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ON THE INTERPRETATION OF ASYMMETRIES OF POSTURE AND LOCOMOTION PRODUCED WITH DOPAMINE AGONISTS IN ANIMALS WITH UNILATERAL DEPLETION OF STRIATAL DOPAMINE

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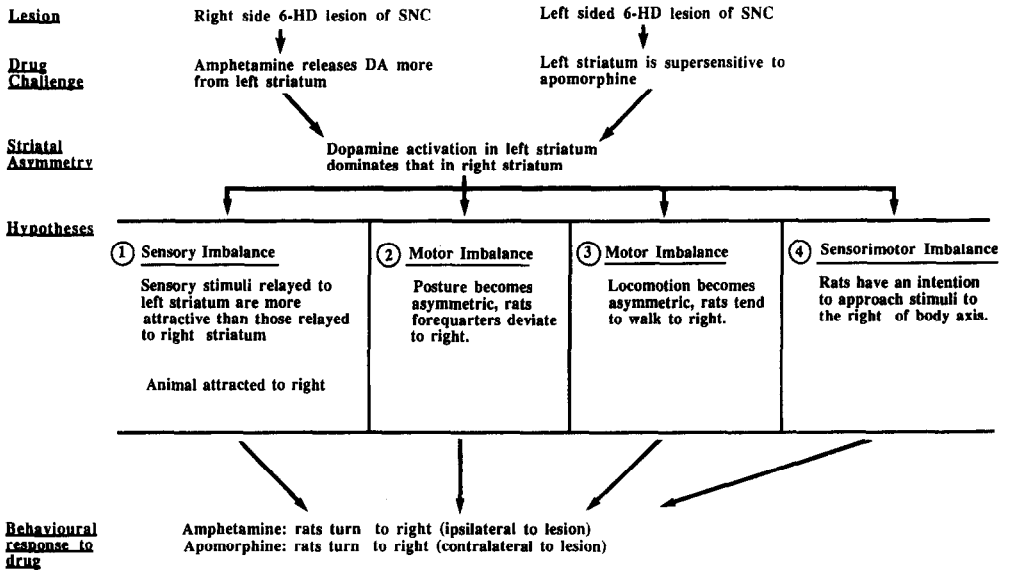

FIG. 1. Hypotheses to explain Ungerstedt's rotating rats.

1. INTRODUCTION

In 1971, Ungerstedt reported on some seminal experiments on the function of the mammalian striatum, using rats (Ungerstedt, 1971a). Unilateral lesions of the substantia nigra were made in these animals with the catecholamine-selective neurotoxin 6-hydroxydopamine, and at various times after the lesion, the animals were challenged with dopamine agonist drugs. The major findings, now very well known, were as follows: When direct dopamine receptor stimulants (such as apomorphine) were administered, the rats displayed rotatory movements, circling *away* from the lesioned side (henceforth "*contralateral* circling"). When indirect dopamine agonists (such as amphetamine) were given, the rats circled *towards* the lesioned side (henceforth "*ipsilateral* circling"). These observations have been very influential in analyses of drug properties and brain mechanisms, and have led to many hundreds of later publications exploring these and related examples of drug- and lesion-induced asymmetries of locomotion and posture (see reviews by Pycock, 1980; Pycock and Kilpatrick, 1989).

The explanations offered by Ungerstedt for his findings were as follows: since amphetamine-like drugs act by releasing dopamine from intact dopaminergic terminals, in the above experiments they would act preferentially to activate the dopamine receptors on the intact (*unlesioned*) side. On the lesioned side there should be very few dopaminergic nerve terminals, and consequently the dopamine receptors on that side should proliferate, an example of the widely known phenomenon of denervation supersensitivity. Thus, when a direct dopamine agonist such as apomorphine is given, there is preferential activation of dopamine receptors on the *lesioned* side. The behavioural findings in either case can then be explained by a single hypothesis: *that the animal turns away from the side where dopamine activity is greatest* (see Fig. 1).

This explanation has generally been followed in later publications on this subject, and there is no reason to doubt it. However, it is only a partial explanation of the original phenomena. A full explanation requires elucidation of the mechanism by which elevated dopamine activity on one side leads the animal to turn away from that side. A variety of matters then become relevant as potential factors in analysis of this issue: (i) What is the sign of the relationship between dopamine activity in the striatum, and changes in motor and locomotor activity? That is: does striatal dopamine produce an overall activation or an overall suppression of motor or locomotor activity? (ii) To which side is this motor or locomotor activity referred? Is it referred ipsilaterally, contralaterally, or is it an organized pattern involving both sides. In the latter case is there a lateral bias of the pattern organized from a single striatum, and is this bias to the ipsilateral or contralateral side of the body? (These questions can be answered empirically by observing behaviour. Alternatively, it might be thought relevant to consider the striatal output pathways [and their side and their sign] by which asymmetrical dopamine activity in the striata is expressed as asymmetrical posture or locomotion.) (iii) What is the nature of the interaction between dopamine, its various receptor types, and the cellular components of the striatum upon which asymmetrical behaviour depends? (iv) What is the difference between the case of apomorphine-induced contralateral rotation and amphetamine-induced ipsilateral

rotation? Is it simply a difference in the side on which dopaminergic stimulation is greatest? Is there a more fundamental difference between the normal and the denervated striatum? Or is there some other basic difference between the dopaminergic effect of indirect agonist such as amphetamine and a direct one such as apomorpine? (v) What aspects of motor behaviour are actually represented in the striatum which can produce these asymmetrical behaviours when dopamine activity in the two striata is asymmetrical?

Although there has been much work bearing on each of these questions, it has seldom been used to clarify the aspects of Ungerstedt's observations (referred to above), which are left unexplained. Currently there is little discussion and no consensus on this matter. This is puzzling, because *prima facie* the direction of turning in Ungerstedt's rats is paradoxical when viewed in a neuroanatomical light. The paradox comes about as follows: one of the most basic facts of neuroanatomy is apparently that the anatomical components of the forebrain (whether motor, sensory, cortical or striatal) are related to input and output on the *opposite* side of the body. For instance, the akinesia and tremor of Parkinson's disease, or the abnormal movements of chorea, occur on the side opposite to the abnormal striatum (see Section 2.4 below). One might therefore expect that excess dopaminergic activity in one striatum would bring about increased motor activity on the *opposite* side of the body; and if that motor activity was expressed as forward locomotor movements of the limbs, the animal should turn *towards* the side of excess striatal dopaminergic activity. The aim of the present review is to discuss the relation between dopaminergic activity and asymmetries of locomotion and posture, including the issues referred to above. This leads to a hypothesis about the receptor types involved in these phenomena, the corresponding psychomotor processes of each, and (tentatively) the subregions of the striatum (in rats) which underlie each of these psychomotor processes resulting in drug-induced circling.

2. CONCEPTS OF THE FUNCTIONAL ROLE OF STRIATAL DOPAMINERGIC ACTIVITY

2.1. INTRODUCTION

A central question to ask in relation to the drug-induced circling behaviour in unilaterally lesioned animals is: "To what behaviour (if any) does it correspond in unlesioned animals given the same drugs?" It is thus necessary to review briefly existing concepts of the relation between striatal dopaminergic activity and behavioural output.

2.2. THE BEHAVIOURAL ACTIONS OF DOPAMINE IN THE STRIATUM: UNITARY OR DIVERSE?

It is well known that dopamine agonists such as apomorphine or amphetamine are behavioural stimulants. In moderate doses they increase locomotor activity (apomorphine: Maj *et al.*, 1972; Thornberg and Moore, 1974; amphetamine: Costall and Naylor, 1973a; Fibiger *et al.*, 1973; see also Beninger, 1983; Wickens, 1990), though at higher doses stereotyped behaviour patterns appear associated with a reduction of locomotor activity (Ernst, 1967; Costall and Naylor, 1973b; Schneiden and Cox, 1976; McDevitt and Setler, 1981). Conversely, systemically administered dopamine-blocking drugs reduce locomotor activity (Janssen *et al.*, 1960). They also reduce vigour of performance, or ease of initiation of a variety of trained responses (Posluns, 1962; Fibiger *et al.*, 1975; Tombaugh *et al.*, 1979). Neuroleptic drugs given systemically in doses larger than those resulting in locomotor hypoactivity will also produce catalepsy (e.g. Costall and Naylor, 1973c; Niemegeers, 1974), a state in which abnormal postures may be maintained without movement for a period of minutes. A reduction of locomotor activity, amounting sometimes to complete akinesia, can also be produced by bilateral destruction of the ascending dopaminergic pathways with 6-hydroxydopamine (Ungerstedt, 1971b, 1979). This procedure will also reduce the vigour of performance or ease of initiation of a variety of trained responses (Cooper *et al.*, 1974; Clavier and Fibiger, 1977; Howard *et al.*, 1974). Thus there is little doubt that the overall effect of dopamine in the brain is motor or locomotor activation, and this is implied in the designation of amphetamine-like drugs as "psychomotor stimulants".

Nevertheless, this easy conclusion about the overall effects of dopamine actually conceals a much more complex relation between dopamine and behaviour. From studies in which 6-hydroxydopamine is injected into striatal regions, it has been concluded that the nucleus accumbens is more important in locomotor activation by dopamine than is the neostriatum (Kelly *et al.*, 1975; Koob *et al.*, 1978; Iversen and Koob, 1978; Pycock and Marsden, 1978). Similar lesions of the neostriatum do not reduce locomotor hyperactivity produced by dopamine agonists (Costall *et al.*, 1977), although this region does have some influence on locomotion (Fink and Smith, 1979; Makanjuola and Ashcroft, 1982). However 6-hydroxydopamine lesions of the caudate nucleus impair motor control of the limbs (Siegfried and Bures, 1980; Sabol *et al.*, 1985). The precise nature of these deficits will be considered below. The dopaminergic innervation of the prefrontal cortex has an influence on motor and locomotor activity which is sometimes different from that of striatal dopamine: for instance, when dopamine in this region is depleted by 6-hydroxydopamine lesions, locomotor activity is subsequently *increased* (Tassin *et al.*, 1978; Carter and Pycock, 1980). This indicates a role of dopamine which is the opposite sign of that of dopamine in the neostriatum or nucleus accumbens (a fact obscured in studies in which forebrain dopamine systems are modified in a global manner). It should however be pointed out that *acute* modifications of the dopaminergic innervation of the prefrontal cortex produce effects of the same sign as those produced by the corresponding modifications of striatal dopamine. For instance, acute unilateral injections of amphetamine or cocaine into the medial prefrontal cortex produce contralateral turning (Stewart *et al.*, 1985; Morency *et al.*, 1987), while acute unilateral injections of dopamine antagonists (metoclopramide,

sulpiride) produce ipsilateral turning (Stewart *et al.*, 1985; Morency *et al.*, 1985). Moreover, bilateral microinjection of the dopamine-blocker haloperidol into the medial prefrontal cortex induces catalepsy, an effect similar in sign to the action of haloperidol in the striatum (Klockgether *et al.*, 1988).

Intrastriatal injections of dopamine have revealed evidence of a different kind about the complexity of dopamine's relations to behaviour. Working with cats, Cools and Van Rossum (1970) and Cools (1971) showed that injections of dopaminergic agents (L-DOPA, dopamine, apomorphine or *d*-amphetamine) into the striatum on one side led to contralateral head turning, and periodic extension of the contralateral forelimb or ipsilateral hindlimb. In a later paper (Cools, 1972), these movements were divided into two types: first there were alternating movements occurring only in distal parts of the contralateral forelimb which took place regardless of other behaviours and without attracting the animal's attention. In addition there were rapid jerky movements of the whole limb (contralateral forelimb or ipsilateral hindlimb) which attracted considerable interest from the animal, including cleaning, licking, etc. These injections also made the animals lie down. Thus in these cases the effects of the dopamine agonists are multiple, bilateral and are not always a clear cut activation. This is also indicated by other experiments of Cools (1971) in which the dopamine antagonist haloperiodol or the dopamine synthesis inhibitor alpha methyl-*p*-tyrosine were injected into the caudate. These also led to movements, but in this case the head was turned ipsilaterally, and limb movements were seen in the ipsilateral forelimb and the contralateral hindlimb. Another result suggesting that a multiplicity of responses can be elicited from the striatum is that of Yurek and Randall (1985) who found that certain dopamine antagonists, when administered into the lateral ventricle, could simultaneously produce catalepsy and enhance apomorphine-induced stereotypy (the latter result to be expected of dopamine agonists rather than antagonists). Experiments in which dopamine agonists are administered systemically sometimes demonstrate clear differences between strains of animals in the topography of the elicited responses (Szechtman *et al.*, 1982). Clinical studies also suggest that the functions of the striatum cannot be considered as unitary. For instance, the separate components of the classic triad of symptoms in Parkinson's disease (rigidity, tremor, bradykinesia) vary independently across patients (Selby, 1968).

2.3. Regional Differences in the Striatal Functions Revealed by the Actions of Dopamine

The apparent diversity of dopaminergic responses elicited from the striatum also has its anatomical aspects. Cools (1973) provided some early evidence that the behavioural repertoire controlled from the striatum differs from one part of that structure to another. A number of syndromes, produced by intrastriatal injection of various drugs was described. Significantly the contralateral syndrome (see above) produced by injection of dopamine into the rostromedial caudate could not be elicited when, simultaneously, 5HT was used to activate another region of the caudate (anteroventral caudate), a procedure, which, given alone, produced its own distinctive pattern of behaviour. Since then a variety of other evidence has been obtained by intrastriatal injection of dopaminergic and other agents, showing that there are regional variations in behaviours elicited from the striatum. This evidence is still rather fragmentary, and so does not merit detailed review. Nevertheless, since the principle of regional localization of function in the striatum is important for the present paper, it is appropriate to give a few other examples.

Klockgether *et al.* (1988) showed that the catalepsy response produced by systemically administered neuroleptic drugs can be mimicked by intrastriatal injection of a neuroleptic drug, but this depends critically on the location of the intrastriatal injection. Bilateral injections of haloperidol into the rostral part of the caudate head produced such a response (Fig. 3A), that into the rest of the caudate head did not. Ellenbroek *et al.* (1988) found that haloperidol injection into a rostral region of the neostriatum produced catalepsy in the hindlimbs, that into the nucleus accumbens produced catalepsy in the forelimbs. Kelley *et al.* (1988, 1989) defined a small region of the ventrolateral caudate in rats from which oral stereotyped behaviour could be produced with bilateral local injection of amphetamine (Fig. 3F). According to Arnt (1985a) injection of a dopamine antagonist into the same region, suppressed the oral stereotyped behaviour produced by systemically-administered apomorphine. The fact that different aspects of the behaviour controlled by striatal dopamine appear to have separate localizations thus raises an interesting possibility: *that some of the effects of dopaminergic agents produced by systemic administration may really be an amalgam of a variety of independent effects produced at separate locations in the striatum.*

2.4. The Side to which the Striatum's Behavioural Effects are Referred

2.4.1. *The traditional view*

The received view is that the striatum on one side represents motor function on the opposite side of the body. This traditional view is of course influenced by an inference from the anatomical fact that most long pathways descending from the forebrain to the spinal cord decussate. It is also based partly on empirical clinical evidence. For instance, when motor symptoms of basal ganglionic disease occur unilaterally, neuropathological evidence usually shows a disease process in the contralateral basal ganglia (hemiparkinsonism: Barolin *et al.*, 1964; Brodal, 1969, p. 217; hemiballism: Schwarz and Barrows, 1960; hemichorea: Davison and Goodhart, 1939; Goldblatt *et al.*, 1974; Kawamura *et al.*, 1988). A similar relationship holds for caudate infarcts (Caplan *et al.*, 1990). Other clinical evidence for this traditional view comes from experience with stereotaxic surgery (thalamotomy or pallidectomy) for relief of Parkinson's disease. When this operation was popular, it was usually performed unilaterally, and led to lessening of symptoms contralateral to the side of the operation (Gillingham *et al.*, 1960; Cooper, 1962).

This view is also supported by some modern experimental evidence. Alexander and DeLong (1985) applied electrical microstimulation to regions of the monkey putamen, and the body movement this elicited was exclusively on the contralateral side. DeLong (1971, 1972) recorded unit activity in the globus pallidus of monkeys, which correlated with active and passive movement of limbs. This neural activity was overwhelmingly related to body movement on the opposite side (i.e. for 82% of neurones in the internal segment, and for 88% of neurones in the external segment). Responses which did not have exclusively contralateral correlations with movement were usually bilaterally related. Hore *et al.* (1976) produced impairments in reaching movements (in absence of visual guidance) by local cooling of the basal ganglia, and these impairments were contralateral.

Evidence obtained by unilateral lesion of the striatal dopamine innervation has also frequently shown a predominantly contralateral relation to the locomotor apparatus. In monkeys, Imai *et al.* (1988) showed that unilateral MPTP infusions into the caudate caused Parkinsonian symptoms (hypokinesia, flexed posture) in the contralateral forelimb. Bankiewicz *et al.* (1986) made similar observations in monkeys where MPTP had been injected unilaterally into the carotid artery. Similar contralateral effects have been seen in rats after unilateral dopamine depletion. Evenden and Robbins (1984) showed that unilateral 6-hydroxydopamine lesions, placed centrally in the rat striatum caused long-lasting shifts of paw preference away from the limb contralateral to the lesion. Uguru-Okorie and Arbuthnott (1981) and Uguru-Okorie (1982) made similar observations for 6-hydroxydopamine lesions made unilaterally in the medial forebrain bundle.

2.4.2. *Qualifications to the traditional view*

Although this evidence appears to support a role for the striatum in representation of the contralateral motor apparatus, it all suffers from the same weakness: it refers to only a small part of the striatum (or globus pallidus). Even in the case of global dopaminergic denervation eliciting Parkinsonian symptoms, it is known from human neuropathological studies (Nyberg *et al.*, 1983; Kish *et al.*, 1988) that the critical region of the striatum for production of Parkinsonian symptoms is a part only of the putamen, rather than the striatum as a whole (a result compatible with Alexander's evidence referred to above). Thus, the possibility is left completely open that other regions of the striatum may exert ipsilateral motor control, or control over organized patterns of behaviour which have implications for the motor apparatus on both sides.

There is actually plenty of other evidence for such a proposition. For instance, in the clinical literature, Schwartz and Barrows (1960) found one case out of ten of hemiballismus where a striatal lesion was found only on the ipsilateral side. Hunter *et al.* (1978) found ipsilateral pathology in one case of hemi-Parkinsonism. Amongst the early stimulation studies of the striatum and globus pallidus, a variety of responses have actually been described. Most commonly described are contralateral head turning, or contralateral limb movements (reviewed by Delong and Georgopoulos, 1981; see also Ohno and Tsubokawa, 1987), but there have been occasional reports of ipsilateral head turning (Hassler and Dieckmann, 1969). Delong and Georgopoulos (1981), echoing Foreman and Ward (1969), remark on the inconsistency of effects produced by striatal stimulation, and conclude that stimulation studies "have thrown little light on the actual function of the caudate nucleus". Nevertheless, if the idea of regional specialization of striatal function is taken seriously, there may yet be new findings to be made in this sort of experiment. The diversity of findings may reflect regional specialization of function.

Another example of ipsilateral motor control by the striatum is to be found in the paper of Johnels (1983) who produced muscle rigidity by injection of reserpine into the striatum. When this was done unilaterally, the rigidity was ipsilateral. Compatible findings have also been reported by McKenzie *et al.* (1972) and Costall *et al.* (1972) who both describe *ipsilateral* turning behaviour when neuroleptic drugs are injected unilaterally into the striatum. The latter of these two papers mentions that this is associated with rigidity which prevented manual straightening of the body, presumably due to greater muscle tone on the ipsilateral side of the trunk. In this context it is also significant that in unilateral Parkinson's disease there is usually a scoliosis directed away from the side of Parkinsonian symptoms (Duvoisin and Marsden, 1975). In experiments in primates in which unilateral MTPT lesions produce contralateral Parkinsonian symptoms, the animal as a whole still tends to turn ipsilaterally (as in the above studies) (Bankiewicz *et al.*, 1986; Imai *et al.*, 1988). The same phenomenon has also been reported in humans with hemiParkinsonism (Bracha *et al.*, 1987).

These data are really quite compatible with the rotatory effects described by Ungerstedt in rats. Ungerstedt (1976) points out that in these rats, although movement was asymmetrical, the rats used all four limbs to turn, and would turn the same way when a limb on one side was strapped to the side of the body. In rats which have had the caudate nucleus on one side destroyed, the remaining caudate nucleus can nevertheless control postural deviation and rotatory movements to either side: to the lesioned side under the influence of dopaminergic agonists, and to the unlesioned side under the influence of dopamine antagonists (Anden *et al.*, 1966; Lotti, 1971; Keller *et al.*, 1973). All these examples of ipsilateral turning or ipsilateral rigidity cannot be explained as a consequence of Parkinsonian symptoms in the contralateral motor apparatus. They appear to be an independent phenomenon.

Other behavioural effects elicited from the striatal complex also clearly have implications for the motor apparatus bilaterally. The nucleus accumbens is known to be involved in the production of locomotor hyperactivity in response to dopamine agonists, since dopamine injected bilaterally into this region also produced locomotor hyperactivity (Pijnenburg and Van Rossum, 1973), and destruction of dopaminergic terminals in this region prevents the locomotor response to amphetamine (Kelly *et al.*, 1975). Most of

the available evidence suggests that *unilateral* modification of dopamine activity in nucleus accumbens does not result in turning. For instance, rats with unilateral 6-hydroxydopamine lesions of this region do not turn when administered apomorphine or amphetamine (Kelly, 1975; Costall *et al.*, 1976). In addition, injection of a dopamine agonist unilaterally into this region elicits locomotion, but not turning (Elkhawad and Woodruff, 1975), although turning can be produced by unilateral injections elsewhere in the striatal complex. (Aramakis and Beninger (unpublished observations) have, however, shown that this is not always the case: unilateral microinjections of amphetamine into the nucleus accumbens were seen to produce significant turning effects, as well as locomotion.) Thus, the balance of evidence suggests that the locomotor effect of dopamine in the nucleus accumbens of a single side appears to be expressed bilaterally, even though not always by strictly symmetrical locomotion.

Other evidence demonstrates a potentiality for the striatum on one side to control turning to either side. Unlesioned rats, especially female rats, which are administered amphetamine tend to turn to one direction or the other. Usually they turn away from the striatum with highest dopamine levels, but in some cases they turn *towards* this side (Robinson *et al.*, 1980). Carey *et al.* (1986) also showed that dopaminergic stimulation of the striatum on one side, can, under certain conditions, mediate turning towards, as well as away from that side. These experiments involved conventionally-prepared rats with unilateral 6-hydroxydopamine lesions. Amphetamine injections could sometimes initiate contralateral turning (instead of the usual ipsilateral turning), provided that the rats were housed in an environment in which they had previously been administered apomorphine (for which contralateral turning would be expected). Furthermore, Vaccarino and Franklin (1984) showed that different parts of the substantia nigra on one side could control circling in opposite directions. After injection of the neuroleptic drug alpha-flupenthixol into the *medial* substantia nigra, systemic amphetamine administration led to contraversive turning, but when the neuroleptic drug was injected into the *lateral* substantia nigra, ipsiversive turning occurred after amphetamine injections.

Motor (as opposed to locomotor) activity may also be controlled bilaterally from a single striatum. The stereotyped behaviour seen on administering dopamine agonists involves the motor apparatus symmetrically on both sides. When a dopamine agonist is injected unilaterally into the striatum, components of this are also produced (Fletcher and Starr, 1987), and, while overall behaviour at this time is markedly asymmetrical, components such as paw nibbling do occur involving the motor apparatus on both sides. The data of Cools and co-workers, referred to above, also includes clear examples where dopamine injected unilaterally into the striatum could produce movement of limbs on both sides of the body.

Viewed in a neuroanatomical light, the bilateral influence of the striatum on one side should come as no surprise. There are two main axonal pathways as outflow routes from the striatum to brainstem and spinal cord; those influencing the outflow of the cerebral cortex, and those relayed directly to the brainstem. The role of each of these pathways in rotatory effects, and other behavioural effects produced from the striatum has been investigated by lesions, stimulation, and intracerebral injection of drugs (e.g. Pope *et al.*, 1980; Redgrave *et al.*, 1980; Di Chiara *et al.*, 1982; Leigh *et al.*, 1983; Worms *et al.*, 1985). These approaches have not definitely identified the relevant pathways, probably because a wide variety of pathways is involved, so that after a single lesion, remaining pathways can sustain many striatal behaviours. However, connectional studies of the various fibre trajectories by which striatal activity could produce circling behaviour undoubtedly contain many bilateral connections. The pathways passing by way of the cerebral cortex (either via globus pallidus, or by the pars reticulata of the substantia nigra) influence the motor thalamus (nucleus *ventralis medialis* of the rat), which thence projects to the motor cortex and regions on either side of it. While many of the projections from these cortical regions to the spinal cord are purely contralateral (Brown, 1971; Donatelle, 1977), those to the reticular formation have been shown to be bilateral in rat (Zimmerman *et al.*, 1964), from which projections to the spinal cord are also bilateral (Nudo and Masterton, 1988). One area of the cortex, the supplementary motor area, is known to have extensive bilateral connections with brainstem and spinal cord at least in primates (see Wiesendanger, 1981). The *second* major outflow from the striatum leaves the pars reticulata and entopeduncular nucleus and projects directly to several other structures in the brainstem, including the superior colliculus, pedunculopontine tegmental nucleus (physiologically identified as a midbrain locomotor region: see Garcia-Rill, 1986), as well as other parts of the midbrain and pontine tegmentum. While the projections from pars reticulata and entopeduncular nucleus to these brainstem regions appear to be ipsilateral (Garcia-Rill *et al.*, 1983a; Moon Edley and Graybiel, 1983; Williams and Faull, 1985; Moriizumi *et al.*, 1988), many of the projections thereafter are bilateral. For instance the pedunculopontine tegmental nucleus projects bilaterally to medulla and spinal cord (Garcia-Rill *et al.*, 1983b; Moon Edley and Graybiel, 1983; Rye *et al.*, 1988). This may explain the fact that, although this region is known to be involved in locomotion, no turning behaviour is seen when it is stimulated unilaterally (Motles *et al.*, 1988). The angular complex, a region of the midbrain dorsal tegmentum identified by Leigh *et al.* (1983) as of particular importance for rotatory movements, also projects to regions of pontine reticular formation about equally on both sides (Miller and Sinnamon, 1980). With all these possible bilateral output pathways from the striatum, it is not surprising that a single striatum influences the locomotor system on both sides of the body.

2.5. Discussion and Conclusion So Far

The conclusions to be drawn from this brief survey of evidence are mainly caveats to traditional views. The behavioural actions of dopamine in the striatum are largely but not entirely activations of behaviour, and they are not unitary but an amalgam of separate

effects. There is some evidence that different regions of the striatum exercise control over topographically different behaviours. The traditional view that the striatum exercises control over the contralateral motor apparatus is an over-simplification. It probably applies only to a portion of the tissue in the striatum. Other effects elicited from the striatum are ipsilateral or bilateral, and the evidence contains suggestions that these may be functions of parts of the striatum other than those which exercise control over the contralateral motor apparatus.

Thus the paradox apparent in the circling rats described by Ungerstedt is a relatively superficial one. Interpretation of the direction of circling in terms of neuroanatomy of outflow pathways from the basal ganglia controlling motor functions is inappropriate. The ipsilateral or contralateral turning seen in Ungerstedt's rats is *intentional*, that is it will occur despite asymmetrical disturbance of the motor apparatus which might bias the animals' turning. This leaves the questions: "What are the striatal mechanism or mechanisms of this intended turning behaviour; and why is it usually in the direction away from the striatum with highest dopamine activity?" To start to answer these questions there is another very fruitful line of experimentation; the study of turning behaviour using *receptor selective dopamine agonists and antagonists*. These are all, of course, direct agonists, so one would expect that overall they would cause turning away from the side of the 6-hydroxydopamine lesion, as does apomorphine. Although this is true, the detail revealed using such drugs allows one to subdivide the phenomenology of drug-induced rotation. This evidence thus forms a nice complement to studies of local differences in the effects produced by intrastriatal injection (see Section 4). Taken together the two types of evidence permit a tentative hypothesis (Section 6) to be formed of the several behavioural components which led Ungerstedt's rats to rotate.

3. EVIDENCE, USING RECEPTOR-SELECTIVE DRUGS, THAT MORE THAN ONE MECHANISM IS INVOLVED IN TURNING PHENOMENA

Since the turning behaviour of the rats described by Ungerstedt can be measured in an automated fashion, it has been possible to study the detailed time course of drug-induced rotatory behaviour. A surprisingly complex set of phenomena has thus been revealed, for the different classes of direct dopamine agonist drugs.

3.1. TIME COURSE OF EFFECTS WITH RECEPTOR-SELECTIVE DOPAMINE AGONISTS

3.1.1. *Mixed direct agonists such as apomorphine*

Ungerstedt (1971a) found that when unilaterally-lesioned rats were administered apomorphine, the intensity of contralateral rotatory behaviour showed a peak shortly after the drug was administered, and again towards the end of the drug's period of action. In between these two peaks rotatory movement was less intense (a "trough" in the time/intensity curve: see schematic depiction in Fig. 2B,C). This characteristic time course has also been seen by Oberlander *et al.* (1980), Ungerstedt and Herrera-Marschitz (1981), Coward (1983), Herrera-Marschitz and Ungerstedt (1984), Herrera-Marschitz *et al.* (1984) and Arnt and Hyttel (1985). The same pattern has also been seen when lesioned rats are administered L-DOPA (Ungerstedt and Herrera-Marschitz, 1981), a drug which (as judged from the fact that it, too, causes contralateral rotation) should also be classed as a direct dopamine agonist. It is not, however, seen for amphetamine-induced ipsilateral rotation. Since this apparently depends on the action of dopamine on a normal striatum, it is plausible to suggest that the trough seen with apomorphine-induced contralateral turning is a feature of the supersensitive denervated striatum.

The two-peaked time course of apomorphine-induced rotation is not always seen. In Ungerstedt's original paper the lowest doses of apomorphine (0.05 and 0.1 mg/kg i.p.) produced a single peak of rotation, the biphasic pattern appearing only at higher doses (see Fig. 2A). The higher the dose, the longer the trough intervening between the initial and the final peak (compare schematic depictions in Fig. 2B and C). Oberlander *et al.* (1980) and Coward (1983) find that the two-peaked curve with apomorphine is present only when the drug is administered more than two weeks after the lesion. Before that, the curve is bell shaped. This observation may reflect the fact that proliferation of dopamine receptors takes two weeks to occur, so that, before that time, the administered drug is equivalent to the lowest doses used by Ungerstedt. The absence of an intervening trough at the lowest doses has not been reported by later studies which used such low doses (Herrera-Marschitz *et al.*, 1984; Oberlander *et al.*, 1980; Coward, 1983). However, these studies did not evaluate the response pattern over a range of doses, as did Ungerstedt, and the low dose of apomorphine (0.05 mg/kg) was administered subcutaneously rather than intraperitoneally.

The trough in the time-curve with apomorphine might be explicable if some aspect of the behavioural response becomes so intense, at high doses, that it competes with the factors leading to rotation, and thus slows it down. Phenomenological details compatible with such an account are provided by Ungerstedt (1971a) and confirmed by Herrera-Marschitz and Ungerstedt (1984): during the two peaks of rotation, the behaviour was a free locomotion in circles. During the trough, the behaviour changed, and the rats showed vigorous twisting to the unoperated side, so that the head came close to the tail and contralateral hindleg. The animals often pivoted around the contralateral hindleg, with biting and gnawing of legs and tail. Ungerstedt (1971a) comments that "the behaviour obviously interfered with rotation". Such competition at the behavioural level can explain not only the trough in the time course of a single experiment with apomorphine, but also a feature of the dose–response curve. For amphetamine-induced ipsilateral rotation, the dose–response curve is much steeper than for apomorphine-induced contralateral rotation. The gentle slope in the latter case can be accounted for by the fact that a trough in the middle region of the drug's time course occurs, at higher doses, only for apomorphine.

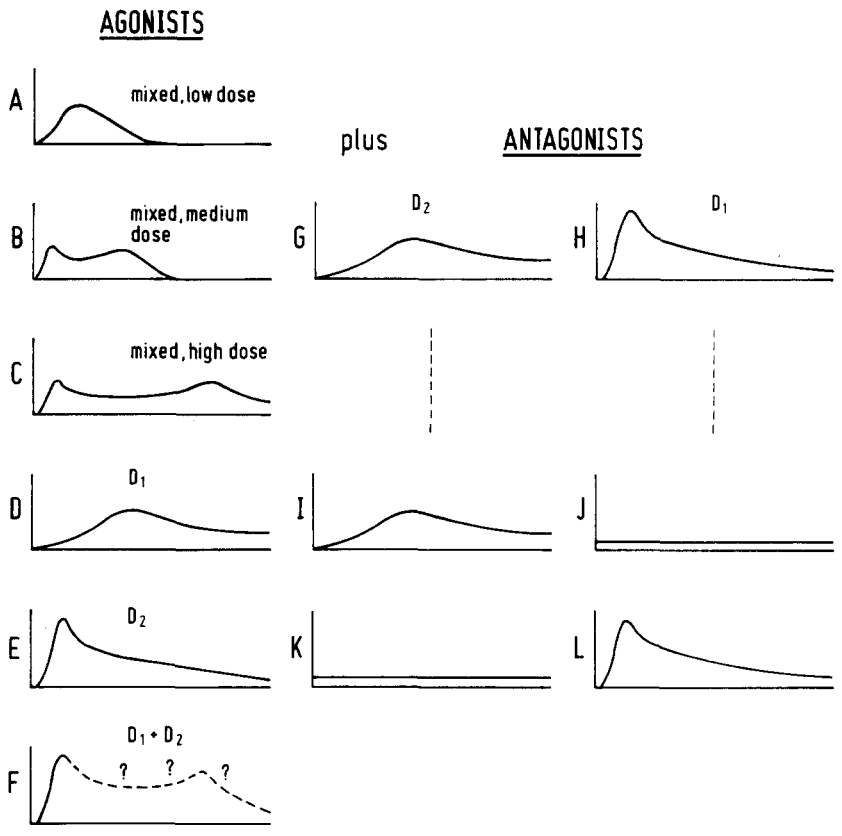

FIG. 2. Schematic illustration of the time/intensity curves for rotatory effects produced by systemic injection of various types of dopamine agonists, alone, or in combination with various types of dopamine antagonists, in rats with unilateral nigrostriatal lesions. A: Low dose of mixed agonist such as apomorphine produces single-peaked (bellshaped) curve. B: Medium dose of apomorphine produces two closely spaced peaks, with a small trough between. C: A large dose of apomorphine produces a two-peaked curve, with extended trough between them. D: A D-1 selective agonist (e.g. SKF 38393) produces a single bell-shaped curve with delayed onset, maximal in the position of trough found with apomorphine. E: A D-2 selective agonist, such as bromocriptine produces a single, short-latency, intense peak with a long tail. F: D-1 and D-2 selective agonists combined produce an immediate intense peak. The dotted line, for the later parts of the curve, is conjectural (see text) since there are no reports which provide experimental data on this period. G: Medium or high dose of apomorphine, combined with a D-2 antagonist such as haloperidol produces a single bell-shaped curve in the position of the apomorphine trough. H: Medium or high dose of apomorphine, combined with a D-1 selective antagonist such as SCH 23390, abolishes the second peak of the apomorphine response, i.e. converts the response to a D-2-agonist-like response. I: A D-1 agonist vs a D-2 antagonist produces the same effect as the D-1 agonist alone. J: A D-1 agonist vs a D-1 antagonist eliminates the response completely. K: A D-2 agonist vs D-2 antagonist eliminates the response completely. L: A D-2 agonist vs a D-1 antagonist produces the same effect as the D-2 agonist alone.

Although, from this description there appears to be competition between different behavioural components, it is nevertheless possible that a single pharmacological action could underlie all this phenomenology. However, there is a suggestion in Ungerstedt's description, that *at low doses* of apomorphine, circling involves free locomotion, while *at higher doses* a postural bias plays a part as well, and competes with the locomotor effect. This suggestion might be an indication that more than one pharmacological effect is involved. Further support for this conjecture comes from Coward (1983) who notes that the double-peaked curve never occurs unless the animal has had several previous experiences with apomorphine. Possibly, therefore, the behaviour which leads to the trough in the time course requires a conditioning effect to develop. The idea that there are separable components to the apomorphine-induced rotation is suggested much more strongly by the evidence obtained using receptor-selective dopamine agonists, as described in the next subsections.

The phenomenon of tight postural asymmetry which competes with measures of circling is not seen with amphetamine-induced ipsilateral rotation, which is typically in wide circles (as during the initial and final peaks of the apomorphine-induced circling), with little lateral bending of the trunk (Pycock, 1980; Szechtman and Ziegler, unpublished results, cited in Ziegler and Szechtman, 1988). It is pertinent to ask why there should be such a difference between these two drugs. One possibility is that amphetamine,

which releases noradrenaline as well as dopamine from nerve terminals, owes its distinctive properties to the combined action of the two transmitters. However, this does not explain why the early and late parts of the apomorphine time course are similar to the time course with amphetamine. In addition, an analysis of the behavioural role of noradrenaline in amphetamine-induced behaviour (Ljungberg and Ungerstedt, 1976a) found that its contribution related to behaviours other than locomotor activity, which is prominent in amphetamine-induced rotation or the early and late peaks of the apomorphine-induced rotation. Another possible explanation of the difference between these two drugs is that amphetamine acts on a normal intact striatum, whereas apomorphine acts on one which has developed denervation supersensitivity, the competitive interaction being characteristic of the latter only. Thirdly, there may be some difference in the relative efficacy at the D-1 and D-2 receptors of apomorphine, and the transmitter dopamine released by amphetamine. This complex topic is pursued further in Sections 3.1.5.2, 3.3.1 and 5 below.

3.1.2. *Direct D-2 agonists*

A variety of drugs are available which act selectively on dopamine D-2 receptors. These elicit contralateral rotation, when tested in unilaterally lesioned rats, according to Herrera-Marschitz *et al.* (1984), and Arnt and Hyttel (1985), with the drugs pergolide and LY171555. Rouillard and Bedard (1988) found that only 11 out of 22 lesioned rats responded to the D-2 agonist RU 24213 with contralateral rotation. Herrera-Marschitz and Ungerstedt (1985) find that the time course of this effect has a single peak, with very intense rotation, and a long tail of less intense rotation following this (schematically illustrated in Fig. 2E). When pergolide is given intrastriatally it also gives a single-peaked time course for rotatory response (Herrera-Marschitz *et al.*, 1985). Herrera-Marschitz and Ungerstedt (1984) give a phenomenological description of pergolide-induced rotation: compared with apomorphine-induced rotation, it was looser, with locomotion more dominant and animals more responsive to environmental stimuli. Tentatively this allows one to identify the mechanism involved in the initial and final peak of the response to apomorphine as involving D-2 receptors. This implies that, to produce the apomorphine pattern of rotation, some other competing action is added to the D-2 effect, dividing the single peak of the D-2 action into two by an intervening trough. Conceivably this additional influence is that of the D-1 receptors.

3.1.3. *Direct D-1 agonists*

The drug SKF 38393 is generally used as a receptor-selective D-1 agonist. This can produce contralateral rotation in unilaterally lesioned rats (Setler *et al.*, 1978; Arnt and Hyttel, 1985; Fenton *et al.*, 1985; Robertson and Robertson, 1986; Rouillard and Bedard, 1988). The rotatory response to SKF 38393 differs from that to apomorphine or D-2 agonists in that it does not start until 10–20 min after the drug injection (Arnt and Hyttel, 1985; Robertson and Robertson, 1986) (schematically illustrated in Fig. 2D). Moreover, it has a single peak in its time course (Setler *et al.*, 1978; Arnt and Hyttel, 1985), somewhat later than the first peak seen with apomorphine. The dose response curve is steep (Setler *et al.*, 1978). When SKF 38393 is administered by intrastriatal injection the delay in response is considerably longer than this (up to 2 hr), even when injections are made simultaneously into several striatal loci (Fletcher and Starr, 1987). None of the papers using SKF 38393 provides a detailed phenomenological description of SKF 38393-induced turning. However, in view of the steep dose response curve, it is unlikely that the distinctive phenomenology seen in the trough of the apomorphine response is found with SKF 38393.

Another difference between the rotation mediated by D-2 agonists, or mixed agonists, and that mediated by D-1 agonists is that the latter does not seem to be so robust as the former, and there are some discrepancies over the effective dose for this response: Setler *et al.* (1978) found an ED 50% of 0.3 or 1.0 mg/kg, dependent on the testing conditions. Arnt and Hyttel (1985) found an ED 50% of about 0.6 mg/kg. Robertson and Robertson (1986) found that 1.0 mg/kg was ineffective though 2.0 mg/kg was so. Rouillard and Bedard (1988) found that only 8 out of 22 rats responded with a dose of 2.5 mg/kg. Fenton *et al.* (1985) found that their rats could be divided into two groups: a highly sensitive group, rotating to all classes of dopamine agonist tested, and to SKF 38393 with an ED 50% of about 1 mg/kg; and a low sensitivity group which required high doses of apomorphine and were unresponsive to SKF 38393.

One possible explanation of these discrepancies is that differing degrees of supersensitivity develop, relating to different degrees of dopamine denervation or time for supersensitivity to develop. On the other hand, the results of Fenton *et al.* (1985) indicate a 15–20 fold difference between the high-sensitivity and the low-sensitivity groups (see also Marshall and Ungerstedt, 1977; Mandell and Randall, 1985). This is a far greater discrepancy than can be explained by the degree of receptor proliferation occurring after denervation (usually about 30–70%: see Mishra *et al.*, 1978, 1980). It is also a far greater difference than the behavioural supersensitivity produced by chronic regimes of dopamine antagonist drugs (Randall, 1985). Thus, since Fenton *et al.* (1985) did not show that their high- and low-sensitivity groups did in fact have differing degrees of dopamine denervation, an alternative explanation must be sought. One possibility, to be developed in more detail below, is that the different groups of animals have regional differences in the locality of most intense dopamine depletion. As a result, there may be qualitative as well as quantitative differences between the groups. Alternatively, if there are multiplicative effects between the behaviour elicited from different regions, the overall effect may be more dramatic than would be suspected from the overall degree of dopamine depletion.

3.1.4. *Combinations of D-1 and D-2 agonists*

Of the studies mentioned above, several found that SKF 38393-induced rotation failed to occur in some rats (Fenton *et al.*, 1985; Robertson and Robertson,

1986; Rouillard and Bedard, 1988). In the latter two of these cases it has been possible to show that combinations of D-1 and D-2 agonists can elicit rotation, when either alone was ineffective. Robertson and Robertson (1986) studied combinations of the D-1 agonist SKF 38393 with either of the D-2 agonists LY 171555 or bromocriptine. When SKF 38393, in a dose which produced no rotation when given alone, was combined with LY 171555, turning was elicited immediately (unlike the response to SKF 38393 alone) (schematically illustrated in Fig. 2F), and at a higher rate than could be produced by any dose of LY 171555, given alone. When SKF 38393 was combined with bromocriptine, it was possible to produce vigorous rotation with doses of both drugs which, given alone, were ineffective. In the experiments of Rouillard and Bedard (1988), D-1 and D-2 agonists were combined in doses half those which had previously been shown incapable of eliciting rotation in only a proportion of rats. Nevertheless, all rats responded to the combination half-doses with contralateral rotation. An additional example of synergic interaction between D-1 and D-2 effects in the production of rotation comes from Gershanik *et al.* (1983). Both D-1 and D-2 agonists alone could produce contralateral turning in lesioned rats. When the same agonists were tested in lesioned rats pretreated with the dopamine synthesis inhibitor alpha-methyl-*p*-tyrosine, the effect of the D-2 agonists was severely reduced, while that of the D-1 agonist was only slightly reduced. The dependence of rotation induced by D-2 agonists on dopamine synthesis has also been reported by Fuxe *et al.* (1978) and Mandell and Randall (1990). This result implies that the D-2 agonist-induced rotation requires concomitant D-1 receptor stimulation (from endogenous dopamine release) at some site in the brain; while the D-1 agonist-induced rotation has a smaller requirement for concomitant D-2 receptor stimulation.

Together, these results show that there can be a synergistic interaction between D-1 and D-2 agonist-induced rotation. This conclusion seems at first sight to be at odds with the conjecture put forward above (Section 3.1.2) that the trough in the effects of apomorphine's effect depended on a *competitive* interaction between separate D-1 and D-2 effects. However, this cannot be seen as definitely contradictory until the synergy has been observed with many different doses of the interacting drug types. It is possible that the above experiments have used drug doses whose combined effect is less than that of apomorphine which produces a recognizable trough. An approach to defining the interaction between D-1 and D-2 agonists in rotatory behaviour would be to seek the distinctive phenomenology seen in the trough which occurs between the initial and final peaks of the apomorphine response. As yet there are no reports which give such detail. However it is suspected that, although there may be synergistic interactions between D-1 and D-2 receptors in rotatory effects at low doses, dose combinations equivalent to the moderate or large doses of apomorphine would have a competitive manner of interaction, rather than a synergistic one.

3.1.5. *Discussion of synergism and antagonism between D-1 and D-2 induced rotatory effects*

It is clear that the rotatory effects seen with D-1 and D-2 selective agonists are different. Synergic interaction between the two effects can occur, to bring about rotatory effects, when drugs acting on either receptor alone are incapable of doing this. Under other circumstances, there are also suggestions of a competitive interaction between the rotatory effects of D-1 and D-2 agonists. It is important to determine at what level each of these interactions take place. They could reflect interactions of different receptor types on the same populations of striatal cells which play a part in the generation of locomotion or posture. Alternatively it may be that the effects of the two receptor types are separate at this level, and some other interaction (e.g. downstream from the striatum) determines whether small effects of each class of drug cooperate to produce rotatory behaviour, or (for larger doses) show a competitive interaction.

3.1.5.1. *Synergic interactions*

Synergic interaction between D-1 and D-2 receptors has been analyzed before for other behavioural effects of dopamine in unlesioned animals (see Wickens, 1990; Miller *et al.*, 1990). The synergy has been attributed to influences of D-1 and D-2 receptor effects converging on the same striatal output neurones. The same synergy can certainly apply to rotatory models which do not involve dopamine denervation: Arnt and Perregaard (1987) studied the effects of dopamine agonists and antagonists in rats with a hemitransection which allowed only one striatum to influence behaviour. Dopamine agonists produced circling ipsilateral to the lesion (in accord with Ungerstedt's maxim), and a synergy between D-1 and D-2 receptor activation was demonstrated. However, in the case of rats with unilateral 6-hydroxydopamine lesions, one striatum has been partly or completely depleted of its supply of dopamine. Therefore, there are two possible versions of this hypothesis which may be applied to the rotatory effects: the D-1/D-2 interaction could be occurring *either* in the intact striatum, *or* in the lesioned striatum (using the residual dopaminergic innervation to activate the alternate receptor type). The first of these alternatives is difficult to maintain, because, according to much other evidence about rotational effects, one would predict that ipsilateral rotation would occur, not contralateral rotation. The second alternative thus seems preferable. Supporting this idea are the results of Giorgio and Biggio (1990). After unilateral depletion of D-1 and D-2 receptors (using an irreversible receptor blocker), which amounted to only about 50% of the D-1 and D-2 receptors, synergism between endogenous dopamine release and D-2 agonists was observed in producing rotatory behaviour directed *towards* the side of receptor depletion. This experiment was performed within 24 hr of receptor depletion, leaving insufficient time for supersensitivity to develop on the depleted side. The side where synergistic D-1/D-2 effect was greatest was contralateral to the side of depletion, and so the ipsilateral

direction of rotation is in accord with Ungerstedt's maxim. Following this analysis of the synergistic effects of D-1 and D-2 receptors, one would explain the inconsistency of rotatory effects with D-1 agonists, described above, by supposing that synergy (and rotation) can occur only in a partially denervated striatum, not in a completely denervated one.

3.1.5.2. *Competitive interactions*

The rotatory response to mixed agonists such as apomorphine is complex, with some evidence for a behavioural component appearing at the peak of the response at higher doses which competes with the free circling at the start and finish of the drug response. It is possible that this competitive interaction is a particular feature of the denervated striatum, since there is no evidence for it with amphetamine-induced ipsilateral circling. However, a recent paper casts doubt on this argument, by showing that apomorphine can produce the phenomenology typically seen in the unilaterally dopamine-denervated rat in a rotational model without dopamine denervation. Konitsiotis and Kafetzopoulos (1990) injected the D-2 antagonist sulpiride unilaterally into the striatum of unlesioned rats, and then challenged the rats with 1 mg/kg systemic apomorphine. Despite the fact that there was no supersensitivity in either striatum, ipsilateral rotation occurred which was similar to that seen in the trough of the apomorphine effect in the unilaterally lesioned rat. This single result is in itself not sufficient to decide the issue. Further evidence will be considered later (Sections 3.3.1 and 5).

The components of the apomorphine response described so far have not yet been identified here, except phenomenologically. However, in view of the existence of distinct D-1 and D-2 responses, which interact at some level, it is plausible to suggest that the interaction between the components of the apomorphine response (which produces the "trough") is indeed an interaction between D-1 and D-2 effects, a competitive effect as opposed to the synergism described above. The evidence considered so far does not establish this, although it is a promising conjecture. Evidence obtained using agonist/antagonist interactions, considered in the next section is more helpful in this respect.

3.2. CHALLENGE WITH VARIOUS DOPAMINE ANTAGONISTS

3.2.1. *Dopamine antagonists versus mixed agonist*

3.2.1.1. *D-2 antagonists versus mixed agonist*

Several studies have reported on the interaction between D-2 selective antagonists and apomorphine induced rotation. Heal *et al.* (1980) and Gower and Marriott (1982) found that apomorphine-induced rotation was reduced by haloperidol, pimozide or fluphenazine, but never by more than 50% of the total turns seen without the antagonist. Similarly, according to Arnt and Hyttel (1984, 1985), haloperidol could reduce the turning behaviour of lesioned rats given apomorphine, though never by more than 50% of the total number of turns seen. Herrera-Marschitz and Ungerstedt (1984) found that haloperidol in low doses (0.2 mg/kg) induced a 50% reduction of apomorphine-induced rotation. However, in larger doses (2 mg/kg) it increased the maximum intensity of the apomorphine response but reduced its duration. This finding is supported by several earlier reports (Oberlander *et al.*, 1980; Ungerstedt and Herrera-Marschitz, 1981; Coward, 1983) that haloperidol converted a double-peaked curve with apomorphine into a bell shaped curve, its peak lying in the position of the trough seen when apomorphine alone is administered. Arnt and Hyttel (1984, 1985) made a similar observation using spiroperidol against apomorphine. A possible interpretation of this pattern of results is as follows: in the lower dose the antagonist drug partially reduces the D-2 component of rotation. In the higher dose it does this to the extent that the competition (between the behavioural component appearing during the trough of the apomorphine response and the free circling characteristic of the D-2 response) does not occur. This then reveals a component of the response which is presumably similar to that seen with D-1 agonists. This interpretation is made more plausible by the fact that the peak of the rotatory effect seen with a D-1 agonist alone is delayed to a point after the initial peak seen with apomorphine.

The D-2 antagonist drug sulpiride has also been used in some studies. According to Rouillard and Bedard (1988), the synergic effects of D-1 and D-2 agonists are blocked by sulpiride. This is easily accommodated in the above schema, though the interaction between D-1 and D-2 effects which Rouillard and Bedard study is a synergism, rather than a competition. However Herrera-Marschitz and Ungerstedt (1985) find that sulpiride is relatively ineffective against apomorphine-induced rotation. This result cannot be explained by poor penetration of the blood–brain barrier by this antagonist, since sulpiride was highly potent against pergolide-induced rotation (see below).

3.2.1.2. *D-1 antagonists versus mixed agonist*

Arnt and Hyttel (1984, 1985) find that the D-1-selective antagonist SCH 23390 can also produce a partial block of apomorphine-induced rotation. Once again, the blockade was never more than 50% of the total number of turns seen with apomorphine. Similar observations were made by Herrera-Marschitz *et al.* (1984) and Herrera-Marschitz and Ungerstedt (1985). In these studies it was noticed that the D-1 antagonist abolished the second peak of the apomorphine response, but not the first. In other words the D-1 antagonist appeared to subtract a component from the apomorphine response, making it like the response to a selective D-2 agonist (whose single peak occurs quite soon after administration).

Rouillard and Bedard (1988) study the influence of SCH 23390 on the synergic effects of D-1 and D-2 agonists. Unlike the effect with a D-2 antagonist, the D-1 antagonist had no effect on this synergy. This may be related to the fact that the D-2 component of the synergy described by these authors appears to be greater than the D-1 contribution (since a larger proportion of rats responded to the D-2 agonist alone

than to the D-1 agonist alone). They comment that D-2 supersensitivity may have been better developed than D-1 supersensitivity. (It deserves comment here that in this experiment the D-2 component was less dependent on concomitant D-1 stimulation than was the D-1 component on D-2 stimulation. On the other hand in the experiment of Gershanik *et al.* (1983), the D-1 agonist-induced rotation was less dependent than the D-2 agonist-induced one on stimulation of the alternate receptor type. The reasons for this discrepancy are not clear.)

3.2.1.3. *Mixed antagonists versus mixed agonist*

It would be interesting to know whether the D-1 and the D-2 components of rotating behaviour comprised the whole of the phenomena seen when lesioned rats are given apomorphine. To answer this it would be necessary to administer both types of antagonist together in rats rotating under the influence of apomorphine, and see if any response remains. This experiment has not been performed. The nearest to it is the experiment of Ungerstedt and Herrera-Marschitz (1981) in which alpha-flupenthixol was given to rats rotating under apomorphine. This antagonist blocks the D-1 and D-2 receptors with roughly equal potency. It shortens the time between two peaks of apomorphine-induced rotation. In other words, it acts in a manner similar to the lowering of the dose of apomorphine, a result to be expected from its pharmacological profile.

3.2.1.4. *Conclusions*

Apart from the result of Rouillard and Bedard (1988), these findings imply that the non-D-2 component of the apomorphine response, is similar to the D-1 agonist properties of apomorphine. Thus, *the competition between the behavioural component seen during the trough of the apomorphine response and the free-circling response which predominates before and after this part of the response can now be identified as the result of an interaction between D-1- and D-2-related components of the total response.* However, we still cannot determine whether this competitive interaction occurs in the brain structure where dopamine exerts its main influence (viz: the denervated striatum) or at some other site, for instance by interactions between the denervated and intact striata, or downstream from the striatum. Evidence using combinations of selective antagonists and selective agonists (considered below) help to answer this question however.

3.2.2. *Dopamine antagonists versus selective agonists*

3.2.2.1. *D-2 antagonists versus D-2 agonists*

According to Heal *et al.* (1980), haloperidol produced a total inhibition of turning induced by either bromocriptine or lergotrile. Likewise, Arnt and Hyttel (1984, 1985) find that the D-2 antagonists (clebopride, spiroperidol) as well as the non-selective antagonist flupenthixol block rotation produced by the D-2 agonist pergolide. Similarly, Herrera-Marschitz and Ungerstedt (1985) find that sulpiride is highly effective against pergolide-induced rotation (actually 1000 times more potent than against apomorphine-induced rotation).

3.2.2.2. *D-1 antagonists versus D-2 agonists*

Arnt and Hyttel (1984, 1985) found that SCH 23390 is almost completely ineffective against rotation induced by pergolide or LY 171555. This is confirmed by Herrera-Marschitz *et al.* (1984) and by Herrera-Marschitz and Ungerstedt (1985). The latter authors found that, although SCH 23390 failed to inhibit pergolide-induced rotation, it somewhat reduced the initial peak in the first hour, and prolonged the response. The net effect was an increase in the total number of turns elicited.

3.2.2.3. *D-1 antagonists versus D-1 agonists*

Arnt and Hyttel (1984, 1985) found that SCH 23390, as well as the non-selective antagonist flupenthixol blocks rotation elicited by SKF 38393. The result of Gower and Marriott (1982), that clozapine inhibits SKF 38393-induced rotation, should also be mentioned here, since there is some evidence that clozapine's actions rely mainly on D-1 blockade (see Miller *et al.*, 1990).

3.2.2.4. *D-2 antagonists versus D-1 agonists*

Gower and Marriott (1982) found that SKF 38393-induced rotation was not inhibited by haloperidol, pimozide or fluphenazine. Likewise, Arnt and Hyttel (1984, 1985) found SKF 38393-elicited rotation was not blocked by the D-2 antagonists spiroperidol or clebopride.

3.2.2.5. *Conclusion*

The results considered above can be summarized quite simply: rotation induced by either selective dopamine agonist is blocked only by the corresponding antagonist, but not by the antagonist that acts at the alternate receptor type. Although interaction (both competitive and synergistic) occurs between the behavioural manifestations of D-1 and D-2 receptor stimulation, the two effects appear to be separate in studies of agonist/antagonist interactions. This important conclusion implies that at some level close to the site of the receptors themselves the influences that lead to rotation when one receptor type is stimulated is independent of those when the other receptor type is stimulated.

In many other dopamine-dependent behaviours there is a synergy between D-1 and D-2 receptors, such that the behaviour can be elicited by either agonist, reduced in vigour by either antagonist, and the effectiveness of the antagonist does not depend critically on which agonist was used to produce the behaviour. This data has recently been reviewed by Miller *et al.* (1990). The neuronal model which was used to explain these data involved the two receptor types having a combined effect on each of the medium-size spiny striatal output neurons. The D-2 receptor mechanism was directed specifically to the large cholinergic striatal interneurons, which in turn

influenced the medium spiny striatal output neurons, to mediate performance effects of dopamine. The D-1 receptors were envisaged to act upon corticostriatal synapses upon the same medium spiny neurones, as a reward signal which could selectively strengthen these synapses. While this schema is still hypothetical, it is envisaged to apply throughout the striatum, the neuronal basis of a repeated processing unit. Therefore, the conclusion we have reached in the discussion of turning effects, that D-1- and D-2-mediated effects are quite independent of each other in lesioned rats, is an awkward one for the hypothesis of Miller *et al.* (1990). Thus, from the point of view of understanding turning behaviour in lesioned animals we have a promising postulate. But before we can use that postulate it is appropriate to consider why D-1 and D-2 effects become dissociated in dopamine-denervated animals.

3.3. DISCUSSION

3.3.1. *Denervation supersensitivity as a possible means of uncoupling the D-1 from the D-2 receptors*

The independence of D-1 and D-2 effects in dopamine-denervated animals may be a general feature of a striatum showing denervation supersensitivity to dopamine. In rats treated *bilaterally* with 6-hydroxydopamine, locomotor hyperactivity produced by either selective agonist is blocked only by the corresponding antagonist (Arnt, 1985b; Breese and Mueller, 1985), a pattern similar to that seen with unilaterally lesioned rats giving rotatory responses to drugs. This might suggest that some aspect of the supersensitivity which develops after denervation may prevent the effects elicited from the two receptor types from interacting as they do in normal animals. There is also some evidence from agonist/antagonist studies that the two receptor types become independent after pretreatment with reserpine, which, like 6-hydroxydopamine, also depletes dopamine and can cause supersensitivity (but without destroying the dopaminergic fibres) (Breese and Mueller, 1985; Arnt, 1985c; Rubenstein *et al.*, 1988). However, here the evidence is not so clear cut: in some studies (Arnt, 1985b; Breese and Mueller, 1985), D-1 antagonists block only the effects of D-1 agonists. In others they block those of both agonists (Rubenstein *et al.*, 1988). It is also not clear in these reserpine studies whether the changed agonist/antagonist interactions were associated with the development of supersensitivity, since in some of these studies (Breese and Mueller, 1985) only 24 hr of reserpine pretreatment was needed to see the effect.

Given that there is some evidence that D-1- and D-2-mediated effects may be dissociated in the denervated striatum, how could this come about? Electrophysiological results throw some light on this question. *In the intact striatum*, spontaneous activity of the principle neurones is very low (DeLong, 1972; Buser *et al.*, 1974; DeLong and Strick, 1974), probably due to the fact that the striatum is a network of mutually inhibitory neurones. The threshold depolarization needed to initiate an action potential is unusually large (Wilson and Groves, 1981), an indication that the principle striatal neurones are probably tonically under active inhibitory influence. *In the dopamine-denervated striatum*, however, spontaneous depolarizing synaptic potentials become more common (Galarraga *et al.*, 1987) and an increased frequency of action potentials has also been seen in striatal neurones after dopamine denervation (Orr *et al.*, 1986; Galarraga *et al.*, 1987). It is known that the large cholinergic neurones (which form a small minority of the striatal neurones) are tonically inhibited by dopamine release in the intact striatum. It might be suggested that the change occurring after dopamine denervation represents increased activity confined to this small minority of striatal neurones, from which electrophysiological recordings are more easily made in an otherwise silent striatum. However, other considerations make this rather unlikely. The results of Galarraga *et al.* (1987) were obtained in striatal slices, a preparation in which there would be least sampling bias, and in which tonic dopamine release (in the striata with intact dopamine innervation) would be little higher than in the denervated striata. In addition, in these papers, recordings made many months after dopamine denervation showed the same increased activity, although compensatory effects might have restored the firing of cholinergic neurones towards their normal state. Thus, it seems more probable that the increased number of depolarizing potentials, and the increased firing rate, seen in dopamine-denervated striata represents a change in the principle neurones, the medium-sized spiny output neurones. Additional indirect evidence supporting this conclusion comes from Waszczak *et al.* (1984) and Weik and Walters (1987). In these studies it was found that apomorphine injections produced very variable effects on the firing of neurones in the pars reticulata of the substantia nigra of intact animals. These effects were reduced by striatal lesions and therefore were presumably mediated by activity in striatonigral afferents to the pars reticulata. When the effect of apomorphine was studied in dopamine-denervated animals, the drug produced a stronger effect, which was a consistent inhibition of the pars reticulata neurons. This change is compatible with a greater activity in the striatal output neurones of the dopamine-denervated striatum. While the biophysical basis of this change is at present uncertain, it provides a possible explanation for the fact that D-1 and D-2 effects become independent in the denervated striatum.

The model of the basic striatal processing unit advocated by Miller *et al.* (1990) is that dopamine has a net excitatory effect on the medium spiny principle neurones of the striatum, both for the D-2 effects and the D-1 effects. The D-2 action of dopamine was envisaged to inhibit striatal cholinergic interneurones. The cholinergic tone of these interneurones is envisaged to increase potassium conductance in the medium spiny neurones (see also Wickens and Miller, 1990). Thus when cholinergic tone decreases, so does potassium conductance in the principle neurones, a net excitatory effect. The D-1 action of dopamine is envisaged to increase the potency of corticostriatal afferents upon the principle neurones. Since these afferents are glutamatergic excitatory ones, the effect of D-1 receptor activation would also be a net excitatory one.

In the intact striatum, the spontaneous activity of the principle neurones is very low, and threshold for

firing is high (as explained above), presumably indicating that most neurones are under tonic inhibitory control from neighbouring neurones. Under these circumstances, it is plausible to suggest that a combination of *both* the D-2 effect (required to reduce the persisting high potassium conductance in these neurones) *and* the D-1 effects (to enhance excitatory synaptic input) is needed before dopamine can influence neuronal firing in the intact striatum. A computer simulation of these interactions (Wickens, unpublished) supports this suggestion: striatal output neurones cannot generate large EPSPs and action potentials, even when the excitatory synaptic input is large, if the potassium conductance in these neurones is high. However, in the intact striatum there is likely to be some degree of spontaneous activity in the dopaminergic pathways. Therefore, selective agonists for either receptor type could produce a combined D-1/D-2 activation which is sufficient to produce action potentials in the medium spiny neurones, and consequent behavioural effects, provided that synthesis and release from dopaminergic terminals (and hence activation of the alternate receptor type) is not blocked. Moreover, in the intact striatum, either D-1 or D-2 selective antagonists could prevent the behavioural effects of mixed agonists such as apomorphine, a combination of D-1 and D-2 selective agonists, or a D-2 selective agonist in an animal with significant tonic dopamine release.

However, *in the dopamine-denervated striatum*, the situation would be different. The principle neurones would be much closer to the threshold for firing, so that the excitatory influence of either selective dopamine agonist could precipitate or increase firing, and so could have behavioural consequences. Then, since it is not necessary to have a combination of the two agonists to produce a behavioural effect, receptor-selective antagonists would block only the effects produced by the corresponding agonist. Such an effect could not be shown in the intact striatum because the combined effect of activation of both receptor types is required before behavioural consequences are seen.

Following this tentative analysis, a few comments are appropriate on the different interactions between the effects of the two receptor types that were mentioned above. There are two possible ways in which those interactions might occur: they may occur downstream from the dopaminergic mechanisms which tend to initiate rotatory behaviour (i.e. an interaction between the signals already generated by the striatum, or the behavioural consequences of them). Alternatively, interactions may occur because of special circumstances (such as poorly developed supersensitivity) such that, as in the intact striatum, both D-1 and D-2 activation together is necessary to produce changes in outflow. The competitive interaction envisaged to give rise to the trough in the apomorphine time course is probably explained by the first of these mechanisms, since there is evidence suggestive of competition at the behavioural level between components of the response, and the trough is a relatively robust effect, unlikely to depend on poorly developed supersensitivity. The synergistic interaction described by Rouillard and Bedard (1988) and others is more likely to be explained by the second of these two explanations, since it varies considerably between studies and between animals.

3.3.2. *A possible anatomical basis for the independence of D-1 and D-2 effects*

Given that the D-1- and D-2-mediated effects do usually become dissociated in the dopamine-denervated striatum, how can we use this fact in elucidating the mechanisms of turning? There is one way in which the data on turning effects in rats can be reconciled with the hypothesis of a single but repeated basic processing unit serving the various functions of the striatum. As discussed above a variety of evidence shows that different functions of the striatum are localized in different parts of that structure. It is possible that all these different functions are mediated by the operation of the same sort of processing unit repeated in each region. What differs is the afferent and efferent connections of each region which feed into (and out of) the basic processing unit. Therefore, it is possible that the two (or more) components we have identified using receptor-selective drugs to elicit the turning effects in lesioned rats differ not only in the dopamine receptor type which dominates each one, but also in the striatal locality at which each effect is produced. Both D-1 and D-2 receptors may be involved at each site, and either one alone can produce a behavioural effect. However *we suggest here that it is the D-1 receptor (alone) at one site and the D-2 receptor (alone) at another site which imposes the* asymmetry *upon posture, or locomotion*, and thus produces the overall turning response. Given such a framework for analyzing the turning phenomena, is it possible to identify the actual behavioural elements which produce each component of the turning response? This is the objective of the rest of this paper.

4. THE BEHAVIOURAL COMPONENTS UNDERLYING TURNING BEHAVIOUR INDUCED BY DOPAMINE AGONISTS, AND THEIR REGIONAL REPRESENTATION IN THE STRIATUM

4.1. Possible Behavioural Components Underlying Turning Behaviour

The evidence considered above suggests that turning behaviour is intentional, and not directly related to the relative capability of the motor apparatus on one side versus the other. This leaves several other possible behavioural strategies which could lead to the turning behaviour described by Ungerstedt (see Fig. 1). (i) It is possible that dopamine is involved in the attractiveness of certain sensory stimuli to the animal. When dopamine is asymmetrically distributed, the stimuli on one side (hypothetically the contralateral side) will be more attractive (other things being equal) than those on the other. The animal will then turn towards the (contralateral) stimuli that have greatest attractiveness. (ii) Dopamine may control posture, and when dopaminergic activity is asymmetrical so is the resulting posture. This asymmetry, in combination with normal locomotor driving signals will create circling movements. (iii) On the other hand,

it is possible that dopamine controls the symmetry of locomotion, so that when striatal dopamine activity is asymmetrical, turning may occur even if there is no postural asymmetry. (iv) The striatum on one side may have a bias in its representation of intentional responses, so that other things being equal, the signals it generates tend to make the animal turn to the contralateral side (by anatomical pathways which are bilateral [see Section 2.4.2 above]).

Of these possible behavioural components of the turning phenomena, the first is clearly an asymmetry of the inputs to the striatum. The second and third are clearly asymmetries of the output from it, while the fourth may be a combination of the two. There are also other combinations of effects which may produce turning behaviour. For instance, in lesioned animals, dopamine agonists might free movement bilaterally, but enhance the attractiveness of sensory stimuli (which is unsymmetrical) unilaterally; or there may be a combination of strong postural asymmetry together with enhanced attractiveness of the rear portions of the animal, which then become a focus of sensory orientation.

4.1.1. *Contralateral sensory attractiveness*

It has been demonstrated in a variety of species that a chance to observe novel stimuli is rewarding (Barnett, 1981). There is some evidence from unlesioned animals that dopamine plays a part in the attractiveness of stimuli. When mice are given dopamine agonists they tend to show an increased tendency to climb their cages (Protais *et al.*, 1976). As they do so, they continuously move around (Costall *et al.*, 1978). This pattern of behaviour suggests that the mice are actively seeking out new stimuli, whose attractiveness has been increased by the dopaminergic drug. In place preference conditioning (see Miller *et al.*, 1990), animals prefer to approach a compartment of the cage in which they have previously been given a dopamine agonist (Spyraki *et al.*, 1982). Szechtman (1983) showed that *asymmetrical* restriction of sensory input (with a unilateral head bandage) in intact rats could lead to *circling* behaviour away from the bandaged side when the rats were given apomorphine. The sensory input from the unbandaged side of the body appears to have an unsymmetrical power to attract the animal in these circumstances. Rotatory locomotion may also be produced by another way of introducing asymmetry into the sensory input: a small proportion of normal rats, when injected with apomorphine, will walk round the edge of a table on which they are placed, always in the same direction. These rats systematically walk in the opposite direction round the inner edge of a "hole" in the table compared with their direction of walking round an outer edge (Pisa and Szechtman, 1986), thus showing that the effect is not a motor asymmetry, but an asymmetry in attractiveness of stimuli of one side relative to the other. This result does not establish a relation between the direction of edge-walking and the side of greatest striatal dopaminergic activity, but does show that dopaminergic mechanisms control the attractiveness of stimuli. Ziegler and Szechtman (1988) studied a similar phenomenon in rats with unilateral striatal dopamine denervation. When swimming in a tank of water, apomorphine treated rats circled contralateral to the lesion if they were in the middle of the tank (the direction predicted by Ungerstedt's (1971a) results), but when they were close to one of the walls they circled ipsilaterally. This seems to suggest that the asymmetrical attractiveness of sensory stimuli from the edge wall may be so strong, under the influence of apomorphine, that it can reverse the rotation resulting from supersensitivity to dopamine on one side. (Whisker contact with the edge wall of the tank may be the most important component of this asymmetrical sensory input.) Whether this reversal of asymmetry depended on the enhancement of attractiveness of ipsilateral stimuli relayed to the lesioned, supersensitive striatum, or of ipsilateral stimuli relayed to the intact contralateral striatum cannot be decided on the basis of the results provided, but once again it is clear that the attractiveness of sensory stimuli is under dopaminergic control. Direction of turning appears, in this experiment, to be a product of both imbalance in dopaminergic activity and the imbalance in sensory stimulation. The latter effect can sometimes override the former.

There is, in addition, a significant literature relating striatal dopamine *depletion* to loss of attention (or *neglect*) of environmental stimuli. Ljungberg and Ungerstedt (1976b) studied the ability of rats with 6-hydroxydopamine lesions to orient to visual, auditory, olfactory and tactile stimuli. From 48 hr after a unilateral lesion, a stable deficiency appeared in the rats' response to contralateral stimuli of all types; in other words, there was a contralateral sensory neglect. From the sixth day after the lesion there was a gradual recovery in some of these deficits, but the neglect of tactile stimuli was permanent. Because rates of recovery were different for different classes of stimuli, it was concluded that this was not a motor deficit. These findings have been confirmed both in rats (Marshall, 1979) and in cats with electrolytic lesions of the substantia nigra or internal capsule (Feeney and Weir, 1979). Marshall and Gotthelf (1979) also confirmed the role of dopamine, by showing that apomorphine administration (for most doses tested) restored visual, olfactory or tactile orientation. On the other hand, spiroperidol or alpha-methyl-*p*-tyrosine reinstated the deficit (Marshall, 1979). In these experiments, the extent and rate of recovery of contralateral tactile neglect varied considerably between subjects. *Contralateral rotation on administration of apomorphine occurred only in rats which had not recovered from the tactile neglect* (see also Ungerstedt and Herrera-Marschitz, 1981). (A similar correlation between turning and lateralized responsiveness to stimuli has been reported by Huston *et al.* (1979). Unilateral microinjection of the GABA agonist muscimol into the substantia nigra produced contralateral turning, which correlated, on an animal-by-animal basis, with increased responsiveness to contralateral tactile stimuli.)

This evidence leads to the suggestion that the relative attractiveness of stimuli on either side plays a part in the rotatory effects seen by Ungerstedt. In the unilaterally lesioned rats without drugs, there is insufficient dopaminergic tone to sustain the attractiveness of contralateral stimuli. In the same rats

given apomorphine, the denervated striatum is supersensitive to the drug, the rat is thus rendered hyperattentive to contralateral stimuli, and so turns contralaterally. Likewise in Szechtman's experiment the striatum on the bandaged side received the full complement of sensory stimuli (from the unbandaged side) and so turns to the unbandaged side. (It seems most probable that the most important sensory stimuli here are somatosensory ones, for instance from the whiskers, rather than visual ones. The striatal afferents from these cortical regions, though partly ipsilateral, are mainly contralateral [McGeorge and Faull, 1989]. On the other hand, due to the presence of the optic chiasma, visual input comes to each hemisphere equally from either side. Thus, disregarding the commissural fibres in the corpus callosum, there is greater potential asymmetry in somatosensory inputs to the cortex from either side of the body, than in visual inputs from either eye.)

Experimental evidence does not clearly indicate whether D-1 or D-2 receptors contribute most to making contralateral stimuli attractive. In the experiments on climbing in mice elicited by apomorphine, D-1 antagonists are much more powerful than D-2 antagonists (Gerhardt *et al.*, 1985; Vasse *et al.*, 1988). On the other hand in place preference conditioning D-2 agonists mediate place preference, while D-1 agonists mediate an *aversion* to the place in which it is administered (Hoffmann and Beninger, 1988; Hoffmann *et al.*, 1988). In the situation of the unilaterally dopamine-denervated rat which has shown a recovery from the tactile neglect, the neglect can be reinstated by administration of a D-2 antagonist, spiroperidol (Marshall, 1979). This confusing situation may be compared with the theoretical expectation put forward by Miller *et al.* (1990), that the dopaminergic control of sensory attractiveness is a reward effect and so should be dominated by D-1 receptors. The situation is currently far from clear.

Despite these uncertainties, we have a role of striatal dopamine which could contribute to the rotatory behaviour seen by Ungerstedt. It is definitely separate from the postural deviations described above. To relate this component to the discussion above about the different components of rotatory behaviour it should be recollected that during the initial and final peaks of the time course of apomorphine's effects, the rats not only moved freely, but also were quite responsive to external stimuli. During the trough in the time course however, the animals' responsiveness to external stimuli was impaired, but at the same time the animal paid a great deal of attention to the parts of its own body to which its head approached most closely—the contralateral hindlimb and tail. Thus, a preliminary conjecture may be advanced: that during the trough of apomorphine's action, sensory hyperattention may be a dominating influence, becoming focused upon neighbouring parts of the animal's own body.

4.1.2. *Ipsilateral postural bias*

The rats of Ungerstedt (1971a), responding to amphetamine, or to apomorphine in the initial and final peaks of the response, engaged vigorously in rotatory locomotion when given dopamine agonists, but without a distinct postural component. In the "trough" of the apomorphine response there was a postural component ("vigorous twisting of the body towards the unoperated side"). Nevertheless, even in the absence of drugs, the unilaterally-lesioned rats show some abnormalities of posture, as distinct from movement: immediately after the lesion, rats have an asymmetrical posture, directed towards the side of the lesion. This may be similar to the postural abnormality seen in Parkinson's disease, and possibly gives rise to the ipsilateral scoliosis referred to above when Parkinsonian symptoms are unilateral. Several other papers have studied the effect of dopaminergic drugs on a different preparation—the animal with the striatum on one side destroyed—rather than denervated of its dopaminergic fibres. In these cases dopamine agonists (whether direct or indirect) cause postural deviation towards the lesion (Anden *et al.*, 1966; Lotti, 1971; Dunnett *et al.*, 1988), although much larger doses are required. The same has been seen when rats with unilateral spreading depression (to inactivate the striatum on one side) are given dopamine agonists (Keller *et al.*, 1973). In these preparations, dopamine antagonists produce a postural deviation *away from* the side of the lesion.

4.1.3. *Asymmetrical locomotion*

The initial and final peaks of the apomorphine-induced rotation, and the behaviour produced by D-2 agonists are a free locomotion, without postural bias, which nevertheless causes the animal to turn. Thus, one has some basis for thinking that dopamine (via D-2 receptors) can control the symmetry of locomotion.

4.1.4. *Contralateral intentional response bias*

Although the above results show that altered attractiveness of stimuli on one side, and other effects play a part in the rotatory responses of Ungerstedt's rats, there has been a recent demonstration of an effect which is different from this, and also different from any postural bias. Carli *et al.* (1989) trained rats with unilateral 6-hydroxydopamine lesions in a task where a stimulus was presented on either side, and the required response was either on the same side as the stimulus or on the opposite side. It was thus possible to distinguish neglect of a stimulus on one side from a response bias on one side. All groups of lesioned rats showed a bias towards the lesioned side, but this was a response bias, and not a contralateral sensory neglect. Any responses that were made away from the lesioned side were initiated more slowly than those to the lesioned side. In conclusion, there appears to be a fourth contender in the list of psychomotor functions which underlie the turning behaviour of the Ungerstedt's rats.

4.2. REGIONAL REPRESENTATION OF THE VARIOUS COMPONENTS OF STRIATAL FUNCTION INVOLVED IN TURNING BEHAVIOUR

4.2.1. *Bias of sensory attractiveness*

Of the four behavioural components defined above which could contribute to drug-induced turning

behaviour, the most evidence of regional localization in the striatum is available for the sensory neglect/hyperattention syndrome. From experiments with regional 6-hydroxydopamine depletion, Marshall *et al.* (1980) concluded that the contralateral neglect syndrome was related to lack of dopamine in the neostriatum rather than in other dopaminergic structures (nucleus accumbens, olfactory tubercle, prefrontal cortex or septum). In this study it was also found that dopaminergic terminals in the anterior part of the caudate nucleus were most important for orientation to tactile stimulation of the rostral body surface, those in the posterior part of the caudate for orientation to the caudal body surface.

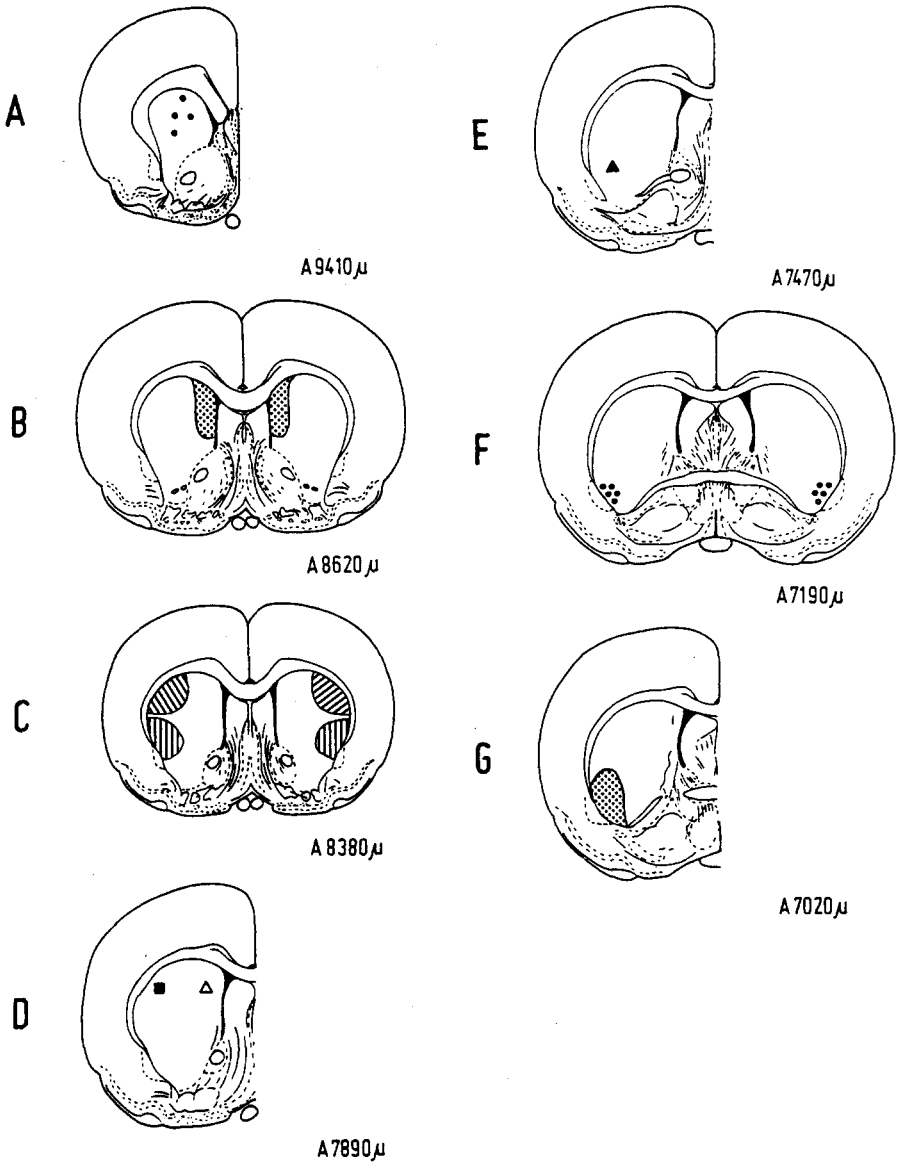

FIG. 3. Examples of regional localization of functions in the rat striatum. Sections are from the atlas of Konig and Klippel, with each result depicted at the most relevant antero-posterior level. Symbols show regions at which specific function were positively localized. (For negative results, refer to original publications.) A: Data derived from Klockgether *et al.* (1988), for striatal sites at which microinjections of haloperidol elicit catalepsy. B: Data derived from Fink and Smith (1979), showing region of dopamine depletion, following local 6-hydroxydopamine lesion, which reduced the number of full length traverses of the activity cage, when the animals were challenged with 1.5 mg/kg *d*-amphetamine. C: Data derived from Pisa and Schrantz (1988) for sites of ibotinic acid lesion of striatum which impaired skilled use of forelimbs only (oblique lines), and of both tongue and forelimb (vertical lines). D: Data derived from Joyce and Van Hartesveldt (1984). Open triangle: site of microinjection of dopamine which produced the strongest rotatory response. Closed square: site of dopamine microinjection which produced the strongest contralateral postural deviation. E: Data derived from Sabol *et al.* (1985) showing site of 6-hydroxydopamine microinjection which impaired skilled forelimb use. F: Data derived from Kelley *et al.* (1988) showing site of amphetamine microinjection which produces intense stereotypy. G: Region of dopamine depletion produced by local 6-hydroxydopamine lesion, which results in impairment of sensorimotor orientation contralaterally.

Microinjection of apomorphine into these regions could restore orientation to somatosensory stimuli. Dunnett and co-workers defined the striatal region required for sensory orientation with greater precision. Dunnett *et al.* (1981b) showed that, in rats with 6-hydroxydopamine lesions of the striatum, it was possible to restore sensory neglect for visual, auditory, tactile and olfactory stimuli, with grafts of embryonic substantia nigra positioned in the ventrolateral striatum. On the other hand grafts of embryonic tissue positioned in the dorsal striatum had no effect on sensory neglect (tested with olfactory or somatosensory stimuli) (Dunnett *et al.*, 1981a). The implications of these results were confirmed by Dunnett and Iversen (1982a) who showed that localized lesions of the striatum made either with 6-hydroxydopamine or kainic acid produced long lasting impairment in sensorimotor orientation to contralateral stimuli if made in the ventrolateral striatum (Fig. 3G).

The tests for these impairments included assessments of limb use in various tasks, as well as strictly sensory orientation. All other locations for kainic acid lesions were without effect on this measure, and 6-hydroxydopamine lesions in any other region of the striatum caused only mild and temporary impairment. The identification of the lateral striatum as important for sensory orientation is also confirmed by Fairley and Marshall (1986) who found that lateral striatal injections of 6-hydroxydopamine were more effective than medial ones in impairing orientation to tactile stimuli. Sabol *et al.* (1985) confirm (using localized 6-hydroxydopamine lesions) that the lateral neostriatum in rats is involved in skilled contralateral forepaw use (Fig. 3E). No deficit was seen with medial lesions. The impairment was again thought to reflect a primary deficit of sensory orientation. Pisa (1988) and Pisa and Cyr (1990) have provided evidence of impairment in skilled use of parts of the body after ibotinic acid lesions of the lateral striatum. Pisa and Schrantz (1988) have also produced suggestive evidence of a topographical representation of body parts in the lateral striatum: lesions of the dorsolateral striatum impaired forelimb reaching movements. Those in the ventrolateral striatum impaired reaching movements using either tongue or forelimb (Fig. 3C). A similar locus for representation of tongue protrusion has also been reported by Grgurich and Beninger, using intrastriatal injections of haloperidol (unpublished, see Fig. 4). According to Pisa and Schrantz (1988), lesions of the medial striatum had no effect on either tongue or forelimb reaching movements. Likewise, the data of Grgurich and Beninger (Fig. 4) show that the striatal region where local injection of a dopamine blocker impairs tongue protrusion, is highly circumscribed.

Dunnett *et al.* (1981a,b) made other observations which allow these findings to be related to the drug-induced rotation of Ungerstedt's rats. The ventrolaterally-grafted lesioned rats showed contralateral rotation when challenged with apomorphine (0.05 mg/kg), as did lesioned ungrafted animals. However the impairment of contralateral limb use was restored by the graft, as was sensory orientation. Thus, although drug-induced rotation might depend in part on a bias of sensory orientation, represented in this part of the striatum, other mechanisms in other parts of the striatum can still elicit rotation when the dopaminergic innervation in the ventrolateral region is restored by a graft. An indication of another region involved in rotation was provided by Dunnett *et al.* (1981a). The dorsally grafted rats no longer exhibited contralateral turning behaviour when injected with 0.05 mg/kg of apomorphine. With a larger dose (0.25 mg/kg) their contralateral turning occurred as in ungrafted lesioned animals. However, it should also be noted that Dunnett and Iversen (1982b) found no regional differences in the spontaneous rotatory effects or those produced with apomorphine, amphetamine for 6-hydroxydopamine lesions in 12 different regions of striatum.

These results are too fragmentary to prove any case. But if it is assumed that the positive results of Dunnett *et al.* (1981a,b) are a better approach to the truth than the negative ones of Dunnett and Iversen (1982a), some interesting interpretations can be derived. First, since sensory neglect and impairment of limb use co-vary for dopamine depletion and grafting in the ventrolateral striatum, the apparent impairment of skilled motor function may well be a secondary consequence of sensory inattention. Second, since dorsal grafts have no effect on sensory neglect, but prevent a low-dose component of apomorphine-induced rotation, the contribution of sensory neglect to the rotational effect (for which there is suggestive evidence) must be accompanied by other components with different pharmacological and anatomical bases. Thirdly, the discussion in Section 3.1.2 above led us to the conjecture that the behaviour shown with lowest doses of apomorphine, and at the start and end of the time course with higher doses, is dominated by the actions at D-2 receptors. Thus, it appears that the dorsal grafts in a denervated striatum selectively restored a component of rotation mediated by D-2 receptors. The ventrolateral grafts had no effect on this component. It is not clear from these experiments whether they have an effect on the component of rotation in the trough of apomorphine's time course (the part which putatively depends on interaction between D-1 and D-2 actions), because at the larger dose of apomorphine required to elicit this component, rotation will inevitably occur due to the low dose D-2-mediated action on other denervated regions of the striatum. However, bearing in mind that during the trough there is behaviour suggestive of sensory hyperattention (to the contralateral hindlimb and tail), and some evidence that D-1 receptors control sensory attractiveness in intact animals (see above), the hypothesis can be proposed *that the ventrolateral striatum is important for a contralateral hyperattentiveness component of the overall rotatory response, possibly relying on D-1 mechanisms.* Further experiments must be conducted to test this conjecture. It would be predicted that if sensory neglect and D-1 mechanisms in the ventrolateral striatum play a part in rotatory behaviour, then in ventrolaterally grafted rats only the D-2 component should remain. When challenged with doses of apomorphine greater than 0.05 mg/kg there should be no trough in the time course, as is found in lesioned animals without such a graft.

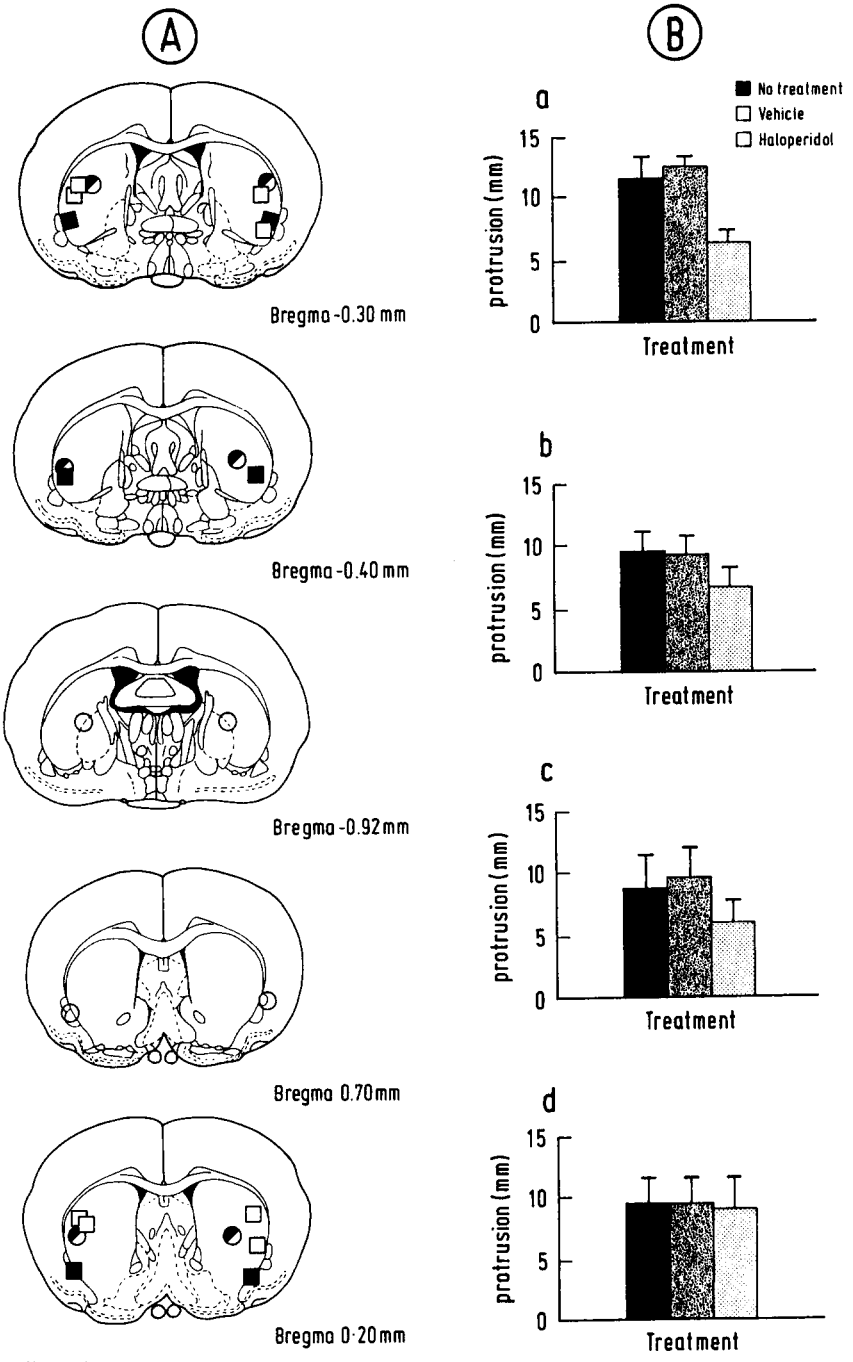

FIG. 4. Effect of local intrastriatal injections of haloperidol on tongue protrusion in rats. Food deprived rats were trained to eat wet food mash from a spatula located outside a small hole in the wall of the test apparatus. This arrangement required the rats to extend their tongues as far as possible to get the maximum amount of food. A: Location of bilateral cannulae placements for injections: (i) "Hit" subgroups: Filled squares: ventrolateral placements; Empty squares: lateral placements; Half-filled circles: mixed placements (one lateral and one medial): (ii) Empty circles: "misses". Numbers indicate antero-posterior distances from bregma of coronal sections taken from stereotaxic atlas of Paxinos and Watson (1986). B: Mean (±SEM) distance of tongue protrusion (mm) as a function of treatment for each of the three Hit subgroups [(a): ventrolateral group; (b): lateral group; (c): mixed group] and the Miss group (d) from A. The first bar in each set shows the extent of tongue protrusion when the rats received no treatment. Treatments were either vehicle, bilaterally (buffered lactic acid, 0.5 μl; second bar) or bilateral injections of haloperidol (2.5 μg in 0.5 μl; third bar), and were given in counterbalanced order across rats. Analysis of variance of the results for the hit group revealed a significant treatment effect and *post hoc* comparisons showed the haloperidol group to differ from the other two. Individual analyses of the Hit subgroups, although the numbers were small, revealed a significant treatment effect for the ventrolateral group. There appeared to be no significant effect of haloperidol on tongue protrusion for the misses. (Unpublished results of L. A. Grgurich and R. J. Beninger.)

4.2.2. *Postural bias*

The result of Dunnett *et al.* (1981a) described above, that dopaminergic grafts into the dorsal striatum of unilaterally lesioned rats had no effect on sensory neglect, but abolished turning behaviour with low dose apomorphine, suggests that this region contributes to turning in some way other than by biassing sensory attractiveness. The same conclusion is suggested by the result of Joyce *et al.* (1981): microinjections of dopamine (25 or 10 μg) into the striatum caused all spontaneous behaviour to be directed contralaterally, the time course of this effect being much longer for injections into the dorsal than the ventral striatum. A postural bias combined with symmetrical locomotion has already been suggested as one of the possible components of rotatory behaviour. Joyce and Van Hartesveldt (1984) obtained definite evidence for this. They followed their earlier study with one in which smaller injections of dopamine (25 μg) were delivered into different parts of the dorsal striatum. Injections into the lateral part of the dorsal striatum caused contralateral postural deviation. Those into the medial part of the dorsal striatum caused contralateral rotatory movement rather than postural deviation (Fig. 3D). *This result provides a basis for thinking that postural bias is an independent effect of striatal dopamine from rotatory locomotion, and suggests that it may be represented in the dorsolateral part of the striatum in rat.* More work is required before these conjectures can be accepted. Fletcher and Starr (1987) have found that a contralateral postural bias can be obtained with intrastriatal injections of dopamine agonists in very diverse regions of the striatum. It is also not yet clear what receptor types may be involved in a dopamine-induced postural bias. Fletcher and Starr (1987) have observed postural biasses with intrastriatal injections of both D-1 and D-2 agonists.

4.2.3. *Locomotor bias*

The localization of representation of locomotion in the dorsomedial striatum (Joyce and Van Hartseveldt, 1984, Fig. 3D) discussed in the previous subsection, receives confirmation from Fink and Smith (1979), who found that 6-hydroxydopamine lesions of the anteromedial dorsal striatum caused an abnormal running pattern, with fewer runs from one end of the cage to the other (but the same number of midline crossings) (Fig. 3B). (On the other hand, it should be pointed out that ibotinic acid lesions of the striatum in the dorsomedial part did not impair gait, according to Pisa and Schrantz [1988].) The component of free, but asymmetrical locomotion was identified above (Section 3.1.2), in pharmacological analyses of circling, as a D-2 effect. It is therefore relevant that Fletcher and Starr (1987) found that circling initiated in rats by intrastriatal injection of the D-2 agonist lisuride is produced preferentailly with injections into the medial strip of the striatum. (SKF 38393-induced rotation was produced best from a somewhat different region, the mediocentral striatum, especially anteriorly. However this circling may have been based on different psychomotor processes from the asymmetrical locomotion suggested as a D-2 mediated effect.)

4.2.4. *Response bias*

Carli *et al.* (1989) showed that unilateral 6-hydroxydopamine lesions of the striatum produced a response bias to the lesioned side in animals which were tested undrugged. Assuming a similar process operates in drug-treated animals, this could be a basis for contralateral rotation with apomorphine, or ipsilateral rotation with amphetamine. This possibility does not, however, exclude any of the other behavioural components as playing a part in drug-induced rotation. In Carli *et al.*'s work, the response bias correlated best with depletion in the posterior but not the anterior part of the head of the caudate, and not with depletion in nucleus accumbens. These indications of a possible locus of representation in the striatum of an intentional response bias obviously require further work for clarification.

4.2.5. *Summary and discussion*

In conclusion, there is confirmed evidence that the lateral and ventrolateral striatum of the rat are involved in sensory attention for forepaws and other body parts, and it is likely that this is the basis for loss of skilled motor function after lesions in this region. Asymmetry of D-1 activation may be significant in this effect. There is also some evidence of a topographic representation of body parts in the lateral striatum of rat (compatible with that demonstrated by Alexander and DeLong, 1985, in the primate putamen). Unconfirmed reports suggest that the mediodorsal striatum may be involved in contralaterally directed locomotion, possibly involving an asymmetry of D-2 activation. The laterodorsal striatum may control postural deviation to the contralateral side. A posterior part of the caudate head may be involved in the response bias demonstrated by Carli *et al.* (1989).

Developing from these rather tentative conclusions, two recent papers deserve mention, which suggest combinations of some of the above components in rotatory behaviour. Koshikawa *et al.* (1990) found that microinjections of either D-1 or D-2 antagonists into the ventral striatum of intact rats, followed by systemic injections of apomorphine, led to ipsilateral rotation. This effect is in accord with Ungerstedt's maxim, that rats turn away from the striatum with highest dopaminergic activity. The rotatory effect produced by apomorphine after microinjections of D-2 antagonists were more potent than those produced after microinjections of a D-1 antagonist. The rotatory effects of D-1 and D-2 antagonists were additive, and so it seems that separate but synergistic effects were involved. Microinjections into the dorsal striatum had no such effect. It is unclear how far the microinjected drugs spread in this experiment, so that, although all effect were elicited from the same injection site, there may also have been regional differences between the D-1 and the D-2 antagonist-mediated effects. In a similar experiment, Konitsiotis and Kafetzopoulos (1990) confirmed most of these findings, adding some

phenomenological detail. With unilateral microinjections of sulpiride into the ventrolateral striatum, apomorphine elicited vigorous head-to-tail rotation, with marked postural bias, pivoting around the ipsilateral leg, with sniffing, gnawing and biting. When the D-1 antagonist SCH 23390 was used, rotation was weak and loose, without postural bias, but with rearing and climbing. In contrast to Koshikawa *et al.* (1990) they found similar results after microinjection into the dorsal striatum, but only for the D-2 blocker sulpiride.

If the ventral region involved deals with sensory attention, which is controlled mainly by D-1 receptors, D-2 antagonists delivered into this region would produce no asymmetry of D-1 activation. However, if it is assumed that the microinjected D-2 antagonist produced an ipsilateral postural deviation, then the subsequent administration of apomorphine would enhance sensory attention to whatever stimuli the sensory receptors of the head encountered. One can thus explain the phenomenology described by Konitsiotis and Kafetzopoulos (1990) without requiring asymmetrical sensory attractiveness. The weaker and looser rotation elicited by apomorphine after microinjections of D-1 antagonists into the ventral striatum obviously did not involve a postural bias. It may have depended on a combination of ipsilateral bias of sensory attractiveness together with symmetrical stimulation of locomotion (by the D-2 agonist activity of apomorphine).

5. ON THE RELATION BETWEEN STEREOTYPY AND TURNING BEHAVIOURS PRODUCED BY DOPAMINE AGONISTS

A further implication of some of the above arguments concerns not so much the dopamine-denervated animal as the intact one, responding to dopamine agonists with a characteristic behavioural syndrome. Low to moderate doses of dopamine agonists (both direct and indirect) increase locomotor activity, as well as limb and head movements. Higher doses produce repetitive actions commonly involving the mouth, tongue and lips. These vary from species to species. In rats they consist of repetitive sniffing, licking, chewing and gnawing. In human psychotic patients (which are, in a way as yet undefined, probably also in a hyperdopaminergic state) related signs have been documented. This collection of behavioural pathologies is generally referred to as "stereotyped behaviour".

The low-dose components of the stereotypy can be elicited with D-2 selective agonists. However, to produce the high-dose, oral components of stereotypy, the interaction of both D-1 and D-2 receptor activation is required (see Miller *et al.*, 1990). Moreover, when these high-dose effects appear, the concurrent locomotor hyperactivity declines.

We offer the following proposal to understand stereotyped activity in animals, and potentially also in man: the low-dose locomotor stereotypy is in some ways equivalent to the early and late peaks in the rotatory response to apomorphine, discussed in the present paper, both being characterised by free locomotion, and selectively elicited by D-2 agonists. The high-dose oral component of stereotypy is in some ways equivalent to the trough in the time course of apomorphine's rotatory response. Both require interaction of D-1 and D-2 mediated effects; both are produced at higher doses of the non-selective agonist apomorphine than are the corresponding free locomotor effects; and both are accompanied by a reduction of concomitant locomotor movements. It can also be argued that the underlying psychomotor processes are the same: in the case of the apomorphine trough, there is hyperattention to the contralateral hindlimb and tail, the part of the body to which the head has preferential exposure in the lesioned circling rat. In the case of oral stereotypy in the unlesioned animal, it may be that the animal is in a hyperattentive, but symmetrical state, orientating mouth, lips and tongue to forepaws and anything else near the midline of the head region.

If it is suggested that the psychomotor basis of stereotyped behaviour is sensory hyperattention of (and to) the midline parts of the head region, this may be compatible with the regional localization of the sensory attention function in the ventrolateral striatum, discussed above: Kelley *et al.* (1988) found that stereotypy could be produced by local microinjections of amphetamine into the ventrolateral striatum (see Fig. 3F). This supports the idea that stereotypy is a behaviour based on sensory hyperattention. Kelley *et al.* (1989) also report stereotyped biting of the forepaws after amphetamine microinjections into this region, but not after corresponding injections into the dorsolateral striatum. However, Arnt (1985a) showed that sulpiride injected into the ventro*medial* striatum impaired oral components of stereotypy; that into dorsal striatum did not, or even enhanced it. There is some difference in the regional localization of stereotypy shown by this datum, and that for sensory orientation discussed above. However, the amount of data is limited, and the discrepancy may be resolved if more injection sites are tested for the two behavioural effects.

There are of course some clear differences between the stereotyped behaviour and the apomorphine trough. Stereotyped behaviour is symmetrical while the apomorphine trough is highly asymmetrical. Secondly, the phenomenology characteristic of the apomorphine trough is produced at a lower dose of apomorphine than is the corresponding stereotyped behaviour produced with apomorphine in intact rats. This dose difference is in fact not very large: according to Ungerstedt (1971a) the trough for rotation in unilaterally lesioned rats occurs only for doses above 0.25–0.5 mg/kg apomorphine, while oral stereotypy in intact rats occurs with doses of apomorphine above about 1.0 mg/kg (Ernst, 1967; Costall and Naylor, 1973b). Such a difference can plausibly be explained by the receptor proliferation and consequent supersensitivity of the denervated striatum in the former case, compared with the normosensitive striatum in which stereotypy is generated, in the latter (see Randall, 1985). (As noted in Section 3.1.3 above, the difference in sensitivity of intact and lesioned striata for rotatory effects *per se* is much larger than this, and is explained only partly on the basis of supersensitivity.)

A more difficult piece of evidence for this analysis is that oral stereotypy can be produced in the intact animal by amphetamine as well as by apomorphine; but the trough in the time/intensity curve of rotation is seen only with apomorphine, not with amphetamine. However there are reports that even in unlesioned animals the phenomenology of amphetamine-induced stereotypy differs from that of apomorphine-induced stereotypy. Fray *et al.* (1980) find that with the CBY strain of male albino rats, amphetamine administration elicited locomotion, rearing, and sniffing, but not licking or gnawing. On the other hand, apomorphine administered to rats of this strain produced increases in licking and gnawing, as well as locomotion and sniffing, but no changes in rearing. Ziegler and Szechtman (1988) have also documented detailed phenomenological differences between the effects of amphetamine and apomorphine in unilaterally dopamine-denervated Sprague–Dawley rats. Under apomorphine, the rats rotate by backward stepping with the contralateral hindlimb, while pivoting on the ipsilateral hindlimb. Under amphetamine, rotation involves a variety of more normal stepping patterns. While this description does not emphasize sensory attention as a mediator of the apomorphine induced rotation, it is compatible with this hypothesis: the markedly flexed trunk, and the abnormal stepping pattern may be a secondary effect resulting from the strong attraction of the contralateral hindquarters to the head of the rat. Other studies with apomorphine, in unlesioned rats emphasize the close contact between snout and ground throughout most of the period of drug action (Szechtman *et al.*, 1980, 1985), an effect strongly suggesting hyperactive, but symmetrical attractiveness of sensory stimuli. An additional difference between apomorphine- and amphetamine-induced behaviours has been documented by Ziegler and Szechtman (1988). With apomorphine, "edge-effects" are commonly seen, as described in Section 4.1.1 above, where they are analyzed as due to asymmetrical attractiveness of sensory stimuli. Such effects were not seen in rats responding to amphetamine.

Thus, there is a case to be made that, even in unlesioned animals, amphetamine's behavioural effects have a smaller component of enhanced sensory attractiveness and a higher component of enhanced locomotion than do apomorphine's behavioural effects. Why this should be so is not yet clear. Possibly there is a difference in the relative activation of D-2 versus D-1 receptors between apomorphine and the dopamine released by amphetamine.

6. SUMMARY AND HYPOTHESES ABOUT CIRCLING RATS

The argument developed so far has been an intricate step-by-step inference from evidence which in several places is rather scanty. No firm conclusion can be advanced, but a hypothesis can be presented which is consistent with much of the evidence discussed, although by no means forced by that evidence. Drug-induced rotation in lesioned animals is not a unitary piece of behaviour. It can be subdivided phenomenologically, pharmacologically and anatomically. The most clearly identifiable component is a sensory hyperattention towards the side contralateral to the striatum with highest dopaminergic activity. This probably is related to asymmetrical activation of D-1 dopamine receptors, with a possible contributory role from D-2 receptors, and depends on the functioning of the lateral and ventrolateral striatum in rats. A second component is a contralaterally biassed locomotion, which probably depends mainly on asymmetrical D-2 receptor activation, and a representation in the dorsomedial striatum. A third possible component may be a contralateral bias of intentional responses with head or limbs. Its pharmacological profile is uncertain, but may be represented in the posterior caudate head. The fourth component is a contralateral postural deviation, whose pharmacological profile is again uncertain, but which may be represented in the dorsolateral striatum.

This complex synopsis is in one respect supported by the argument of a previous work (Miller *et al.*, 1990). In that paper the D-1 receptor effects were equated with a reward effect, whose physical basis was the strengthening of selected synapses in the corticostriatal afferents of the striatal output neurons. The D-2 effect was equated with an effect on performance of various tasks, rather than the learning-related function of reward, and hence modulated output alone rather than specific input–output relations. In the present work it is postulated that D-1 actions are primarily concerned with sensory orientation, a function which several workers believe to be linked with skilled use of the motor apparatus. This seems compatible with a reward role for D-1 receptors in strengthening input–output connections. As argued in the earlier paper such a reward effect may be highly selective (the situation envisaged to obtain for normal reward-mediated learning), but when the dopaminergic signal is a direct agonist such as apomorphine, the reward effect is indiscriminately achieved on all active corticostriatal afferents. Most of the effects on sensory attention described in the present paper are a manifestation of the latter aspect of reward. On the other hand, the D-2 effect identified most clearly here is in locomotion. This can be recognized as mainly a performance function which, as discussed in Miller *et al.* (1990), is predominantly influenced by D-2 rather than D-1 mechanisms.

Given this breakdown of the behavioural components underlying rotatory behaviour, there are at least three ways in which D-1- and D-2-mediated effects may interact. Firstly, *in the intact, or partially dopamine-denervated striatum* D-1 and D-2 activations act synergistically at the level of the medium spiny neurones in each striatal region (see Miller *et al.*, 1990). Secondly, *in the supersensitive striatum* D-1 and D-2 receptors appear to become independent, i.e. dissociated from one another. This appears to be because striatal neurones are closer to firing threshold in the chronically dopamine-denervated striatum, and therefore activation of a single receptor type by itself can have important behavioural consequences, and can be blocked just by its own selective antagonist. Thirdly, there can be a *competitive* interaction between the two agonists, at the behavioural rather than the neuronal level, such that enhancement of sensory attractiveness (on one or both sides)

interferes with locomotion (in the intact animal) or with the locomotor component of rotation (in the unilaterally lesioned animal). We suggest here that this behavioural competition can occur *with either denervated or intact striatum*: it has been seen in rotational models with no chance for denervation supersensitivity to develop, and also there are strong similarities between the trough in the time course of apomorphine's rotatory effects and aspects of oral stereotypy seen in intact animals. In addition the mild degree of sensitization of the apomorphine trough for rotatory effect, compared with the oral stereotypy seen in intact animal, is not so large that one needs to postulate qualitative changes between the denervated and the intact striatum in this regard, merely the quantitative differences anticipated from observed mild degrees of receptor proliferation.

A few final comments are required on this third (competitive) interaction between the behavioural effects of D-1 and D-2 receptor activation. *In the intact animal*, responding to apomorphine, stereotyped behaviour can be interpreted as symmetrical hyperattention to available stimuli, which has the ability to occlude locomotor activity concomitantly stimulated by the drug. For *unilaterally lesioned animals*, this interaction may be envisaged as a combination of potent postural deviation to the contralateral side combined with sensory hyperattention to the same side, directed at the objects the animal is then most likely to encounter, namely the contralateral hindleg and tail. This combination reduces the measured rate of rotatory movement at the peak of apomorphine's effects below that seen at the start or end of apomorphine's effect. The fact that this interaction, producing the trough in apomorphine's action, appears to require several experiences with the drug (Coward, 1983) is compatible with the fact that D-1 as well as D-2 receptor activation is required, since the D-1 receptors are envisaged to be involved in the reward signal of learning and Coward's result suggests a conditioning effect. (See also Miller *et al.* (1990) for a discussion of the role of conditioning in behavioural sensitization after repeated doses of dopamine agonists.) The fact that D-1 agonists produce rotation only after a latency of some tens of minutes may also have an explanation in conditioning terms.

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