatum: the nucleus accumbens, the ventrolateral striatum and the anterodorsal striatum. Our findings demonstrate that site-specific behavioural responses are induced by microinjections of amphetamine, but not of quinpirole, into the striatum. Our results suggest that widespread areas of the striatum are implicated in the induction of a syndrome of sedation, yawning and motor inhibition, observed readily following microinjections of quinpirole into the striatum. This evidence supports both homogeneity and segregation of function in the striatum at the behavioural level. Further, the results suggest that the elicitation of site-specific action sequences at the level of the striatum seems to require cooperative interactions between D_1-class and D_2-class dopamine receptors.

Keywords: Striatum; Microinjection; Quinpirole; Amphetamine; Motor behaviour

1. Introduction

A large body of evidence suggests that the striatum is organised as a mosaic of neurochemical compartments that maintain specific relationships with its afferent and efferent systems (Graybiel, 1990; Groenewegen et al., 1991; Gerfen, 1992). The entire cortical mantle provides topographically organized projections to the striatum (DeLong and Georgopoulos, 1981; McGeorge and Faull, 1989; Parent and Hazrati, 1995). These anatomical findings encouraged the view that the striatum is functionally heterogenous. More recent anatomical studies provided further support for this notion by suggesting that cortical information is segregated at the anatomical and functional levels through multiple basal ganglia-thalamo-cortical circuits, of which the striatum is an intrinsic part (Alexander and Crutcher, 1990; Groenewegen et al., 1990; Hoover and Strick, 1993). The striatum is the major target not only for cortical, but also for limbic inputs, and its complex mosaic-like ordering of afferent/efferent connections and neurochemical compartments provides the basis for parallel processing of motor, associative and cognitive functions.

The evidence provided by anatomical and neurochemical studies was reinforced by the finding that specific subterritories of the striatum made selective contributions to behavioural processes (Iversen, 1984; Pisa, 1988; Robbins and Everitt, 1992). In this context, focal lesion and microinjection studies indicated that different sectors of the striatum are selectively involved in complex forms of behaviour. For example, in the rat, selective excitotoxic lesions of the ventrolateral striatum resulted in selective impairments in feeding behaviours and skilled motor performance, as observed in reaching and food-manipulation tasks (Dunnett and Iversen, 1982a,b; Pisa, 1988; Pisa and Cyr, 1990). By contrast, lesions of the nucleus accumbens specifically affected the appetitive aspects of motivated behaviour, including food hoarding induced by deprivation and approach to primary reinforcers (Iversen, 1984; Robbins and Everitt, 1992). The use of the intracerebral microinjection technique added convincing evidence supporting heterogeneity of function in the striatum in terms of responsiveness to drugs acting as direct or indirect dopamine

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agonists. In this regard, it became well-documented that the nucleus accumbens was crucially implicated in the psychomotor-activating and the reinforcing effects of dopamine and of the psychostimulants amphetamine and cocaine (Costall and Naylor, 1975; Taylor and Robbins, 1984; Jones et al., 1981; Hooks et al., 1993). In turn, the ventrolateral striatum was linked to the induction of stereotyped oral behaviours, including biting and directed movements of the paw to the mouth, which were observed readily after intracerebral microinjections of amphetamine into this sector (Kelley et al., 1988; Delfs and Kelley, 1990; Dickson et al., 1994).

While studies on the behavioural effects of intrastriatal administration of indirectly acting dopamine receptor agonists, such as amphetamine and cocaine, clearly show functional differences across subterritories in the striatum, the contribution of the different classes of dopamine receptors within these striatal sectors to the expression of behaviour has been less studied. Drugs which result in release of endogenous dopamine activate all classes of dopamine receptors. There are, however, dopamine agonists with greater degrees of selectivity for particular classes of dopamine receptors. In the present experiments, we compare the behavioural effects of microinjections of amphetamine with those elicited by the D_2-class dopamine receptor agonist quinpirole following administration into three anatomically distinct sites in the striatum: the nucleus accumbens, the ventrolateral striatum and the anterodorsal striatum.

2. Materials and methods

2.1. Animals and surgery

Wistar rats ($n = 30$), weighing 200–275 g at arrival in the laboratory, were used for these experiments, allowed to acclimatise to the laboratories for at least three days, and handled extensively for another four days before surgery. They were initially housed in pairs under constant conditions of temperature (19.0–21.0°C), relative humidity (60–65%) and light–dark cycle (12:12 h, lights on at 8:00 a.m.), with standard laboratory rat chow and tap water available ad libitum. Rats weighed 250–325 g at the time of surgery. They were anaesthetised with Avertin, which consists of 100 g of 2,2,2-tri-bromo-ethanol dissolved in 62 ml of tertiary amyl alcohol, and thereafter, 1.25 ml of this concentrate is diluted in 5 ml of absolute alcohol and 62.5 ml of physiological saline. Avertin was administered i.p., at a dose of 1 ml/100 g. All animals received a 1 ml/4 kg s.c. injection of the antibiotic enrofloxacin (Baytril®, Bayer, England) before surgery. Animals were then placed in a dual stereotaxic apparatus (Stoelting, USA), the skull was exposed and holes were drilled as appropriate. Three stainless steel mounting screws were implanted to provide anchoring support to the cannulation assembly. Guide cannulae were bilaterally lowered into the brain and dental acrylic was carefully applied. Coordinates for cannulae placements were: nucleus accumbens ($n = 10$) (A-P 1.6, L 1.4, D-V 4.7), ventrolateral striatum ($n = 10$) (A-P 0.2, L 3.9, D-V 4.1) and anterodorsal striatum ($n = 10$) (A-P 1.6, L 3.0, D-V 3.6), according to Paxinos and Watson (1986). Wire stylets were inserted into the guides to ensure they remained patent and sutures were applied as required. Small injections, totalling 0.2 ml of lignocaine hydrochloride (Lignavet® Plus, C-Vet, England) were made under the skin on either side of the assembly and dressing powders were sprinkled on the wound. Animals were then allowed to recover from the anaesthesia in thermal chambers set at 30°C and subsequently placed in individual cages.

2.2. Microinjections and drugs

Animals were allowed at least five days to recover from surgery. Microinjections were made by replacing the wire stylets with microinjection needles. For injections into the nucleus accumbens and the ventrolateral striatum, needles protruded 2 mm beyond the guide cannulae. In order to allow a similar degree of penetration of the guide into the brain in all three groups of animals, needles protruded 1 mm for infusions into the anterodorsal striatum. Guide cannulae of the 22-gauge and injection needles of the 29-gauge were utilised in these experiments. Needles were connected via polyethylene tubing to Hamilton® microsyringes driven by a precision micropump (SP250i, World Precision Instruments, England). Microinjections were made bilaterally into the striatum at a rate of 0.5 μl/min, in a volume of 0.5 μl per side. Needles were left in place for an additional 1 min to allow for diffusion of the drugs. Quinpirole (Research Biochemicals, USA) and amphetamine (Sigma, England) were dissolved in physiological saline and administered at doses of 3 μg/0.5 μl and 20 μg/0.5 μl, respectively. Dosage was selected on the basis of previously reported findings and of our own pilot experiments. First, animals received microinjections of quinpirole or saline in a counterbalanced order, followed by saline or amphetamine, also according to a counterbalanced design. In total, each animal received four microinjections. In all cases, at least 72 h elapsed between microinjections.

2.3. Histology

On completion of the experiments, animals were deeply anaesthetised with an overdose of pentobarbital (Sagatal) and perfused transcardially with isotonic saline followed by 10% formal saline. The brains were carefully removed and stored in a 30% sucrose solution. Coronal 40 μm sections were cut in a sliding microtome, and every other section was mounted on slides, dried overnight and routinely stained with cresyl violet. Placements were verified and drawn for each individual animal (Fig. 1). All animals

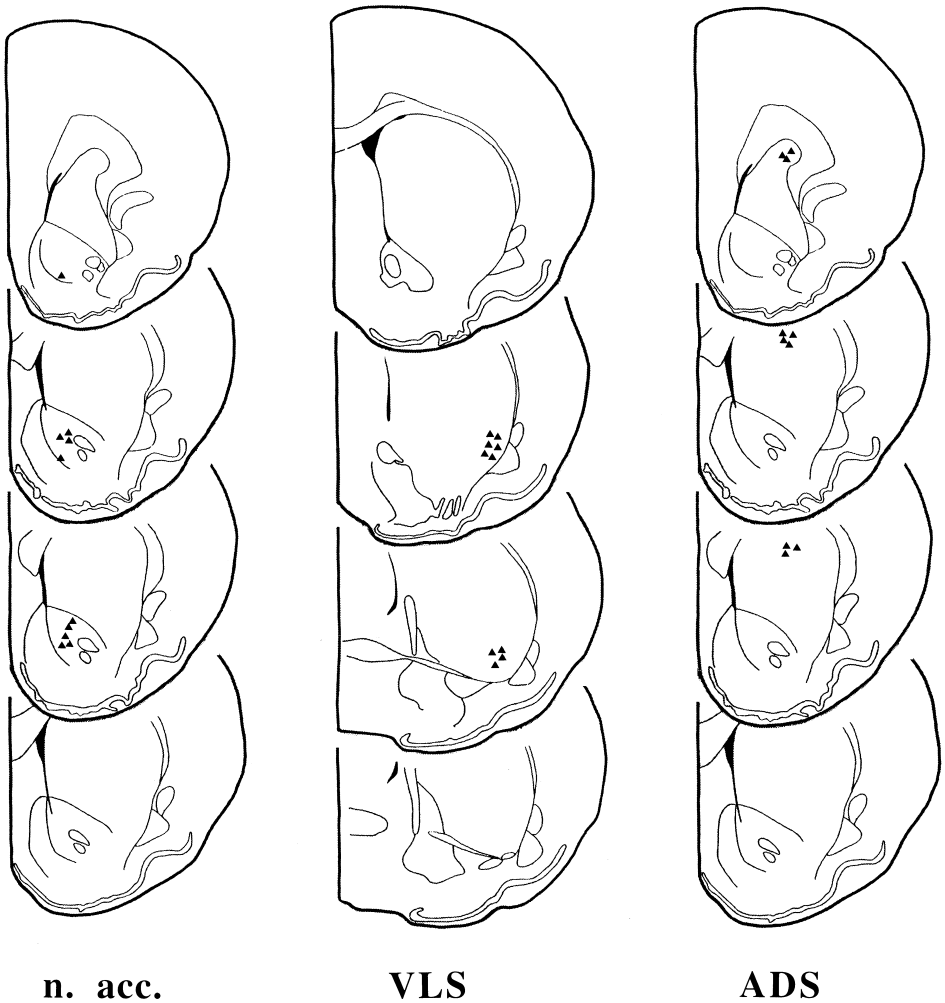

Fig. 1. Coronal sections showing quinpirole and amphetamine microinjection sites (filled triangles) into the nucleus accumbens (n. acc.), the ventrolateral striatum (VLS) and the anterodorsal striatum (ADS), in modified serial sections from Paxinos and Watson (1986).

were included in the statistical analyses, since all injection sites fell within the boundaries of the relevant brain structures targeted. Nonspecific damage to these structures caused by the microinjections was considered negligible in all cases.

2.4. Behavioural procedures and measures

The testing apparatus consisted of a rectangular, transparent perpex box (46 cm long, 21 cm wide and 24 cm deep) placed in the centre of the test room. Behavioural observations were made by means of a video camera connected to a video recorder and a television monitor. The apparatus contained four rectangular wood blocks ($5 \times 2 \times 3$ cm) placed in its corners and a bedding of wood chips. The habituation procedure involved one single exposure to the apparatus. During this habituation phase, animals were taken individually into the test room and pre-exposed to the observation box for a period of 10 min. Animals were then removed from the box and received a sham microinjection. Fresh sterile stylets were inserted into the cannulae and animals were further habituated to the observation cage for 20 min. On test days, the same procedure was carried out except that, in this case, drugs were intracerebrally delivered. In all cases, filming was conducted in a way such that animals were tracked from close range, so that information relative to the face and mouth of the animal could be collected. Upon completion of the experiments, video tapes were examined blind to the experimental conditions and behavioural elements were scored continuously over a 20-min post-injection period. A number of behavioural categories representing different combinations of related responses were selected, as follows: (a) *rearing*, episodes of rearing in the centre and the periphery of the experimental cage; (b) *crossovers*, crosses through a line dividing the experimental apparatus through its centre; (c) *purposeless oral behaviour*, individual elements of oral behaviour not directed at any stimulus, including mouth movements, tongue protrusions and facial tremors; (d) *yawning behaviour*; and (e) *sedation*, judged by the presence (score = 1) or absence (score = 0) of

ptosis and drowsiness in experimental animals. Scores for *directed oral stereotypy*, including biting, gnawing, paw nibbling and movements paw-to-mouth, were given using a rating scale (1, absent; 2, mild; 3, moderate; 4, intense; 5, very intense).

2.5. Statistical analysis

Analysis of variance (ANOVA) was calculated to test the statistical significance of the treatments, and to obtain the sampling error term with which to perform planned contrasts (drug vs. control at each of the three sites in the striatum). Appropriate protection against familywise error was afforded by the Bonferroni's correction method. Thus, in all cases, the overall error was never allowed to exceed $\alpha = 0.05$. For the analysis of sedation and oral stereotypy, the nonparametric test of Friedman for k correlated samples was used.

3. Results

The ANOVA indicated significant effects of quinpirole [$F(1,27) = 29.262$, $p < 0.0001$] and of amphetamine [$F(1,27) = 59.557$, $p < 0.0001$] on rearing behaviour. Quinpirole produced a significant reduction in *rearing* behaviour when administered into the nucleus accumbens ($t = 3.27$, $p < 0.01$), or into the ventrolateral striatum ($t = 4.05$, $p < 0.01$) (Fig. 2). A nonsignificant trend was observed in animals treated with quinpirole into the anterodorsal striatum ($t = 2.06$, $p < 0.10$). In turn, amphetamine microinjections revealed a contrasting pattern of behavioural responses; following injections into the nucleus accumbens, amphetamine induced a 4-fold increase in rearing behaviour ($t = 11.91$, $p < 0.01$). This effect was site-selective, since it was not observed in animals receiving amphetamine into the ventrolateral striatum or into the anterodorsal striatum.

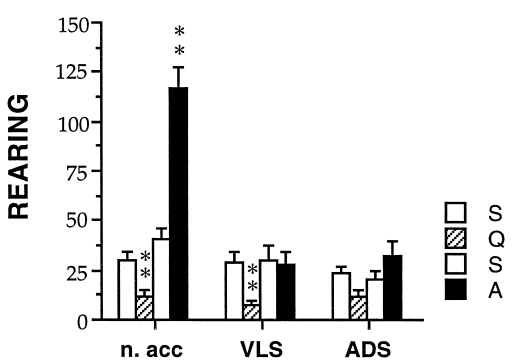

Fig. 2. Effects of quinpirole (Q) and amphetamine (A) microinjections into the nucleus accumbens (n. acc.), the ventrolateral striatum (VLS) and the anterodorsal striatum (ADS) on rearing behaviour, compared to control injections (S). *Abscissa*: site in striatum; *ordinate*: rearing counts per session. Quinpirole reduced rearing significantly in the n. acc. and the VLS groups, whereas amphetamine induced a selective increase in the n. acc. ($* p < 0.05$ vs. control; $** p < 0.01$ vs. control).

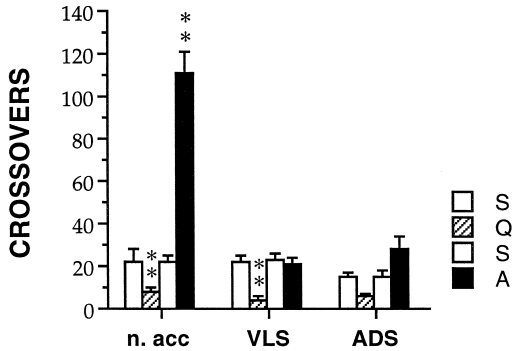

Fig. 3. Locomotor activity induced by quinpirole (Q) and amphetamine (A) microinjections into the nucleus accumbens (n. acc.), the ventrolateral striatum (VLS) and the anterodorsal striatum (ADS). *Abscissa*: site in striatum; *ordinate*: crossovers per session. Following administration of quinpirole into the n. acc. or into the VLS, locomotor activity was significantly decreased relative to controls (S). However, amphetamine produced behavioural hyperactivity in the n. acc., but not in the VLS or the ADS groups ($* p < 0.05$ vs. control; $** p < 0.01$ vs. control).

For *crossovers*, the same differential pattern of behavioural responses to quinpirole and amphetamine administration was observed (Fig. 3). The ANOVA revealed significant effects of quinpirole [$F(1,27) = 34.502$, $p < 0.0001$] and of amphetamine [$F(1,27) = 68.384$, $p < 0.0001$]. Quinpirole microinjections produced sustained locomotor inhibition of similar magnitude following application into the nucleus accumbens ($t = 3.53$, $p < 0.01$) or into the ventrolateral striatum ($t = 4.37$, $p < 0.01$). Injections of quinpirole into the anterodorsal striatum also reduced locomotor activity, although non-significantly ($t = 2.27$, $p < 0.10$). It must be noted, however, that baseline levels of locomotor activity in this group were lower than in the nucleus accumbens and the ventrolateral striatum groups, and that in absolute terms, the response to quinpirole was comparable in the three groups. Thus, the inability to detect differences between the control and the quinpirole conditions in the anterodorsal striatum could have been due to a floor effect. Microinjections of amphetamine produced locomotor effects that showed topographical specificity. Pronounced hyperactivity followed amphetamine infusions into the nucleus accumbens, increasing locomotor behaviour 5-fold ($t = 12.72$, $p < 0.01$). In sharp contrast, amphetamine was devoid of locomotor effects in the ventrolateral striatum and in the anterodorsal striatum.

Yawning behaviour was differentially affected by quinpirole and amphetamine microinjections into the striatum (Fig. 4). The ANOVA showed significant effects of quinpirole [$F(1,27) = 38.164$, $p < 0.0001$] and of amphetamine [$F(1,27) = 5.113$, $p < 0.032$]. Quinpirole induced an intense yawning response after infusions into the ventrolateral striatum ($t = 4.65$, $p < 0.01$) and into the anterodorsal striatum ($t = 3.95$, $p < 0.01$), but only a trend was observed in animals treated into the nucleus accum-

bens ($t = 2.10$, $p < 0.010$). However, amphetamine microinjections into the nucleus accumbens, but not into the anterodorsal striatum, completely prevented the expression of spontaneous yawning responses ($t = 2.86$, $p < 0.01$). The effect of amphetamine into the ventrolateral striatum on yawning could not be fully evaluated due to the lack of baseline responses.

Sedation was induced by quinpirole, but not by amphetamine, following infusions into one of the three sites in the striatum. Sedation was significantly increased by quinpirole microinjections into the nucleus accumbens ($\chi^2 = 4.70$, $p < 0.05$) (7/10), into the ventrolateral striatum ($\chi^2 = 4.70$, $p < 0.05$) (7/10) or into the anterodorsal striatum ($\chi^2 = 6.40$, $p < 0.025$) (8/10).

The results of intrastriatal microinjections of quinpirole and amphetamine on *oral behaviours* not directed to goal suggested marked differences between the two drug conditions and between subterritories in the striatum (Fig. 5). The overall ANOVA indicated significant effects of quinpirole [$F(1,27) = 22.954$, $p < 0.0001$], but not significant effects of amphetamine [$F(1,27) = 0.0001$, $p < 0.9907$]. Quinpirole evoked a 2-fold increase in oral behaviours following administration into the nucleus accumbens ($t = 3.61$, $p < 0.01$) or into the ventrolateral striatum ($t = 2.74$, $p < 0.05$), but not into the anterodorsal striatum. These behaviours mainly consisted of purposeless low-frequency chewing and tremulous-type oral responses, including both high-frequency chewing and facial tremors. However, amphetamine demonstrated a complete inability to elicit this kind of oral syndrome after administration into any of the three sites in the striatum.

The analysis of *oral stereotypies* indicated drug-specific, topographically distributed behavioural effects. Quinpirole microinjections did not induce any form of perseverative, stereotyped oral behaviour at any site. Conversely, amphetamine administration into the ventrolateral striatum elicited a syndrome of oral/forelimb motor stereotypies (mean ± S.E.M. for amphetamine = 3.3 ± 0.6; mean ± S.E.M. for saline = 1.0 ± 0.0; $\chi^2 = 4.90$, $p < 0.05$), which mainly consisted of repetitive movements paw-to-mouth accompanied by directed oral responses, such as licking and nibbling of paws and of the experimental cage. These behaviours were never observed in control animals or in those treated with amphetamine into the nucleus accumbens or into the anterodorsal striatum (data not shown).

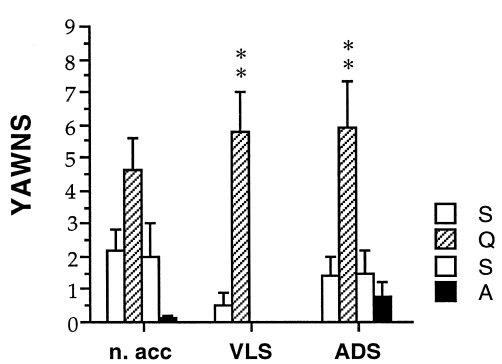

Fig. 4. Effects of quinpirole (Q) and amphetamine (A) microinjections into the nucleus accumbens (n. acc.), the ventrolateral striatum (VLS) and the anterodorsal striatum (ADS) on yawning responses, relative to control infusions (S). *Abscissa*: site in striatum; *ordinate*: yawning responses per session. Administration of quinpirole into the VLS or into the ADS evoked a strong yawning response. Conversely, microinjections of amphetamine abolished spontaneous yawning in the n. acc. (note that effect of amphetamine into the VLS could not be evaluated due to the absence of baseline; * $p < 0.05$ vs. control; ** $p < 0.01$ vs. control).

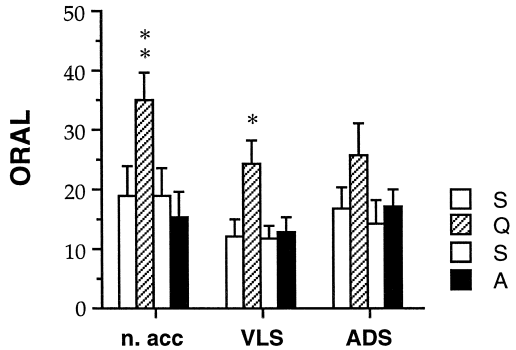

Fig. 5. Oral behaviour not directed to goal elicited by quinpirole (Q) and amphetamine (A) microinjections into the nucleus accumbens (n. acc.), the ventrolateral striatum (VLS) and the anterodorsal striatum (ADS), compared to controls (S). *Abscissa*: site in striatum; *ordinate*: oral movements per session. Oral behaviours were significantly increase by quinpirole in the n. acc. and in the VLS groups. In turn, amphetamine failed to elicit this response after application into the striatum (* $p < 0.05$ vs. control; ** $p < 0.01$ vs. control).

4. Discussion

The results of the present study include several findings related to the effects of the D_2-class receptor agonist quinpirole and the indirect agonist amphetamine on unconditioned motor behaviours following direct administration into the striatum.

4.1. Effects of quinpirole and amphetamine on rearing and locomotion

Regarding the behavioural effects of intrastriatal quinpirole on locomotion and rearing, the present experiments extend previous observations. Mogenson and Wu (1991a,b) demonstrated that injections of quinpirole into the nucleus accumbens reduced locomotor activity in a dose-dependent manner. However, using a similar dose range, quinpirole injections into the nucleus accumbens had been shown previously to have no effect on locomotor activity (Breese et al., 1987; Plaznik et al., 1989) or to slightly enhance it (Dreher and Jackson, 1989). These inconsistencies may be related to the use of different strains of rats and of different methods for measuring locomotor behaviour, e.g.,

open field or automated activity chambers. In this study, the effects of quinpirole on rearing and locomotion were robust after infusions into the nucleus accumbens or into the ventrolateral striatum. In agreement with our observations, Delfs and Kelley (1990) reported that injections of quinpirole into the ventrolateral striatum inhibited rearing and locomotion in a dose-dependent fashion. Our observations suggest that these motor inhibitory effects are probably secondary to a general sedative effect of quinpirole after injection into the striatum, which was apparent following injections at all the striatal sites studied. On measures of locomotion and rearing, the effects of quinpirole in the anterodorsal striatum did not reach significance. It should be noted that the baseline activity was marginally lower in this group, but the levels of locomotion and rearing following quinpirole injections were comparable in the three groups, as indeed were the levels of sedation. Thus, these results suggest that the striatum is homogenous for the inhibitory effects of quinpirole on locomotion and rearing. In contrast, in the present experiments, the effects of microinjections of amphetamine were clearly dissociated at three sites in the striatum. Dopaminergic neurons of the mesoaccumbens projection are known to play a critical role in the mediation of locomotor activity elicited by systemic amphetamine (Kelly et al., 1975). Further, injections of the dopamine or amphetamine into the nucleus accumbens are known to evoke a strong locomotor response (Costall and Naylor, 1975; Pijnenburg et al., 1976; Jones et al., 1981; Essman et al., 1993). In the present experiments, amphetamine infusions into the nucleus accumbens elicited an increase in locomotor activity and rearing behaviour, confirming these observations. Injections of amphetamine into the ventrolateral striatum did not affect locomotor or rearing activity, which is also consistent with previous findings (Kelley et al., 1988, 1989) and injections into the anterodorsal striatum increased these behaviours, although non-significantly. Thus, in this study, it was clear that the locomotor effects of intrastriatal amphetamine, including horizontal and vertical activity, were largely mediated by the nucleus accumbens, suggesting that the substrate mediating amphetamine-induced hyperactivity lies within the ventral striatum.

4.2. Effects of quinpirole and amphetamine on sedation and yawning

In addition to suppression of exploration, systemic administration of low doses of D_2-class receptor agonists evoke yawning and sedation (Mogilnicka and Klimek, 1977; Longoni et al., 1987). In the present study, a prominent yawning response was observed following injections of quinpirole into the anterodorsal and the ventrolateral sectors of the striatum. Although the increase in yawning behaviour observed in animals receiving quinpirole into the nucleus accumbens was not significant, our pilot studies indicate that infusions of quinpirole into the nucleus accumbens elicit yawning in a dose-dependent manner (data not shown). Therefore, wide areas of the striatum mediate yawning behaviour, although with respect to this behaviour, dorsal and lateral areas appear to be more sensitive to D_2-class dopamine receptor activation. Similarly, quinpirole was able to induce sedation when applied to one of the three striatal sectors studied. These results extend previous observations. Dourish et al. (1985) described a syndrome characterised by yawning and chewing after injections of apomorphine into a ventromedial region of the striatum, situated dorsal to the nucleus accumbens, and Scheel-Krüger (1992) reported that injections of quinpirole or apomorphine into the anterodorsal striatum elicited sedation and yawning. In the present experiments, while quinpirole into the striatum stimulated yawning, amphetamine microinjections into the nucleus accumbens selectively prevented the expression of spontaneous yawning behaviour. Drugs that affect dopaminergic neurotransmission in different ways, such as apomorphine, amphetamine and L-DOPA, induce yawning when given at low doses that do not produce locomotor activation (Mogilnicka and Klimek, 1977). Further, yawning, together with locomotor inhibition, was elicited by pergolide or apomorphine in the presence of elevated extracellular levels of dopamine in the striatum, as measured by in vivo microdialysis (Ståhle and Ungerstedt, 1989; Ståhle, 1992). Thus, it would appear that the expression of yawning is unrelated to the extracellular concentrations of dopamine in the striatum. Therefore, it is likely that dopamine-stimulated behavioural hyperactivity mediated by D_1-class and D_2-class dopamine receptors in the nucleus accumbens is accompanied by changes in neurotransmitter systems and hormonal processes implicated in the induction of yawning behaviour. However, the nature of these interactions remains to be explored.

4.3. Effects of quinpirole and amphetamine on non-goal directed oral behaviours

Microinjections of quinpirole into the nucleus accumbens and the ventrolateral striatum elicited oral movements not directed at any external object. These mainly consisted of openings and closings of the mouth, vacuous and tremulous chewing. In agreement with our observations, Koshikawa et al. (1990) also reported rhythmical jaw movements in rats following microinjections of quinpirole into the nucleus accumbens. Delfs and Kelley (1990) observed oral movements, jaw openings and closings, jaw tremors and tongue protrusions, but not intense oral stereotypies, following quinpirole infusions into the ventrolateral striatum. In our experiments, the oral behaviour elicited from the ventrolateral striatum by quinpirole could not be distinguished from that induced from the nucleus accumbens. However, only a mild, non-significant increase in oral activity was observed in the anterodorsal striatum, suggesting that the control of this kind of oral behaviours

is preferentially exerted by ventral regions of the striatum, including the ventrolateral sector and the nucleus accumbens. In the rodent, the functional significance of oral behaviours not directed at any object, which are different from dopamine or amphetamine-elicited oral stereotypies, is not well-understood, but they may be related to forms of neuroleptic-induced tardive dyskinesia and of parkinsonian dystonia and dyskinesia (Kelley et al., 1989; Delfs and Kelley, 1990; Salamone et al., 1990). By contrast, amphetamine failed to elicit oral dyskinetic movements in any of the three striatal sites investigated. In order to explain the effects of quinpirole and amphetamine on oral behaviour, it is of interest to compare the effects of amphetamine with those induced by direct dopamine receptor agonists. For example, the D_1-class dopamine receptor agonist SKF 38393 was reported to induce mouth openings, vacuous chewing, high-frequency jaw movements and facial tremors when administered parenterally (Rosengarten et al., 1983; Collins et al., 1993), although other authors have failed to reproduce these effects (see Waddington et al., 1995). The effects of SKF 38393 were attenuated by co-administration of a D_2-class dopamine receptor agonist, but exacerbated by a D_2-class dopamine receptor antagonist (Rosengarten et al., 1983). Thus, it would appear that D_1-class and D_2-class dopamine receptors regulate the expression of oral dyskinesia through opposing interactions, such that orchestrated activation of both types of receptor would have a 'normalising effect' on this behavioural response. Therefore, shifts in the balance between D_1-class and D_2-class dopamine receptor activation may contribute to the initiation and expression of oral dyskinetic movements. According to this hypothesis, we would not expect amphetamine to elicit this type of oral behaviour, due to its ability to stimulate all classes of dopamine receptors non-selectively through the release of the transmitter from nerve terminals.

4.4. Effects of quinpirole and amphetamine on oral stereotypy

Reinforcing the notion of functional segregation in the striatum, microinjections of amphetamine into the ventrolateral striatum elicited a syndrome mainly characterised by compulsive and perseverative paw-to-mouth movements, which were not observed following local administration into the nucleus accumbens or the anterodorsal striatum. Kelley et al. (1988) previously reported that injections of amphetamine into the ventrolateral striatum produced intense oral stereotypies, including biting, licking and body gnawing. Further, co-administration of SKF 38393 and quinpirole into the ventrolateral striatum elicited biting (Bordi and Meller, 1989), whereas treatment with SKF 38393 or quinpirole alone was ineffective (Kelley et al., 1990), suggesting the necessity for D_1-class and D_2-class dopamine receptor co-activation for the expression of intense oral stereotypies. Because these behavioural responses were not observed in animals injected into the nucleus accumbens or into the anterodorsal striatum, our results confirm the anatomical specificity of the oral stereotypy syndrome elicited by amphetamine.

5. Conclusions

Quinpirole microinjections revealed that a considerable degree of functional overlap exists across striatal territories for the expression of certain motor behaviours. This D_2-class dopamine receptor-mediated substrate is linked to processes leading to behavioural inactivation, together with the emergence of sedation, yawning and oral dyskinesias. Thus, the striatum is not topographically organised for the mediation of D_2-class dopamine receptor-induced sedation, yawning and motor inhibition. However, amphetamine microinjections clearly dissociated three distinctive striatal sites, indicating the heterogenous distribution of amphetamine-mediated motor responses in the striatum. Previously, Dunnett and Iversen (1982c) demonstrated spontaneous and drug-induced rotation in rats with selective 6-OHDA lesions at different loci in the striatum, with all groups showing a similar degree of rotation. These results, therefore, suggested that the striatum is homogeneous for the induction of rotational behaviour. Studies in animals with selective excitotoxic lesions of specific regions of the striatum suggested that associative functions, e.g., visual and olfactory conditioning, appear to be widely distributed in the striatum, and that other specific motor functions show a precise topography (Pisa and Cyr, 1990). Similarly, in our studies, while the quinpirole syndrome appears to be mediated by widespread neural mechanisms in the striatum, the effects of amphetamine show a high degree of anatomical specificity. Taken together, these results suggest that activation of D_2-class dopamine receptors contribute to a uniform background level of tonic stimulation in the striatum, whereas cooperative/opposing interactions between D_1-class and D_2-class dopamine receptors provide functional specificity in the striatum. Further experiments are required to understand the neuroanatomical mechanisms underlying the patterns of functional homogeneity and segregation observed in the striatum at the behavioural level.

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References

Alexander, G.E., Crutcher, M.D., 1990. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 13, 266–271.

Bordi, F., Meller, E., 1989. Enhanced behavioral stereotypies elicited by intrastriatal injection of D1 and D2 dopamine agonists in intact rats. Brain Res. 504, 276–283.

Breese, G.R., Duncan, G.E., Napier, C., Bondy, S.C., Iorio, L.C., Mueller, R.A., 1987. 6-Hydroxydopamine treatments enhance behavioural responses to intracerebral microinjection of D1- and D2-dopamine agonists into nucleus accumbens and striatum without changing dopamine antagonist binding. J. Pharmacol. Exp. Ther. 240, 167–176.

Collins, P., Broekkamp, C.L., Jenner, P., Marsden, C.D., 1993. Electromyographical differentiation of the components of perioral movements induced by SKF 38393 and physostigmine in the rat. Psychopharmacology (Berlin) 112, 428–436.

Costall, B., Naylor, R.J., 1975. The behavioural effects of dopamine applied intracerebrally to areas of the mesolimbic system. Eur. J. Pharmacol. 32, 87–92.

Delfs, J.M., Kelley, A.E., 1990. The role of D1 and D2 dopamine receptors in oral stereotypy induced by dopaminergic stimulation of the ventrolateral striatum. Neuroscience 39, 59–67.

DeLong, M.R., Georgopoulos, A.P., 1981. Motor functions of the basal ganglia. In: Bookhart, J.M., Mountcastle, V.B., Brooks, V.B., Geiger, S.R. (Eds.), Handbook of Physiology, Vol. 2, Part 2. American Physiological Society, MA, pp. 1017–1061.

Dickson, P.R., Lang, C.G., Hinton, S.C., Kelley, A.E., 1994. Oral stereotypy induced by amphetamine microinjection into striatum: an anatomical mapping study. Neuroscience 61, 81–91.

Dourish, C.T., Cooper, S.J., Philips, S.R., 1985. Yawning elicited by systemic and intrastriatal injection of piribedil and apomorphine in the rat. Psychopharmacology 86, 175–181.

Dreher, J.K., Jackson, D.M., 1989. Role of D1 and D2 dopamine receptors in mediating locomotor activity elicited from the nucleus accumbens of rats. Brain Res. 487, 267–277.

Dunnett, S.B., Iversen, S.D., 1982a. Regulatory impairments following selective 6-OHDA lesions of the neostriatum. Behav. Brain Res. 4, 195–202.

Dunnett, S.B., Iversen, S.D., 1982b. Sensorimotor impairments following localized kainic acid and 6-hydroxydopamine lesions of the neostriatum. Brain Res. 248, 121–127.

Dunnett, S.B., Iversen, S.D., 1982c. Spontaneous and drug-induced rotation following localized 6-hydroxydopamine and kainic acid-induced lesions of the neostriatum. Neuropharmacology 21, 899–908.

Essman, W.D., McGonigle, P., Lucki, I., 1993. Anatomical differentiation within the nucleus accumbens of the locomotor stimulatory actions of selective dopamine agonists and D-amphetamine. Psychopharmacology 112, 233–241.

Gerfen, C.R., 1992. The neostriatal mosaic: multiple levels of compartmental organization. Trends Neurosci. 15, 133–139.

Graybiel, A.M., 1990. Neurotransmitters and neuromodulators in the basal ganglia. Trends Neurosci. 13, 244–254.

Groenewegen, H.J., Berendse, H.W., Wolters, J.G., Lohman, A.H.M., 1990. The anatomical relationship of the prefrontal cortex with the striatipallidal system, the thalamus and the amygdala: evidence for a parallel organization. Prog. Brain Res. 85, 95–116.

Groenewegen, H.J., Berendse, H.W., Meredith, G.E., Haber, S.N., Voorn, P., Wolters, J.G., Lohman, A.H.M., 1991. Functional anatomy of the ventral, limbic system innervated striatum. In: Willner, P., Scheel-Krüger, J. (Eds.), The Mesolimbic Dopamine System: From Motivation to Action. Wiley, Chichester, UK, pp. 19–59.

Hooks, M.S., Jones, G.H., Hemby, S.E., Justice, J.B., 1993. Environmental and pharmacological sensitization: effects of repeated administration of systemic or intra-accumbens cocaine. Psychopharmacology (Berlin) 111, 109–116.

Hoover, J.E., Strick, P.L., 1993. Multiple output channels in the basal ganglia. Science 259, 819–821.

Iversen, S.D., 1984. Behavioural effects of manipulation of basal ganglia neurotransmitters, Functions of the Basal Ganglia, Ciba Foundation Symposium 107. Pitman, London, pp. 183–200.

Jones, D.L., Mogenson, G.J., Wu, M., 1981. Injections of dopaminergic, cholinergic, serotoninergic and GABAergic drugs into the nucleus accumbens: effects on locomotor activity in the rat. Neuropharmacology 20, 29–37.

Kelley, A.E., Lang, C.G., Gauthier, A.M., 1988. Induction of oral stereotypy following amphetamine microinjection into a discrete subregion of the striatum. Psychopharmacology 95, 556–559.

Kelley, A.E., Gauthier, A.M., Lang, C.G., 1989. Amphetamine microinjections into distinct striatal subregions cause dissociable effects on motor and ingestive behaviour. Behav. Brain Res. 35, 27–39.

Kelly, P.H., Seviour, P.W., Iversen, S.D., 1975. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Res. 94, 507–522.

Koshikawa, N., Koshikawa, F., Tomiyama, K., Kikuchi de Beltran, K., Kamimura, F., Kobayashi, M., 1990. Effects of dopamine D1 and D2 agonists and antagonists injected into the nucleus accumbens and globus pallidus on jaw movements of rats. Eur. J. Pharmacol. 182, 375–380.

Longoni, R., Spina, L., Di Chiara, G., 1987. Permissive role of D1 receptor stimulation by endogenous dopamine for the expression of postsynaptic D2-mediated behavioural responses. Yawning in rats. Eur. J. Pharmacol. 134, 163–173.

McGeorge, A.J., Faull, R.L.M., 1989. The organization of the projection from the cerebral cortex to the striatum in the rat. Neuroscience 29, 503–537.

Mogenson, G.J., Wu, M., 1991a. Quinpirole to the nucleus accumbens reduces exploratory and amphetamine-elicited locomotion. Brain Res. Bull. 27, 743–746.

Mogenson, G.J., Wu, M., 1991b. Effects of administration of dopamine D2 agonist quinpirole on exploratory locomotion. Brain Res. 551, 216–220.

Mogilnicka, E., Klimek, V., 1977. Drugs affecting dopamine neurons and yawning behaviour. Pharmacol. Biochem. Behav. 7, 303–305.

Parent, A., Hazrati, L.-N., 1995. Functional anatomy of the basal ganglia: I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res. Rev. 20, 91–127.

Paxinos, G., Watson, C., 1986. The Rat Brain in Stereotaxic Coordinates. Academic Press, Sydney.

Pijnenburg, A.J.J., Honig, W.M.M., Van der Heyden, J.A.M., Van Rossum, J.M., 1976. Effects of chemical stimulation of the mesolimbic dopamine system upon locomotor activity. Eur. J. Pharmacol. 35, 45–58.

Pisa, M., 1988. Motor somatotopy in the striatum of the rat: manipulation, biting and gait. Behav. Brain Res. 27, 21–35.

Pisa, M., Cyr, J., 1990. Regionally selective roles of the rat's striatum in modality-specific discrimination learning and forelimb reaching. Behav. Brain Res. 37, 281–292.

Plaznik, A., Stefanski, R., Kostowski, W., 1989. Interaction between accumbens D1 and D2 receptors regulating rat locomotor activity. Psychopharmacology 99, 558–562.

Robbins, T.W., Everitt, B.J., 1992. Functions of dopamine in the dorsal and ventral striatum. Semin. Neurosci. 4, 119–127.

Rosengarten, H., Schweitzer, J.W., Friedhoff, A.J., 1983. Induction of oral dyskinesias in naive rats by D1 receptor stimulation. Life Science 33, 2479–2482.

Salamone, J.D., Johnson, C.J., McCullough, L.D., Steinpreis, R.E., 1990. Lateral striatal cholinergic mechanisms in oral motor activities in the rat. Psychopharmacology (Berlin) 162, 529–534.

Scheel-Krüger, J., 1992. The syndrome of sedation and yawning behaviour in the rat is dependent on postsynaptic dopamine D2 receptors. Psychopharmacology S 32, 104.

Ståhle, L., 1992. Do autoreceptors mediate dopamine agonist-induced yawning and suppression of exploration? A critical review. Psychopharmacology 106, 1–13.

Ståhle, L., Ungerstedt, U., 1989. Yawning and suppression of exploration in amphetamine-treated rats, incompatibility with the dopamine autoreceptor hypothesis. Psychopharmacology 97, 553–560.

Taylor, J.R., Robbins, T.W., 1984. Enhanced behavioural control by conditioned reinforcers following microinjections of D-amphetamine into the nucleus accumbens. Psychopharmacology 84, 405–412.

Waddington, J.L., Daly, S.A., Downes, R.P., Deveney, A.M., McCauley, P.G., O'Boyle, K.M., 1995. Behavioural pharmacology of D-1-like dopamine receptors: further subtyping, new pharmacological probes and interactions with D-2-like receptors. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 19, 811–831.