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DOPAMINE D-1 AND D-2 RECEPTORS IN RELATION TO REWARD AND PERFORMANCE: A CASE FOR THE D-1 RECEPTOR AS A PRIMARY SITE OF THERAPEUTIC ACTION OF NEUROLEPTIC DRUGS

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1. INTRODUCTION

1.1. Dopamine Receptor Subtypes and Neuroleptic Drugs

The beneficial effect of the drug chlorpromazine for patients suffering from acute psychosis was discovered in the early 1950s, and numerous other drugs have since been found which have similar actions. It is now well established that the antipsychotic actions of this family of drugs (the "neuroleptic" drugs) rely on blockade of dopamine receptors at some site in the brain (Carlsson and Lindqvist, 1963; Randrup *et al.*, 1963; Van Rossum, 1966; Angrist *et al.*, 1974; Fielding and Lal, 1978; Seeman, 1980; Peroutka and Snyder, 1980; Iversen *et al.*, 1983; Seeman, 1987).

It has however become clear that there is more than one dopamine receptor subtype, the distinction most commonly being made between the so-called D-1 and D-2 dopamine receptors (Kebabian and Calne, 1979; Leff and Creese, 1983). (Additional varieties of dopamine receptor have also been defined [see: Seeman, 1980; Sokoloff *et al.*, 1980; Creese *et al.*, 1983]). In the striatum (which contains most of the brain's dopamine) it has been possible to identify the D-2 receptor in at least two cellular locations: firstly, the cholinergic interneurones (which are a small minority of striatal neurones) are inhibited by dopamine, and this inhibition depends on actions at the D-2 receptor subtype (Herrting *et al.*, 1980; Stoof *et al.*, 1982; Scatton, 1982; Wong *et al.*, 1983, 1987). Secondly, the presynaptic autoreceptors on dopaminergic fibres themselves, whose activation reduces dopamine release, appear to depend also on receptors of a somewhat similar type (Leff and Creese, 1983).

At present it is widely believed that the antipsychotic effects of neuroleptic drugs are mediated by the D-2 dopamine receptor, the D-1 receptor being irrelevant to this therapeutic action. This view is based mainly on the evidence that relative potency of a wide range of neuroleptics in antipsychotic therapy correlates fairly well with the affinity of the same drugs for the D-2 receptor (Seeman *et al.*, 1976; Peroutka and Snyder, 1980; see also Miller, 1987; Fig. 1A), but correlates poorly with affinity for the D-1 receptor. The latter negative result is based partly on data about the potency of neuroleptic drugs in blocking the dopamine-stimulated adenyl cyclase, the original basis for definition of the D-1 receptor. In this biochemical test the butyrophenone subgroup of neuroleptic drugs is very much less potent, compared with other neuroleptic drugs, than it is therapeutically (Seeman, 1980; Fig. 2). In addition, the binding of the conventional neuroleptic drugs to the D-1 receptor site correlates poorly with clinical potency (Seeman, 1987). In the animal literature it has, until the last few years, been difficult to ascribe a specific functional role to the D-1 receptor, other than its action at the neurochemical level on adenyl cyclase. Thus, both in the clinical data and in animal studies the D-1 receptor has been something of an enigma. Laduron for instance, wrote in 1983: "All the pharmacological and behavioural effects elicited by dopamine agonists and antagonists in the brain can only be explained if such an interaction occurs at the level of the dopamine D-2 receptor site; the D-1 site still remains in search of a function."

1.2. Dopamine's Functional Role: Reward Versus Performance

Dopamine's actions in animals can be classified in behavioural terms as well as neurochemical ones. Broadly speaking, dopamine has two general classes of behavioural action: it can activate *performance* generally; and it can also act as an *internal reward signal*, that is it serves to enhance selectively the ability of stimuli to elicit responses in the future, when motivationally favourable effects are contingent on elicitation of such responses by these stimuli (Miller, 1981 [Chapter 6]; Beninger, 1983; Liebman, 1983; Miller, 1988; Beninger *et al.*, 1989; Wickens, 1989). The precise psychological definition of reward is discussed later in Section 2.1.

The therapeutic response produced by a range of neuroleptic drugs on psychotic symptoms seems to correlate best with their potency in inhibiting the internal reward signal rather than the performance component of dopamine's action in animals (Miller, 1987; Beninger, 1988). In addition the slow time course of therapeutic action of neuroleptic drugs in man can best be accounted for as an effect on a learning process (Beninger, 1983, 1988; Miller, 1984, 1987d) similar in some ways to the extinction-like decline of performance of reward-mediated behaviour produced by neuroleptic drugs in experimental animals. Whether there is also a "performance" effect of neuroleptic drugs on psychotic symptomatology is a matter discussed later in Section 6.4.

1.3. Synergism Between D-1 and D-2 Receptors: A Relation to the Reward/Performance Dichotomy?

In the last few years compounds have become available for animal studies which are highly selective for the D-1 receptor subtype, both as antagonists (Hyttel, 1983; Iorio *et al.*, 1983) (unlike most neuroleptics in clinical use, which are non-selective or D-2-selective) and as agonists (O'Boyle and Waddington, 1984). A substantial literature has also been built up on the relative efficacy of these compounds in modifying a wide range of behavioural effects thought to involve the transmitter dopamine (see reviews by Joyce, 1983; Waddington, 1986; Clark and White, 1987; Beninger *et al.*, 1989). In many of these behaviours there appears to be a complex synergism between the D-1 and D-2 receptors, but the precise nature of the relationship is still an enigma.

In the present paper, some ideas are put forward about the nature of the synergism between D-1 and D-2 receptors. It is suggested that the complex literature on the relative role of D-1 and D-2 receptors on animal behaviour can best be understood if the D-1 receptor is the final target at which dopamine elicits rewarding effects. The D-2 receptor can however also influence the reward target by less direct means. In view of our earlier arguments (Miller, 1987; Beninger, 1988) that the antipsychotic action of

neuroleptic drugs is comparable with antireward effects in animals, we are thus led to the conclusion that the D-1 receptor (not the D-2 receptor) is the final target at which neuroleptic drugs elicit their therapeutic effects, although with most currently available neuroleptic drugs this action is likely to be consequent on, or accompanied by actions at D-2 receptors.

This view has a number of implications for the understanding of clinical actions of neuroleptic drugs. In particular it bears significantly upon the explanation to be given for the long time-course of neuroleptic therapy, the relation between antipsychotic effects and extrapyramidal side effects of these drugs, the significance of dose–response relations established for the clinical effects of neuroleptic drugs, and the site in the brain at which antipsychotic drugs achieve their beneficial effects. Our arguments also have an important implication that the D-1 selective antagonists should be of therapeutic value in treating psychosis. There have been a number of suggestions from the experimental literature that the selective D-1 antagonists may be antipsychotic agents with little propensity to cause extrapyramidal side effects ("non-cataleptogenic" neuroleptic drugs). The present paper gives these suggestions theoretical support. All these matters are discussed in this paper.

The most important evidence which leads us to challenge the prevailing view that it is the D-2 receptors on which the antipsychotic actions of neuroleptic drugs depends, is that relating to the role of different dopamine receptor subtypes on a variety of learned and unlearned behaviours in animals. This literature may appear complex, confusing, and at times frankly contradictory, unless one has an explanatory framework with which to understand it. For simplicity's sake we therefore prefer to explain first the principles we use in accounting for this evidence, before presenting the data themselves, and their detailed explanation.

2. PSYCHOLOGICAL DESCRIPTIONS

2.1. DEFINITIONS OF REWARD

The term "reward" refers both to stimuli that are motivationally favourable (and therefore have the *potential* to change behaviour patterns), and to the *consequences* such stimuli have in the process of behaviour change itself. The characteristics of the reward can be defined in terms of Thorndike's Law of Effect (Thorndike, 1911) as an *enhancement of the ability of specific stimuli to elicit specific responses in the future if the latter responses deliver motivationally favourable ("rewarding") effects.* Alternatively, using the language of incentive learning (Bindra, 1978; Beninger, 1983) *a reward signal is one which enhances the ability of stimuli to elicit approach responses in the future if those stimuli are associated with other, motivationally favourable ("rewarding") stimuli.*

Although these seem rather different statements they can both be seen to derive from a common process, the difference between them lying in the configuration of the stimulus components. Stimuli play two roles in reward-mediated behaviour: they may be involved in eliciting a response; or they may be regularly correlated with occurrence of the favourable ("rewarding") effect of the response. In the former case the stimulus and the response it elicits are the *target* of the reward process. In the latter case the stimulus can become classically conditioned to the primary reward, as a "secondary reward", and thus becomes a *trigger* of reward. In most of what follows (with the exception of a few behavioural paradigms such as conditioned reward [Section 5.7]) we are concerned with stimuli as eliciters of responses, rather than as triggers of reward.

If the stimulus which elicits the response is always spatially associated with delivery of a reward (e.g. a visual signal located near a food hopper), the stimulus plays both roles simultaneously. Then, since the only response which will keep the secondary reward stimulus in view will be an approach response, it is inevitable that approach responses directed at both the reward and the stimuli spatially associated with it will be strengthened by the reward. This situation is best described by the incentive learning formulation of reward. On the other hand, when the stimulus which elicits the response is spatially segregated from the reward (e.g. a tone sounded at the opposite side of a cage from the food hopper, as in the experiments of Grastyan and Vereckei [1974]) the stimulus has a much weaker secondary rewarding effect or none at all. In this case, the animal may initially show orienting responses to the eliciting stimulus, but eventually, when these have habituated, the stimulus will elicit a response in which the animal turns away from the stimulus, to obtain the primary reward. This situation corresponds more closely to that defined by Thorndike's law. Nevertheless, both formulations can be seen as relying on the same underlying mechanisms, analyzed in Section 3.2 in terms of rule-dependent synaptic change.

There is another problem about the reward process, which is at present unresolved: reward can only be directed at the representation of a *single* response sequence on each learning trial. Nevertheless, what is strengthened is not a single response sequence, but a whole category of response sequences fulfilling the same goal, that is an intention. This is true even when the elicited behaviour cannot be generalized as "approach". This issue will not be discussed further here, except to point out that there are, in cortical areas 5 and 7 (Mountcastle *et al.*, 1975) and in the prefrontal cortex (Watanabe, 1989), neurones which respond during the operation of an intention, regardless of the precise motor programme which fulfills the intention on any specific instance. Thus in some way, the brain has a means of resolving this difficulty.

2.2. DEFINITIONS OF THE DISTINCTION BETWEEN REWARD AND PERFORMANCE

This distinction applies throughout studies of learning. Generally speaking, reward is a process involved in one variety of learning (viz: the acquisition of a new relation between stimulus and behavioural output, mediated by a rewarding stimulus; see earlier), while performance is the new relation between input and behavioural output that is then

acquired. In experiments on the role of dopamine on behaviour, this distinction can be made in more than one way, and the different ways are not always equivalent. One aspect of the distinction is in the *time course* of the behavioural effects of dopamine, or a drug acting on dopaminergic systems. *The performance effect of dopamine (or a dopaminergic drug) follows the onset or cessation of action of the drug immediately*: in other words, by this effect, performance should increase suddenly as soon as an agonist starts to act, and should stop equally suddenly when its actions stop. Conversely, performance measures should drop suddenly when dopamine's actions are blocked by a drug, and should be restored suddenly when a blocking drug ceases to act. On the other hand, *the internal reward function of dopamine (being part of a learning process) is one whose effects grow gradually with each instance of rewarded behaviour, and which extinguishes gradually each time the stimulus elicits responding with omission of reward, or in absence of functioning dopamine pathways.* In Fig. 1 the difference between these two concepts of the time course of dopamine's actions on instrumental responding are illustrated in schematic form.

Another way of distinguishing between reward and performance concerns the *selectivity* of the effect. An agent (such as a dopaminergic drug) which acts on performance will increase (or reduce) the vigour of all responses indiscriminately. On the other hand, the reward function (at least under many natural circumstances) strengthens the connection between a *specific* stimulus pattern and a specific behavioural output. Other response patterns will not be affected, nor will other stimuli have an enhanced ability to elicit the specified response pattern.

These two approaches to the reward/performance distinction are not equivalent. Under some circumstances a dopaminergic effect which is really an effect on the reward component of learning (for instance as defined by the time course criterion) can act indiscriminately to enhance the elicitation of many responses by stimuli. In Section 3.3 below some of these circumstances are defined. The convention will be adopted henceforth that the term *reward* will be used when the time course is that expected of a learning process. The term *performance* will be used unequivocally when *both* the time course of the drug effect is that expected of a performance effect, *and* the effect on behavioural output is indiscriminate. In the circumstances where a dopamine agonist drug produces a signal which has no temporal structure, and therefore cannot enhance specific items of behaviour elicited by stimuli at specific points of time, the terminology is more problematical. In this case the drug can only act to enhance responses indiscriminately, and therefore the last of the above distinguishing criteria cannot be applied. Such effects, will sometimes also be called "performance effects" here, but it will be clear from the context that in some of these cases we are arguing that the actual process is a special case of reward. ("Indiscriminate reward" captures this concept, though we do not wish to introduce this as additional jargon.)

In the discussion which follows, it is implicit that in reality dopamine exerts some combination of reward and performance effects. When the time course of a drug's effect can be defined, it is therefore likely to be some combination of those shown in Fig. 1A and 1B. Exactly what this combination is differs in detail according to the instrumental behaviour in question.

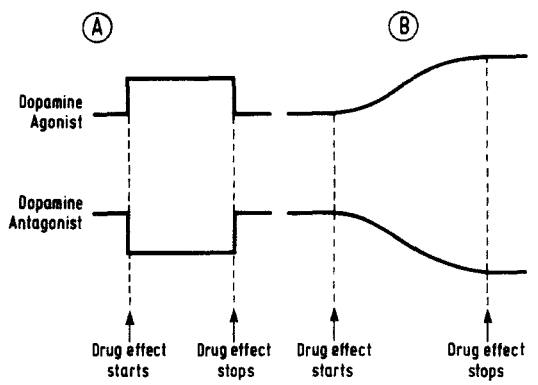

FIG. 1. Schematic illustration of the different time courses to be expected of dopaminergic drugs which act on *performance* (A) compared with those that act on *reward* (B). Dopamine agonists above, dopamine antagonists below. Time is measured horizontally, and vigour of performance of the relevant behaviour is measured vertically. (Note that in practice, drug effects on performance would never be sharp step function as depicted in A, since onset and offset of a drug's actions would be gradual, as determined by the pharmacokinetics of the drug.)

3. PRINCIPLES FOR INTERPRETATION OF EVIDENCE

To account for the complex evidence about the relative role of D-1 and D-2 receptors in learning and performance of reward-mediated tasks we require a combination of five main premises. The first of these is a new conjecture, the second a hypothesis which has been advanced elsewhere on the basis of a variety of evidence, while the other three can be supported directly by currently available experimental results. The conjectural (first) premise is thus to be evaluated by the consistency and completeness with which the new experimental data using receptor-subtype-specific drugs can be explained by this premise in conjuction with the other four.

3.1. D-1 Receptors Mediate the Reward Function

It is suggested that the internal reward signal itself is mediated by dopamine D-1 receptors. (See Section 2.1 for definition of reward.)

3.2. The Paradigm for Synaptic Strengthening During Reward-Mediated Learning

The internal reward effect is envisaged to operate by strengthening of specific synaptic connections, according to a rule which has been formulated elsewhere (Miller, 1981, 1988). This paradigm for synaptic strengthening involves two sequential processes: first there is *prior selection of synapses* (probably

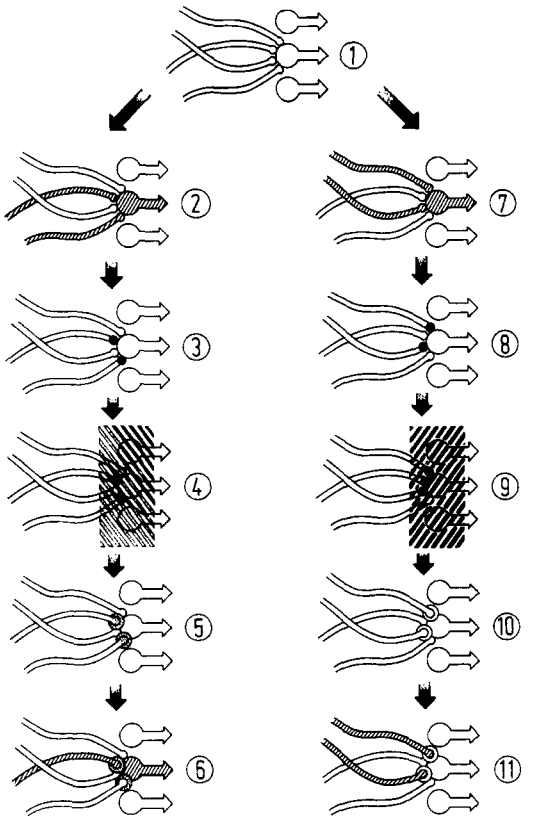

FIG. 2. Diagrammatic representation of the operation of the proposed rules for synaptic modification during instrumental conditioning. Part 1 represents one (amongst many) output neurones in the structure in which instrumental conditioning occurs. Parts 2 to 6 represent the sequence of events taking place during reward-mediated learning. Parts 7 to 11 represent the sequence of events taking place during acquisition of response suppression by punishment. Parts 2 and 7 show activation (oblique lines) of the output neurone by chance activation of inputs converging on the neurone. (Arbitrarily, two such inputs are shown.) In either case a trace of this event (the "state of readiness") remains in the activated synapses (shown as filled circles in parts 3 and 8). If the behavioural response that follows activation of the neurone is motivationally favourable, a diffuse reward signal (oblique stippled stripes) is generated (part 4), which converts the synapses already in a state of readiness into definitively strengthened synapses (dotted halo in parts 5 and 6). Subsequently it is possible to activate the neurone more easily by these synapses (e.g. with only a single active input fibre in part 6). If the behavioural response that follows activation of the neurone is motivationally unfavourable, a diffuse punishment signal (oblique black stripes) is generated which converts synapses already in a state of readiness into definitively weakened synapses (white halo, in parts 10 and 11). Subsequently these synapses are of reduced efficacy (e.g. two active input fibres are insufficient to activate the neurone). From Miller, 1988. (This figure was reproduced with permission of Hans Huber Publishers, from the book entitled *Information Processing by the Brain*, edited by Hans Markowitsch. Copyright 1988 by Hans Huber Publishers, 14 Bruce Park Avenue, Toronto, Ontario, Canada M4P 2S3.)

cortico-striatal synapses) which represent the new input–output relations which the reward signal might subsequently strengthen. These synapses would themselves have been activated as a result of the animal encountering specific environmental stimuli. However, for any such synapses to be selected, *they must have been effective in discharging a striatal neurone. When this has taken place a short-lived "state of readiness" is established* (Miller, 1981, 1988; Wickens 1989). Secondly, *if the behaviour which follows the discharge of the striatal neurone (or group of neurones) has motivationally favourable consequences, reward pathways (i.e. mesostriatal dopaminergic pathways) are activated and enhance the efficacy of transmission at synapses in which the state of readiness is still present* (cf. Beninger, 1983). Thus stimuli will tend to gradually acquire the ability to produce favourable behavioural outcomes. This schema for synaptic modification is illustrated in Fig. 2 (reproduced from Miller, 1988).

The above schema for synaptic modification is envisaged to apply to activation of synapses of the principle neurone-type throughout the matrix of the striatum (as defined by Heimer *et al.*, 1982). (Whether it should also apply to the "striosomes" embedded in that matrix [see Gerfen, 1987] is not clear at present, and is not relevant to the argument of this paper.) Reward-mediated learning is one, amongst a number of the specific functions that arises from this schema. (For discussion of other possible specific functions with the same basis, see Section 6.5.)

3.3. CONTRAST BETWEEN DIRECTLY- AND INDIRECTLY-ACTING DOPAMINE AGONISTS

Since many of the stimulus–response links to be modified are activated at highly specific points of time, in these cases reward can occur only if the dopaminergic signal can also occur at specific points in time, corresponding to the detection of motivationally-favourable consequences of behaviour. Therefore a direct-acting dopamine agonist cannot enhance or mimic this effect, because it activates dopamine receptors continuously. In fact, because it "floods" the relevant receptors over the whole time of its action, it is likely to "mask" any momentary reward signal produced by endogenous dopamine release (Miller, 1981, 1988; Beninger, 1983; Beninger *et al.*, 1989). This argument is supported by evidence about the comparative effects of direct- and indirect-acting dopamine agonists on reward-related learning: the indirect agonists, such as amphetamine, which accentuate the release of endogenous dopamine by nerve impulses, without masking its temporal patterning (Von Voigtlander and Moore, 1973; Shore, 1976) enhance the effects of reward on behaviour (Rensch and Rahmann, 1960; Banerjee, 1971; Crow, 1972; Cooper *et al.*, 1974; Robbins, 1975, 1978; Zarevics and Setler, 1979; Gallistel and Karras, 1984; Mazurski and Beninger, 1986). On the other hand the direct agonists such as apomorphine have equivocal effects on reward processes (Wauquier and Niemegeers, 1973; Liebman and Butcher, 1973; St. Laurent *et al.*, 1973; Davies *et al.*, 1974; Broekkamp and Van Rossum, 1974; Mora *et al.*, 1976; Leith, 1983; Mazurski and Beninger, 1986).

In some cases however, apomorphine *can* be shown to produce reward-related learning. For instance, it

has been shown that undrugged animals are significantly more active in environments where they have previously received apomorphine (Schiff, 1982). Such cases can be explained in the following way: the synapses which are brought into the "state of readiness" in the experimental environment would be those representing stimuli present in that environment. Since these are activated more or less continuously while the animal is in the environment, the state of readiness would exist more or less continuously in a significant population of synapses, rather than a selected few. Therefore, when apomorphine is paired with the test environment it could significantly strengthen synapses in all of this population, even though the drug exerted a tonic influence without temporal patterning. The change of responding would be an indiscriminate increase in locomotor activity, the effect produced by indiscriminate strengthening of many striatal synapses. This can be contrasted with the case of more selective dopamine-mediated learning, associated, for example, with finding a reward in a specific place. The above argument implies that, in any circumstance in which a population of cortico-striatal synapses is tonically active, the behavioural manifestation of that activity can be enhanced by drugs such as apomorphine. Such behaviour includes locomotor activity, elicited by constant environmental stimuli, or repetitive movements such as grooming, or the behaviours involved in ingesting food (for which it is also assumed there is a constant eliciting stimulus). The above argument will be used in accounting for some of the evidence about actions of dopaminergic drugs in such behavioural paradigms, for instance conditioned activity (the case just referred to) and stereotyped behaviour.

3.4. D-2 Receptors are the Main Mediators of the Performance Function

It is envisaged that the performance-enhancing effect of dopamine is mediated mainly by D-2 receptors, this effect being mediated by the actions of dopamine on cholinergic interneurones in the striatum. The detailed validation of this premise is as follows:

It is well established that dopamine acts within the striatum to inhibit the release of acetylcholine (Lehmann and Langer, 1983). (These authors also argue that dopamine acts at the cholinergic *terminals* to produce this effect, rather than at the cholinergic cell bodies. This is depicted in Fig. 3.) The primary way in which this cholinergic link modifies performance capacity may be by adjusting the stiffness of the limbs and other parts of the locomotor apparatus. This is well illustrated by the rigidity of the limbs which occurs in Parkinson's disease. Its occurrence is presumably largely (if not entirely) a consequence of failure of dopamine to inhibit cholinergic tone, since it can be alleviated by anticholinergic (i.e. antimuscarinic) drugs (Doshay, 1956; Doshay and Constable, 1957; Zier and Doshay, 1957), as well as by dopamine agonists. The catalepsy produced by dopamine antagonists in experimental animals appears to represent a stiffening of the limbs in a manner similar to Parkinson's disease, since it is also lifted by muscarinic antagonists (Morpurgo, 1962; Morpurgo and Theobald, 1964; Leslie and Maxwell, 1964; Costall and Naylor, 1974; Klemm, 1983a, 1985c). Correspondingly, cholinergic agonists can *produce* catalepsy (Costall and Olley, 1971; Costall and Naylor, 1974; Asin *et al.*, 1982; Klemm, 1983a, 1985c).

The converse effect, produced by dopamine agonists, should be a "loosening of the limbs", which enables and enhances motor performance. Although detailed evidence for this, in terms of assessment of muscle tone, is lacking, the great increase in locomotor activity and the repetitiveness of motor function during the stereotyped behaviours produced by dopamine agonists are compatible with such an action. Moreover, as expected, central muscarinic blockade mimics or potentiates these actions of dopamine agonists on locomotor activity (Harris, 1961; Pradhan and Roth, 1968) and stereotypy (Fog *et al.*, 1967; Arnfred and Randrup, 1968; Scheel-Kruger, 1970; Klawans *et al.*, 1972; Zambo *et al.*, 1972).

In a corresponding manner self-stimulation is attenuated by anticholinesterases or cholinomimetic drugs (Olds and Domino, 1969; Newman, 1972), this effect being prevented or even reversed by concurrent administration of atropine. Antimuscarinic agents also restore self-stimulation rates previously depressed by neuroleptic drugs (Stephens and Herberg, 1979). Antimuscarinic drugs given alone produce rather small accelerations of self-stimulation (Newman, 1972; Druhan *et al.*, 1989). The smallness of this effect may reflect the fact that, in these particular experiments, there was little tonic cholinergic activity to inhibit with these drugs.

Modern methods for determining whether such cholinergic effects represent changes in performance or reward value of the brain stimulus have not been extensively employed. However, as usually studied, the self-stimulation test is dominated by performance factors, and so it is likely that muscarinic blockade is acting to enhance performance, and cholinomimetics are acting to impair performance. The paper of Stephens and Herberg (1979) produces direct evidence for this: after self-stimulation responding had been completely suppressed by the neuroleptic spiroperidol, scopolamine administration partially restored it, in a step-wise fashion, to a new steady level of performance, with no subsequent extinction-like decline from this level. This seems to imply that both drugs were acting mainly on the performance variables, with little effect on reward. (On the other hand, when responding had ceased as a result of switching off the current, scopolamine enhanced performance for only a short time, followed by the expected extinction of responding. In this case there was apparently an effect of switching off the current, additional to the effect which spiroperidol could produce, which can be designated as curtailment of the rewarding effect.) Other findings support the idea that the cholinergic effects are acting on the performance rather than the reward variable: Edwards *et al.* (1979) could find no effect of scopolamine on the reward component of self-stimulation, separating this from the performance component by using a method of assessing self-stimulation which did not depend on rate of responding. Other recent papers have also demonstrated that scopolamine had no effect on the

stimulation parameters determining the threshold for self-stimulation, a measure which is thought to relate closely to the rewarding effect of the brain stimulus (Gratton and Wise, 1985; Robertson and Lafferiere, 1987). Similarly, Druhan *et al.* (1989) found that cholinomimetic drugs decreased self-stimulation rates, but did not shift the threshold parameters of stimulation. (Scopolamine *did* decrease the threshold for self-stimulation, but only marginally.)

The dopaminergic actions on cholinergic tone, upon which many of the performance effects of dopamine may depend, are mediated by D-2 receptors, according to the results of Herrting *et al.* (1980), Stoof *et al.* (1982, 1987), Scatton (1982) and Wong *et al.* (1983). However, there may be other effects of dopamine, acting via D-1 receptors, which can be easily confused with performance effects. As explained above, enhanced stimulation of dopamine receptors (hypothetically the D-1 subtype) can produce conditioned activity and other indiscriminate enhancement of behavioural output, an affect which, in behavioural terms is akin to a performance rather than a reward effect, although the mechanism can be explained as a special case of reward. In addition it is established that L-DOPA therapy in Parkinson's disease produces benefits beyond those produced by anticholinergic drugs, again suggesting that D-1 receptors (or at least dopamine receptors not linked to cholinergic neurones) contribute to motor performance.

The precise mechanism of control of stiffness versus looseness of the limbs is not clear at present, but the key variable may be the degree to which antagonist muscle pairs are controlled in reciprocally inhibiting fashion as opposed to co-activation. Hayashi *et al.* (1988) for instance have shown that the normal pattern of reciprocal inhibition in antagonist muscle pairs gives way to reciprocal facilitation in Parkinsonian patients. A possible central determinant of this is the degree to which neurones in the striatum are constrained to fire in a reciprocally-inhibiting manner or with co-activation of neighbouring neurones. A little electrophysiological evidence for this exists: Rebec and Curtis (1988) showed that infusion of the excitatory amino acid glutamate into the striatum produced reciprocal zones of excitation and inhibition, this pattern being abolished by the D-2 antagonist haloperidol. This effect is formally similar to the abolition of reciprocal inhibition of antagonist muscle pairs in Parkinson's disease, and may be the central representation which governs whether reciprocal inhibition of co-activation of antagonistic muscle groups occurs. (It has also been shown that, in Parkinsonian monkeys, populations of pallidal neurones exhibit much more uniform tonic discharge compared with the relatively selective firing of neurones there under normal circumstances [Filion *et al.*, 1988].)

These results have been developed further in a recent simulation study of a model striatal network (Wickens and Miller, submitted). This model consisted of principle neurones with mutually inhibitory connections. It was shown that a switch from reciprocal inhibition to co-activation of the model neurones could be achieved by progressively raising potassium conductance in them. Although there is no decisive experimental evidence of the biophysical effects produced by acetylcholine in the striatum, such a change in potassium conductance is a plausible consequence of increased cholinergic tone. If this were the case, the net effect of dopamine acting via D-2 receptors and the cholinergic link would be basically excitatory, with resultant increase in competition between striatal output neurones. Acting via D-1 receptors and the postulated strengthening of corticostriatal connections, dopamine would also have a net excitatory effect. Thus the actions at D-1 and D-2 receptors would in many respects be *synergistic*.

3.5. THE FEEDBACK TO THE D-1 RECEPTOR OF THE MOTIVATIONAL EFFECTS OF D-2-SELECTIVE DRUGS ON PERFORMANCE

The relative stiffness or looseness of the limbs is itself envisaged to be of motivational significance. Specifically, loosening of the limbs should be regarded as a motivationally favourable state, accompanied by increased firing of the midbrain dopamine neurones, while stiffening of the limbs is to be regarded as a motivationally unfavourable state, accompanied by reduced firing of midbrain dopamine neurones.

The exact neural pathways by which loosening of the limbs can activate the midbrain dopamine neurones is uncertain, and is probably both complex and indirect. One possibility is that *sensory input from proprioceptors in the limbs* can activate dopamine neurones when the limbs are capable of moving freely, and reduces their firing if the limbs are stiff. This conjecture is supported by some of the reports of subjective effects of stimulant administration in man, where the sudden euphoriant effect appears definitely to be referred to the body. For instance, Lasagna *et al.* (1955) describe patients whose self-report included phrases such as: "Suddenly my body felt light"; "An 'all-over' good feeling"; "A sense of well-being came over me". Likewise Harris *et al.* (1963) include, in their empirical checklist for subjective effects of amphetamine, items such as: "My hands feel light"; "My head feels light"; "I have a floating feeling". Conversely, it is well known that antipsychotic drugs sometimes have a definite dysphoric effect, which may arise mainly from persistent extrapyramidal side effects of these drugs (Singh and Smith, 1973; Van Putten, 1974). An implication from this line of argument is that the "stimulus properties" of dopaminergic drugs which act at D-2 receptors, as studied in drug discrimination experiments, should depend to a significant extent on true sensory stimuli arising in the peripheral nervous system. While there is no proof of this at present, the data presented in Section 5.14 below show that D-2 agonists have stronger discriminative cues for an animal than do D-1 agonists. This may thus be an indication that true sensory stimuli are involved.

Another way in which loosened limbs could activate dopamine neurones may be that the vigorous movement which is permitted when the limbs are loosened is rewarding *for more global reasons*. Although it may seem implausible that action *per se* (regardless of its consequences) could be rewarding, this idea has support from several different empirical approaches. For instance Premack (1962, 1963) has shown that the opportunity to perform specific

classes of active behaviour may be in itself rewarding, regardless of the consequences of the behaviour. Thorpe (1962) writing from an ethological perspective defines a concept of "action specific energy" which has much the same implications as the Premack principle, namely that there may be a specific motive driving performance of specific actions, even if the usual motivational consequences of those actions cannot occur. Routtenberg and Kuznesof (1967) showed that rats housed in running wheels, with limited access to food, ran in the wheels so much that they did not maintain their body weight, and died of starvation, whereas those housed in ordinary cages could maintain their weight. This result suggests that the chance to run was in itself rewarding, and competed with the rewards associated with feeding. Interestingly, the self-starvation was reduced in animals given the dopamine-blocking drug chlorpromazine. The idea that action *per se* is itself rewarding also has neurochemical support: many studies have reported increased levels of dopamine in various brain regions following the performance of motor tasks (Yamamoto and Freed, 1982, 1984; Freed and Yamamoto, 1985; O'Neill and Fillenz, 1985a,b; Church *et al.*, 1986; Speciale *et al.*, 1986; Hayes *et al.*, 1988).

There is no electrophysiological evidence that blocking or activation of striatal dopamine receptors in *free moving rats* actually does control the firing of the midbrain dopamine neurones in the manner envisaged. Groves *et al.* (1975) microinjected haloperidol into the caudate nucleus of *paralyzed* rats. They showed that this led to a prolonged decrease in firing of neurones in the pars compacta of the substantia nigra. Conversely, microinjection of amphetamine into the caudate led to prolonged increase in firing of neurones in this region. It would be predicted that the same results should be obtainable in free-moving rats, and these effects should be more prominent than in the experiments of Groves *et al.*, and perhaps obtainable with systemic as well as with intracerebral injections.

Given that activation of striatal D-2 receptors, and its consequent changes on the locomotor apparatus, can produce such indirect rewarding effects, it follows that any behaviour which succeeds in loosening the limbs (e.g. a behaviour which delivers a D-2 agonist drug) will also increase the activity of the dopaminergic neurones and strengthen the response-eliciting ability of those stimuli associated with this effect. Such an effect would not however be possible if the pharmacological receptors on which reward is supposed to depend (i.e. the D-1 receptors) were either blocked by an antagonist, or masked by a direct agonist drug.

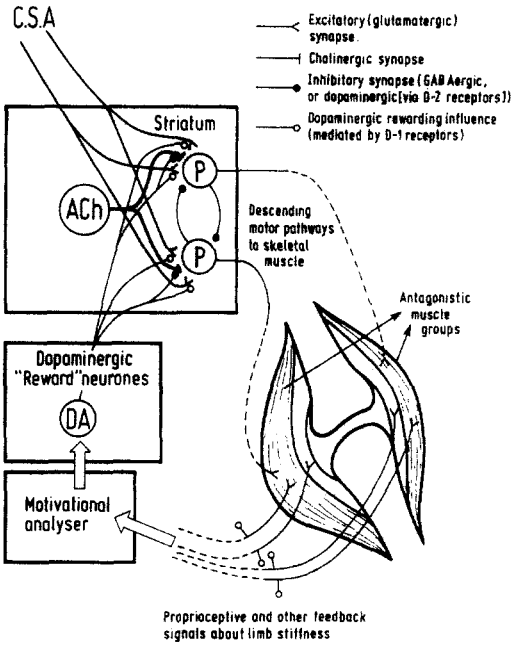

FIG. 3. Schematic illustration of the relation between the reward function (hypothetically mediated by D-1 receptors) and the performance function (hypothetically mediated mainly by D-2 receptors). In the large rectangle are shown two of the principle neurones of the striatum (both labelled "P"). These have mutually inhibitory links. In addition is shown a larger neurone ("ACh") representing the striatal cholinergic interneurone population. Tonic activity in this neurone-type influences the principle neurones, so that mutual inhibition gives way to co-activation. The dopaminergic input to the striatum is represented by the axon DA. It has two actions: (a) it reduces cholinergic tone by an action on the terminals of the cholinergic interneurones; (b) it can strengthen synapses of cortico-striatal axons (CSA) on the principle neurones, according to rules for reward-mediated learning such as those depicted in Fig. 2. In the lower right of the figure is depicted a typical joint in one of the limbs controlled by the above region of the striatum. When striatal neurones fire competitively (high dopaminergic tone, low cholinergic tone) reciprocal inhibition of antagonist muscles prevails, leading to free movement in the joint. In contrast, when striatal neurones are co-activated, antagonist muscles are also co-activated, leading to limb rigidity. These two states of the joint are monitored by proprioceptive and other sensory afferents. By way of a "motivational analyzer" these sensory signals can control dopaminergic tone, so that overall stiffness of the joints causes a slowing of the firing of midbrain dopaminergic neurones, and freely moving limbs causes an acceleration of their firing.

4. COROLLARIES DERIVED FROM THESE PREMISES

To summarize these five premises, the relation between D-1 and D-2 receptors in reward and performance defined in Section 3 is illustrated schematically in Fig. 3. Clearly a variety of complex feedback effects become possible given these relations. Hence a number of further predictions can be made:

(i) Both D-1 and D-2 agonists can activate the *reward* mechanism, the former directly, the latter indirectly. In some circumstances, D-2 agonists may be the more potent of the two, since they do not mask the natural reward signal. However, since dopamine D-1 receptors are the "final common pathway" for reward, D-1 antagonists should prevent reward effects, however they are initiated.

(ii) The *performance* effects of dopamine can be divided into two pharmacologically different-

components. Aspects of performance that are controlled by cortico-striatal projections under the modulating influence of dopamine may be impaired by D-1 antagonists, and enhanced by the activation of D-1 receptors.

(iii) On the other hand, aspects of performance that depend more directly on the stiffness/looseness of the limbs are likely to be controlled independently, via the D-2 receptors. Dopamine D-2 agonists should primarily improve this latter aspect of performance, and D2 antagonists should impair it.

(iv) Thus, the predicted effects of receptor-selective agonists would at first sight appear *not* to support the hypothesis that D-1 receptors mediate reward: D-1 agonists should *impair* reward functions by masking the normal reward signal (except in the case of on-going or repetitive responses where precise timing of the reward signal is not critical). D-2 agonists should improve performance variables. In addition, by increasing the firing of dopaminergic neurones they should be able, under some circumstances, to enhance reward effects.

(v) The true nature of the reward effects apparently dependent on D-2 receptors would be revealed by further pharmacological analysis: this reward effect would be dependent on the actual firing of midbrain dopamine neurones and on the intactness of dopamine synthesis within them. (Evidence of this is presented in Section 5.) This identity of the receptors which ultimately mediates such reward effects would be indicated by the action of concurrently-administered antagonists: D-1 (as well as D-2) antagonists should be able to block these enhanced reward effects. In addition, it is possible that, in appropriate doses, the reward effects of D-2 agonists would be impaired by anticholinesterase drugs, since they would potentiate the suppressed cholinergic effects back towards normal levels. Antireward effects of D-2 antagonists should be lifted by concurrent administration of muscarinic antagonists, because such drugs provide an alternative method of suppressing cholinergic tone, suppression normally carried out by dopamine acting at the D-2 receptors. In all these respects the reward effects of drugs acting on D-2 receptors are different from those of corresponding drugs acting at D-1 receptors.

(vi) A further prediction from the schema shown in Fig. 3 is that the stimulatory effects of muscarinic blockers, like those of D-2 agonists, should be dependent upon the intactness of DA synthesis, and on the consequent activation of D-1 receptors.

(vii) When either D-2 antagonists or D-2 agonists are administered, they will change the pattern of firing of striatal neurones. In the former case there will tend to be co-activation of neighbouring neurones (corresponding to the rigidity in the joints they control). In the latter case there will tend to be reciprocal inhibition (corresponding to free movement in the joints they control) (Wickens and Miller, submitted; Rebec and Curtis, 1988; see Section 2.4). In *either* case, provided the D-1 receptors are not blocked or masked, there is the possibility that the characteristic firing pattern can become conditioned to on-going afferent input, using the premises described in Section 2.2 (illustrated in Fig. 2). Since drugs which act on D-2 receptors change not only the motor output, but also the consequent proprioceptive input, these conditioning processes can link the characteristic firing pattern of striatal neurones, not only to exteroceptive afferent input, but also to the proprioceptive input which obtains at the time the drug is active. Altogether, the behavioural effects of both D-2 agonists and D-2 antagonists may be expected to undergo enhancement (i.e. to show "sensitization"), or other changes if the drug tests are repeated in the same stimulus conditions. Examples of this, for both D-2 agonists and antagonists are analyzed below.

(viii) Since D-2 agonists can activate the dopamine neurones indirectly, which in turn will activate both the D-1 and the D-2 receptors there is a possibility that positive-feedback processes may occur when D-2 agonists are administered. Bearing in mind that conditioning effects might be possible with repeated administration of D-2 agonists (see [vii] above), behavioural pathologies seen with acute administration of dopamine agonists may be expected to become more severe with repeated administration.

(ix) At this point it is appropriate to point out that the five premises of Section 3 are not yet a comprehensive basis for understanding the striatum. There are many facts about the striatum which cannot readily be encompassed by these premises. For instance, D-1 agonists such as SKF 38393 can sometimes act synergistically with D-2 antagonists such as spiperone to increase dopamine metabolites in the striatum (Saller and Salama, 1985), while D-1 antagonists attenuate this action of D-2 antagonists (Saller and Salama, 1986). D-1 antagonists can have effects on cholinergic mechanisms (increase of ACh levels) the opposite of those produced by D-2 antagonists (decrease of ACh levels) (Scatton and Fage, 1986; Consolo *et al.*, 1987). These results indicate that an *antagonism* between D-1 and D-2 receptor mechanisms exists under some circumstances, which is different from the synergy envisaged in the above five premises. Some of these results may involve the autoreceptor actions of D-2 agonists and antagonists, which are opposite in sign to the post-synaptic actions discussed in Section 3.

Another aspect of the above premises which is undoubtedly a simplification of reality is the implicit assumption that striatal function is homogeneous and unitary. While the overt action of dopamine antagonist drugs given systemically is to produce limb stiffness, and of dopamine agonist drugs is to produce activation, more complex results are produced by local intrastriatal injection of such drugs. Arnt (1985) and Koshikawa *et al.* (1987, 1989) have found that the D-2 antagonist sulpiride can block apomorphine-induced stereotyped behaviour if it is injected into the ventral striatum, but paradoxically potentiates it if injected into the dorsal striatum. Thus there seems to be regional differentiation of function in the striatum with some regions generating stereotypy in response to D-2 agonists and others opposing stereotypy.

Despite these, and other complicating factors, we believe that the above premises can account for a very large amount of the available experimental data. Although they may require amendment in detail, they nevertheless define important aspects of striatal function.

5. REWARD AND PERFORMANCE COMPONENTS IN A VARIETY OF BEHAVIOURS IN RELATION TO DOPAMINE RECEPTOR SUBTYPES

Amongst the many behavioural measures to which dopamine is related, the relationship of reward to performance varies considerably according to the behaviour under study. Therefore, in the following paragraphs, for each such type of behaviour, it is necessary to discuss first the behavioural paradigm itself, in order to understand the relation of the behaviour to reward and/or performance. Only then can the detailed evidence about the effects of drugs influencing D-1 and D-2 dopamine receptors be discussed. Some of the paradigms are more suitable for the test of antagonists, some for agonists. As suggested in Section 4, the effects of dopamine agonists can sometimes be analyzed in more detail by challenging the animals with receptor-specific antagonists. The effects of both dopamine agonists and antagonists can be analyzed using cholinergic drugs. In the various parts of Section 5, the reader may notice one significant omission: there is no discussion of the rotatory movements and other types of asymmetry seen when dopamine agonists are given to animals with unilateral dopamine denervation. While these phenomena are certainly relevant to the case being developed in this paper, their interpretation is made very complex because a number of other issues (which are not the otherwise involved here) requiring resolution before a consistent explanation can be presented. These matters will be considered elsewhere (Miller, Wickens and Beninger, in preparation). To aid the reader who is unfamiliar with the various classes of antagonists and agonists at dopaminergic and cholinergic synapses, all drugs mentioned are listed and classified in Appendix 1.

5.1. Unconditioned Effects on Locomotion

Locomotor activity is clearly related mainly to performance variables rather than to reward effects. According to the hypothesis that D-2 agonists loosen the limbs, such drugs would be expected to make possible an increase in locomotion. Conversely, D-2 antagonist should remove this possibility. However, in addition to loosening the limbs, an adequate level of overall afferent input might be needed for this potentiality to be realized. Evidence that this is the case comes from the study of enhancement of locomotion by apomorphine (as documented by Maj *et al.*, 1972, and by Thornburg and Moore, 1974): rats with a unilateral head bandage show rotatory locomotion when injected with apomorphine (Szechtman, 1983). This result implies that the locomotor stimulation by apomorphine is a result of the enhancement of the ability of whatever stimulation remains intact to elicit locomotion. One of the arguments presented above suggested that general enhancement of the strength of linkage of sensory cues to response output could increase locomotion, and this should be achieved by D-1 agonists. Thus for the locomotor stimulant effect of D-2 agonists to appear, there may also be needed a certain level of tonic D-1 receptor stimulation.

A variety of experiments shows that, as predicted, D-2 agonists are potent stimulants of locomotion (McDevitt and Setler, 1981; Beninger *et al.*, 1985; Starr and Starr, 1986b, 1987; Johansson *et al.*, 1987). This effect depends on synthesis and release of dopamine, and on functioning D-1 receptors. For instance alpha-methyl-*p*-tyrosine blocks the locomotor stimulation produced by bromocriptine (Johnson *et al.*, 1976) or quinpirole (Walters *et al.*, 1987; Arnt *et al.*, 1987; Braun and Chase, 1986). Likewise SCH 23390 blocks these stimulatory effects of D-2 agonists (Pugh *et al.*, 1985; Molloy *et al.*, 1986). Interestingly, it has been shown (Thornburg and Moore, 1973) that the locomotor stimulation produced by muscarinic blockers is also dependent on dopamine synthesis.

D-1 agonists certainly have less obvious effects on locomotion than the D-2 agonists. McDevitt and Setler (1981) for instance saw only small increases of locomotion when adult rats were administered SKF 38393 unless very large doses were given. It has been noted that this small stimulatory effect is seen best in animals that are already very well habituated to the test environment (Beninger *et al.*, 1985; Molloy and Waddington, 1985a, 1987; Molloy *et al.*, 1986). When it occurs, the locomotion is not continuous as it is with D-2 agonists, but resembles more the natural exploratory locomotion seen by an animal on first being introduced to a new cage (Molloy *et al.*, 1986). Both D-1 and D-2 antagonists can prevent this locomotor stimulation (Molloy and Waddington, 1985a). D-1 antagonists also suppress spontaneous locomotion (Hoffman and Beninger, 1985). These findings are in accord with predictions: the D-1 agonist may increase the efficacy of environmental stimuli to activate locomotion, giving such stimuli the same characteristics as they might have in a novel environment. This is, as expected, prevented by D-1 antagonists. Likewise the exploratory component of spontaneous locomotion, seen in the first hour in a new cape, is markedly reduced by SCH 23390 (Hoffman and Beninger, 1985). There is no abnormal facilitation of locomotor performance *per se* by D-1 agonists, as found with D-2 agonists, though reduction of normal performance capabilities with D-2 antagonists will prevent the response.

5.2. Stereotypy

When animals are administered moderate to large doses of dopamine agonists (either direct agonists such as apomorphine, or indirect agonists such as amphetamine) they exhibit a complex pattern of repetitive behaviour, generally known as "stereotyped behaviour" (Amsler, 1923; Randrup and Munkvad, 1966, 1968; Ernst, 1967). The precise phenomenology of this varies from species to species (Randrup and Munkvad, 1967). In rats it includes (in addition to the increased locomotion described above), rearing, head movements and sniffing, and also various items of repetitive oral behaviour—licking, biting and gnawing. Under some circumstances the locomotion, head movements and rearing predominate at moderate drug doses, while the oral behaviour comes to predominate at the higher doses, accompanied by decreased levels of locomotion. For this reason several groups (Ernst, 1967; Costall and

Naylor, 1973; Schneiden and Cox, 1976; McDevitt and Setler, 1981) have used a rating scale in which locomotor activity with sniffing behaviour characterizes the less intense measures of stereotypy, while gnawing, with a decrease or cessation of locomotion, characterizes the more intense measure. The latter pattern is seen either at the peak of the time course of a drug's action, or at the upper end of the dose–response curve.

However, even before the availability of receptor-specific agonists and antagonists, there were indications that the locomotor and the oral aspects of stereotypy should be rated independently. Janssen *et al.* (1967) used separate rating scales for these two aspects, and found that different neuroleptic drugs had some selectivity in antagonizing ratings on one or other of these scales of effects produced by dopamine agonists. Ljungberg and Ungerstedt (1977a,b) also rated separately the locomotion-sniffing and the gnawing components. They found that locomotion and sniffing were not influenced much by details of experimental design, but the gnawing component was much more susceptible to such variations. For instance, animals not well habituated to the test environments showed much less gnawing behaviour than those who were habituated. Gnawing was also dependent on availability of objects for the rats to gnaw, and in the absence of such objects, stereotyped licking took place instead. Szechtman *et al.* (1985) give a detailed phenomenological account of the locomotor aspects of stereotypy, seen when animals were tested in absence of objects which activated gnawing. At the peak of the time course of a drug's action, locomotion was still suppressed, although locomotor stimulation was prominent at earlier stages of the drug's action.

The precise relation of these patterns of behaviour to reward processes has been somewhat uncertain. Robbins (1976) has shown that items of behaviour which under normal circumstances are examples of goal directed (i.e. reward-producing) behaviour can become incorporated into stereotyped behaviour when the animals are under the influence of dopamine agonists. In this case they are no longer sustained by the actual rewarding effect of the response item. In other words, at least some aspects of stereotypy are a perseverative manifestation of responses to stimuli that were once rewarded.

With the advent of receptor-specific dopamine agonists, it has become clearer that the phenomenology of stereotyped behaviour can be subdivided. D-2 agonists produce stereotyped locomotion, head movements, rearing and sniffing (Walters *et al.*, 1987; Arnt *et al.*, 1987, 1988; Molloy *et al.*, 1986; Longoni *et al.*, 1987b; White *et al.*, 1988) and (according to Longoni *et al.*, 1987a,b) yawning, genital grooming and licking, but not the full complement of oral behaviour including biting/gnawing. These D-2 mediated affects appear to be partly indirect ones, since they are reduced or abolished by D-1 as well as by D-2 antagonists (Molloy *et al.*, 1986; Longoni *et al.*, 1987b), and also by the suppression of dopamine synthesis and/or release by alpha-methyltyrosine (Walters *et al.*, 1987; Longoni *et al.*, 1987b; Arnt *et al.*, 1988) or reserpine (Longoni *et al.*, 1987a). D-1 agonists such as SKF 38393, given alone, produce far less dramatic effects (Setler *et al.*, 1978; Ongini *et al.*, 1985; Braun and Chase, 1986; Walters *et al.*, 1987; Arnt *et al.*, 1988). However, according to Pugh *et al.* (1985), Molloy and Waddington (1985a) and Molloy *et al.* (1986), this drug produces non-stereotyped (i.e. non-continuous) bouts of sniffing, rearing and locomotion, interspersed with bouts of grooming. Many other workers have described grooming in rodents after administration of SKF 38393 (Ongini *et al.*, 1985; Braun and Chase, 1986; Arnt *et al.*, 1987; Fletcher and Starr, 1985; Starr and Starr, 1986a; Meller *et al.*, 1988; White *et al.*, 1988). All these D-1 related effects appear to be direct ones, since they are antagonized by the D-1 antagonist SCH 23390 but not by D-2 antagonists (Molloy and Waddington, 1985a).

In order to produce the full complement of stereotyped behaviour, such as is produced by apomorphine or amphetamine (and including the oral components), both D-1 and D-2 agonists must be administered together (Walters *et al.*, 1987; Arnt *et al.*, 1987, 1988; Longoni *et al.*, 1987b; White *et al.*, 1988; see also Meller *et al.*, 1988). When a drug such as apomorphine is administered, the full complement of stereotyped behaviour can be prevented by either a D-1 or a D-2 antagonist (Iorio *et al.*, 1983; Molloy and Waddington, 1985a,b; Molloy *et al.*, 1986). Selective D-2 blockade in these circumstances leaves intact the grooming response (attributed to D-1 receptor stimulation), though the other components are inhibited (Starr and Starr, 1986a,b, 1987). The stereotypy produced by either the combination of D-1 and D-2 agonists, or the mixed agonists such as apomorphine can be produced unchanged even after striatal dopamine depletion (Arnt *et al.*, 1988).

This complex set of data would be difficult to predict from the initial premises described earlier. However these premises do help in giving a *post hoc* account of some important features of stereotypy. It was suggested in Section 3.3 that direct stimulation of the D-1 receptors would mask the rewarding effect of any specific item of behaviour. However items of the behavioural repertoire which were either continuous or repetitive could still be reinforced, since in both these cases, activation of the responses by sensory aspects of the environment would be enhanced, regardless of any precisely timed consequence of the response. The slight enhancement of locomotion, and of some other often-repeated aspects of the rat's behaviour by SKF 38393 seem to fall into this category. D-2 agonists on the other hand enhance those behaviours which require full range of movement at the joints of the locomotor system, i.e. behaviours such as locomotion, rearing and head movements. This action depends on at least some degree of tonic activation of the D-1 receptors, and this can be provided by the low level of tonic dopamine release (unless this is prevented). To obtain the complete phenomenology of stereotypy however, there needs to be a combination of the strong enhancement of performance, such as is seen after a D-2 agonist and the D-1-mediated rewarding effects (increasing the activation of continuous or repetitive spontaneous behavioural items by concurrent sensory stimuli). The latter component requires a higher level

of D-1 stimulation than can be provided by normal tonic dopamine release.

Some support for this analysis comes from studies of the interaction of cholinergic mechanisms in the striatum with specific dopamine receptors. Arnt *et al.* (1986) found that scopolamine could lift the blockade of amphetamine-induced stereotypy produced by D-2 antagonists, but they could not lift that produced by D-1 antagonists. With the latter drug combination, the cholinergic tone would be low (because of the inhibitory effect of the dopamine released by amphetamine), but D-1 stimulation would also be required before full stereotypy was achieved. Butkerait and Friedman (1988) produced stereotypy with apomorphine, and could block this with either D-2 or D-1 antagonists. They showed that scopolamine would partially reverse the blockade produced by either type of dopamine antagonist. However the reversal of blockade by scopolamine was somewhat greater if the blocking drug was a D-2 antagonist than if it was a D-1 antagonist. It would be interesting to repeat such experiments with more detailed phenomenological analysis. The prediction is that with the combination of amphetamine and D-2 antagonists, scopolamine would release the full stereotypy (including the oral components), because D-1 receptors would be activated by released dopamine, and the downstream effects of D-2 blockade would be reversed. With amphetamine and a D-1 antagonist low grade stereotypy would probably be undetectable (because both D-1 and D-2 activation are required for this) nor could the oral components be released by scopolamine, due to the concurrent D-1 blockade. In this context it is also relevant to mention the paper of Zambo *et al.* (1972) in which atropine was injected into the caudate nucleus of rats. Stereotyped rearing was produced, an effect similar to that of D-2 agonists (which would also block cholinergic tone) in the presence of normal dopaminergic tone.

If the functional role ascribed here to D-1 and D-2 receptors is correct, the oral aspects of stereotypy presumably require enhancement of both reward and performance capability. However it is not yet clear why it is usually the oral components (rather than sniffing or grooming) that predominate at the peak of the drug's effect. To explain these, and other unaccounted aspects of stereotypy, will require a more detailed integration of the ethological perspective with the psychopharmacological one, as well as a better understanding of the localization of representation of the different components of stereotypy in the different subregions of the striatum.

5.3. Conditioned Activity

Following this analysis of various types of apparently unconditioned behaviour elicited by dopamine agonists, we can consider the same behaviours seen as conditioned effects. The conditioned activity paradigm is one of the simplest tests of reward effects. When natural rewards (McKintosh, 1974, pp. 222–223) or brain stimulus reward (Bindra and Campbell, 1967) are given, a general increase in activity is seen. This hyperactivity becomes conditioned to the environment in which it occurs, so that subsequently the environment alone (without any reward) can elicit locomotor hyperactivity. Administration of dopamine agonists (e.g. cocaine or amphetamine) while the animal is confined in the experimental chamber can also act as a reward to produce such conditioned activity when the animal is again placed in this chamber (Beninger and Herz, 1986; Beninger and Hahn, 1983).

In this test, no particular response is selected for reward, only non-selective locomotion. The fact that D-1 agonists mask the temporal pattern of the reward signal would therefore not prevent them from accentuating locomotion elicited by stimuli in the test environment. Hence, one would expect that D-1 agonists would support conditioned activity. D-2 agonists should also increase locomotion, via an effect on performance, and would also increase firing of dopamine neurones. Since the D-1 receptor would be neither blocked nor masked, locomotor activity would be rewarded and activity conditioned to the test chamber would again be seen in the test phase.

Mazurski and Beninger (1989) reported that both SKF 38393 and quinpirole will produce conditioned activity, in agreement with predictions. If these effects depend on a primary rewarding effect at D-1 receptors they should be blocked by the D-1 antagonist SCH 23390 but (except for conditioned activity induced using a pure D-2 agonist) not by D-2 antagonists. This pattern of results holds for activity conditioned using amphetamine. Activity conditioned on the basis of SKF 38393 was, as predicted, abolished by SCH 23390, but not by metoclopramide. Activity conditioned using quinpirole was blocked by metoclopramide, but, paradoxically, not by SCH 23390. The latter finding is in sharp disagreement with the predictions made. However, it has as yet not been confirmed either by the original workers, or in other laboratories.

5.4. Climbing in Mice

When mice are injected with apomorphine they exhibit an increased tendency to climb up the sides of their cages (Protais *et al.*, 1976). This behaviour is inhibited by neuroleptic drugs, and the test has proved valuable in recognizing such drugs (Costall *et al.*, 1978a). Gerhardt *et al.* (1985) found that the D-1 antagonist SCH 23390 blocked this response at lower doses than it blocked apomorphine-induced stereotypy. However, typical neuroleptics blocked stereotypy at lower doses than climbing. Vasse *et al.* (1988) confirmed that SCH 23390 blocks this response, and showed that stimulation by both D-1 and D-2 agonists was required to elicit climbing behaviour (see also Moore and Axton, 1988).

It is interesting to consider how these results can be integrated with the idea that it is the D-1 receptor which most directly mediates rewarding effects. Ethological study of many mammals shows that a chance to observe novel stimuli is rewarding (see Barnett, 1981, pp. 211–216). In a small mammal like a mouse such an opportunity would be provided by climbing above the cage floor. The behaviour of mice which are induced to climb their cages after apomorphine administration suggests that they are

actively seeking out new stimuli: these mice continually move around while climbing (Costall *et al.*, 1978a). Apomorphine or combined D-1/D-2 activation would make novel stimuli generally even more attractive, and would thus increase the capacity of these stimuli to elicit the response which makes them visible. Since this is an effect with a strong reward component, it should be blocked by D-1 antagonists.

5.5. REVERSE TOLERANCE (SENSITIZATION) TO THE BEHAVIOURAL EFFECTS OF DOPAMINE AGONIST

When stimulant drugs such as amphetamine are given repeatedly over a number of days (and in some cases administration over a few hours is all that is required) the behavioural manifestations produced by the drug increase progressively (Meier *et al.*, 1954; Segal and Mandell, 1974; Rech *et al.*, 1975; Bailey and Jackson, 1978; Klawans and Margolin, 1975; Flemenbaum, 1979; Segal *et al.*, 1980; Rebec and Segal, 1980). According to some reports the full magnitude of this sensitization continues to grow in the period of withdrawal after a chronic regime of stimulant drugs (Hitzemann *et al.*, 1977; Kolta *et al.*, 1985). This sensitization (or "reverse tolerance") applies to several behavioural items (Robinson and Becker, 1986), though it is usually monitored by observation of the locomotor (Meier *et al.*, 1954; Segal and Mandell, 1974; Bailey and Jackson, 1978) or stereotypy (Segal and Mandell, 1974; Klawans and Margolin, 1975; Flemenbaum, 1979; Segal *et al.*, 1980) responses to a test dose of a dopamine agonist. There is some evidence that similar sensitization can occur with repeated administration of direct unselective dopamine agonist such as apomorphine (Bailey and Jackson, 1978; Wilcox *et al.*, 1980), though this has not always been found (Flemenbaum, 1979; Wooten and Cheng, 1979). Whichever type of dopamine agonist is used to generate the sensitized state, cross-sensitization occurs, that is, it can then be detected with test doses of either direct or indirect dopamine agonists (e.g. Klawans *et al.*, 1977; Bailey and Jackson, 1978). One of the more puzzling effects is that a single low dose of a dopamine agonist initially elicits items of the behaviour which are low on the commonly-used stereotypy rating scale (see Section 5.2), whereas after sensitization has occurred, the same dose elicits items at the top of the rating scale (Segal and Mandell, 1974; Klawans and Margolin, 1975; Hitzemann *et al.*, 1977; Segal *et al.*, 1980). (However see also Rebec and Segal (1980) who found that oral stereotypy fell, while head and limb movements rose as sensitization developed.) The topic of reverse tolerance to stimulant drugs has recently been reviewed comprehensively by Robinson and Becker (1986). In the following section, their review will be cited as support for many of the conclusions reached about reverse tolerance to stimulants. However, where the evidence bears most specifically on the case being developed in the present paper, individual research papers will be cited.

Robinson and Becker (1986) review the various attempts which have been made to explain the development of reverse tolerance to stimulant drugs. There is little evidence that it is mediated by proliferation of post-synaptic dopamine receptors. In fact the usual finding is a down-regulation of dopamine receptors as a result of the chronic regime, the neurochemical manifestation of a tolerance to the transmitter rather than of reverse tolerance. There seems to be no change in receptor affinity, such as might explain the shift in drug sensitivity after sensitization. Likewise behavioural sensitization can occur without change in dopamine levels or dopamine synthesis or release rates under baseline conditions. There is however some evidence that the enhancement of dopamine release elicited by a test dose of amphetamine is greater after a chronic regime of stimulant drugs, than in saline-pretreated controls. Most of the evidence for this latter effect has been obtained using *in vitro* methods of assessing the effect of amphetamine on dopamine release (Robinson and Becker, 1982; Robinson *et al.*, 1982; Kolta *et al.*, 1985), though one paper (Nishikawa *et al.*, 1983) makes similar findings using an *in vivo* neurochemical method.

A further hypothesis which has been suggested as the basis for reverse tolerance to stimulant drugs is that of autoreceptor subsensitivity: since the autoreceptors on dopamine neurones normally suppress dopamine release, subsensitivity of them would be associated with enhanced release, and might be the basis for behavioural sensitization to stimulants. According to Robinson and Becker (1986), the *neurochemical* studies which have been performed provide little support for this hypothesis. On the other hand, several *electrophysiological* studies have shown that in rats chronically pretreated with stimulant drugs, amphetamine (Kamata and Rebec, 1983, 1984a; White and Wang, 1984a) or apomorphine (Antelman and Chiodo, 1981; Kamata and Rebec, 1984b; White and Wang, 1984a) have a reduced ability to slow the firing of midbrain dopamine neurones. These studies have mainly been carried out in locally anaesthetized, paralyzed preparations (with the exception of White and Wang's and Antelman and Chiodo's studies which used chloral hydrate-anaesthetized rats). The test dose of dopamine agonist is generally applied intravenously, though in three reports (White and Wang, 1984a; Kamata and Rebec, 1985) subsensitivity to the effects of iontophoretically applied dopamine was also demonstrated. What is more, several of these electrophysiological studies have shown that the chronic regimes of stimulants may *convert an inhibitory response to the test dose* (seen in control animals) *to actual activation of neurones* (never seen in control animals, but seen for a substantial proportion of dopaminergic neurones after the chronic administration of stimulants) (Antelman and Chiodo, 1981; Kamata and Rebec, 1983, 1984a). In the case of Antelman and Chiodo's results, the activation of dopamine neurones by apomorphine was greater if several days of drug withdrawal were allowed before the electrophysiological assessment than if this experiment was conducted immediately after the last dose of amphetamine (in apparent correspondence to some of the behavioural evidence cited earlier). In addition, two of these studies (White and Wang, 1984a; Kamata and Rebec, 1984) found an increase in the spontaneous firing rate in animals chronically pretreated with stimulants. According to White and Wang (1984b) and Mereu *et al.* (1986) the faster the rate of spontaneous firing of a

dopaminergic neurone, the less sensitive it was to suppression of firing by intravenously applied apomorphine or amphetamine or iontophoretically applied dopamine. Whether this relation also applies to animals chronically treated with dopamine agonists is not clear.

Explanations which appear quite different from these have been offered by a variety of experimenters in which the sensitization is seen to be, at least in part, a *conditioning effect* (Ellinwood, 1971; Pickens and Dougherty, 1971; Tilson and Rech, 1973; Wood *et al.*, 1977; Kokkinidis and Zacharko, 1980; Post *et al.*, 1980; Hirabayashi and Alam, 1981; Schiff, 1982). In many of these cases the cues from the test environment establish links with the original drug-induced stimulation (e.g. Tilson and Rech, 1973; Post *et al.*, 1980). As an extreme example of this there are some reports where injections of a dopamine agonist were repeated in a particular environment, and subsequent *saline* injections in the same environment could elicit the behavioural activation originally produced by the active drug (Ellinwood, 1971; Schiff, 1982). In other instances (Wood *et al.*, 1977; Hirabayashi and Alam, 1981) sensitization failed to occur if the acute response to each stimulant injection was prevented. Thus there is no doubt that the behavioural effects of stimulant drugs can become conditioned to the features of the environment in which the drug is given, and both the sensory cues and the response component of the drug-induced response are involved in this process. However Robinson and Becker (1986) argue that this cannot be the whole explanation of the sensitization to the effects of stimulants. The most important part of their argument is based on the fact that sensitization can occur even when the chronically administered drug is given in the home environment, or some other distinct environment, rather than in a unique test environment.

Although the points made by Robinson and Becker are acknowledged, the premises of the present paper allow one to formulate a more plausible explanation of the reverse tolerance phenomenon in terms of conditioning processes which are somewhat more complex than those envisaged by Robinson and Becker. This revised view of the conditioning process is also readily compatible with the electrophysiological data reviewed earlier. The explanation goes as follows: the evidence already cited shows that dopamine agonists (whether receptor-specific or non-specific) can produce a behavioural response (such as stereotypy or locomotor activation) and can progressively strengthen the ability of cues associated with the experiment or the experimental environment to elicit such responses. According to premises given earlier, this strengthening should depend on D-1 receptor activation. However, when receptor non-selective dopamine agonists are given, the loosening of the limbs produced by D-2 activation will provide other distinctive sensory cues from proprioceptors. Their links with the striatal representation of the response pattern may also be strengthened by the D-1-mediated reward function. Therefore, each time the non-selective drug is injected, the link between the proprioceptive sensory cues (resulting from D-2 stimulation) and the response produced by stimulation of D-1 or D-2 receptors (or both together) will be strengthened. This may be one of the factors leading to behavioural sensitization. In addition however, since (according to the premise given in Section 3.5) the consequences of D-2 stimulation are motivationally favourable, firing of dopaminergic neurones should be increased during the drug's action, leading to further activation of both D-1 and D-2 receptors. Thirdly, since the stimulant can strengthen links between any sensory cues from the environment and the striatal output neurones, after a period of repeated stimulant administration, there will be a tendency for dopamine neurone firing to be increased even in the absence of stimulants. Altogether, there is a mechanism here for a very powerful positive feedback process to take place over repeated exposures to the drug.

This analysis fits the electrophysiological data quite well. It is plausible to suggest that the decreased effectiveness of intravenously-administered amphetamine or apomorphine in reducing firing of dopamine neurones results from the fact that the normal autoreceptor-mediated inhibition is being overridden by the proprioceptively-rewarding effect of D-2 stimulation. Admittedly reduction of the inhibitory effect of these drugs given intravenously or of dopamine given iontophoretically could be explained as autoreceptor subsensitivity, and this may indeed take place. On the other hand, the reduction of these inhibitory effects may be a complex result of increased dopamine neurone firing, since the degree of suppression of dopamine neurone firing by apomorphine or amphetamine is inversely correlated with spontaneous activity of the neurone (White and Wang, 1983b; Mereu *et al.*, 1986). Regardless of this issue, the conversion of an inhibitory response to an excitatory one cannot be mediated by autoreceptor subsensitivity, but is well accounted for by the conditioning explanation. The fact that the activation of midbrain dopamine neurones is, in some behavioural (Hitzemann *et al.*, 1977; Kolta *et al.*, 1985) and electrophysiological (Antelman and Chiodo, 1981) tests, seen most potently when some time has elapsed since the last dose of the chronic regime also fits this explanation well. This is because any receptor tolerance to the effects of chronically-administered dopamine agonists would detract from the excitatory effect, but would lessen with time after the last dose, leaving the long-lasting excitatory effects of the conditioning processes more clearly evident. The increased spontaneous activity of dopamine neurones seen after the chronic regime is also accounted for by the proprioceptive conditioning to environmental cues. Finally the fact that, after the chronic regime, a small test dose elicits phenomenology which is usually associated with a higher dose can be explained by the fact that in the sensitized animal the test dose of stimulant will actually be releasing more dopamine than in the unsensitized animal.

If this explanation is correct one would also predict that amphetamine should be capable of releasing dopamine in neurochemical tests more abundantly after a chronic regime of stimulants, than after control saline injections. This effect should occur only in *in vivo* neurochemical tests, where afferent control of dopamine neurone firing was intact. As reviewed above there is evidence for increased

stimulant-induced dopamine release, but most of this evidence has been conducted *in vitro*. The single *in vivo* study (Nishikawa *et al.*, 1983) supports the proprioceptive conditioning explanation. The other studies cited may have some other explanation (for instance an enhancement by the chronic regime of the uptake processes which allow amphetamine to act intracellularly: see Kolta *et al.*, 1985).

A small number of recent papers have investigated the relative role of D-1- and D-2-selective agonists in behavioural sensitization. Braun and Chase (1988) showed that progressive increase in locomotor activation and stereotypy to a test apomorphine injection accompanied an 18-day series of injections of SKF 38393. A similar series of injections of the selective D-2 agonist LY 171555, however, produced only tolerance to apomorphine. The latter finding can be explained if it is assumed that, in the circumstances of these experiments, there was only a low level of dopamine release during the action of the chronically administered D-2 agonist, and therefore relatively little stimulation of D-1 receptors. If both agonists were given together for 18 days, sensitization again developed, but it was phenomenologically different from that after a chronic regime of SKF 38393 alone: with SKF 38393 alone, the augmented behaviours included only oral items, licking, biting and gnawing. With the combined chronic regime, augmented items included stereotypy, and repetitive limb and head movements, but not the oral items. These findings seem to indicate that, with the D-1 agonist, only certain items of repetitive behaviour which tend commonly to occur spontaneously will show augmentation. With the combined chronic administration of D-2 as well as D-1 agonists the fuller movements, whose performance is enhanced by acute administration of the D-2 agonist, will show further augmentation as the drug combination is repeated.

Under some circumstances repeated administration of D-2 selective agonists alone can also lead to sensitization. Nauseida (1978) and Rouillard *et al.* (1987) showed this with chronic regimes of bromocriptine, although the sensitization was less marked than during similar administration of the receptor-non-selective drug L-DOPA. Martin-Iverson *et al.* (1988) showed that the D-2 agonist PHNO led to tolerance of the locomotor response if it was continuously infused during the daytime, but during continuous night-time infusion reverse-tolerance of this response developed. Likewise continuous stress (noise) given during the course of a daytime infusion of PHNO was also accompanied by progressive increase in the locomotor response. These examples of sensitization were similar to the effect of combined infusion of PHNO and SKF 38393. The first result can be explained by the hypothesis that at night rats have a higher level of dopamine release (O'Neill and Fillenz, 1985b). It would also be expected that, during noise-induced stress, dopamine release would also be higher and there is evidence that in some strains of rat this is true (Scatton *et al.*, 1988). (Other intense exteroceptive stimuli also increase dopamine release, according to Keller *et al.* [1983] and Speciale *et al.* [1986]. Under these circumstances, as during concurrent D-1 agonist administration, the behavioural activation by a D-2 agonist can establish strong links to sensory cues via reward mechanisms acting at the D-1 receptor. From this analysis it would be expected that the experiments of Nauseida (1978) and Rouillard *et al.* (1987) were conducted under circumstances where there was some tonic dopamine release. However, the authors do not state the time of day or night at which the chronic drug injections were given.

5.6. CATALEPSY

Catalepsy is a phenomenon in which animals placed in unusual postures, will maintain these postures for some time, before normal movement is resumed. Catalepsy thus appears to be a form of rigidity, arising from co-activation of antagonistic muscle groups. It is a well-known effect following administration of neuroleptic drugs. According to the arguments presented in Section 3, catalepsy should be the classic case of performance being impaired by D-2 antagonists. In reality the situation is considerably more complex than this: catalepsy can be produced by D-1 antagonist (Christensen *et al.*, 1984; Meller *et al.*, 1985; Morelli and Di Chiara, 1985; Amalric *et al.*, 1986; Calderon *et al.*, 1988; Klemm and Block, 1988) as well as by D-2 antagonists (Ahtee and Buncombe, 1974; Elliott *et al.*, 1977; Usuda *et al.*, 1981; Christensen *et al.*, 1984; Klemm, 1985a; Ogren *et al.*, 1986; Klemm and Block, 1988). As expected, the catalepsy induced by D-2 antagonists is lifted by concurrent administration of muscarinic antagonist (Morpurgo, 1962; Morpurgo and Theobald, 1964; Leslie and Maxwell, 1964; Costall and Naylor, 1974; Klemm, 1983a, 1985c).

In contrast, the evidence that D-1 antagonists can also produce catalepsy appears to conflict seriously with the premises put forward earlier. However, the evidence is clarified by several papers (Morelli and Di Chiara, 1985; Kistrup and Gerlach, 1987; Ogren and Fuxe, 1988; Undie and Friedman, 1988) which show that the catalepsy or other motor effects produced by SCH 23390 are reduced or abolished by anticholinergic agents. It is also lifted by concurrent administration of D-2 agonists such as pergolide, lisuride or bromocriptine (Morelli and Di Chiara, 1985; see also Meller *et al.*, 1985) and potentiated by alpha-methyltyrosine. In other words, the final pathway by which D-1 antagonists produce catalepsy is by reducing D-2 inhibitory effects on cholinergic neurones or (equivalently) by increasing cholinergic tone. (N.B. The doses of SCH 23390 which produce catalepsy are considerably smaller than those which *decrease* cholinergic tone, discussed in Section 4, (ix).) We already have reason to believe that activation of D-1 receptors accentuates the effect of afferent input to the striatum. Therefore it is plausible to suggest that D-1 antagonist would reduce the activation of the striatum by such afferents. Following the reasoning of Secton 3.5, this should reduce movement generally, and since this is motivationally unfavourable, it would cut down the activation of dopaminergic neurones. Under these circumstances, reduced D-2 activation can be an indirect consequence of administration of D-1 antagonists. Support for this conjecture comes from evidence that catalepsy can be produced in undrugged mice by repeated restraint ("animal hypnosis") (Klemm, 1983b), and this is facilitated by

administration of a muscarinic agonist, and hindered or prevented by administration of atropine.

A further complication regarding catalepsy is the so-called "repeated measures effect". A number of papers have shown that the intensity and duration of the cataleptic response to haloperidol is greater if the catalepsy test is repeated frequently, than if it is only carried out once per animal (Stanley and Glick, 1976; de Sousa Moreira *et al.*, 1982; Klemm, 1985a; Hillegaart *et al.*, 1987). These results were obtained using haloperidol in doses from 0.4–4 mg/kg i.p. This drug has a 30-fold greater affinity for the D-2 receptor than for the D-1 receptor (Andersen *et al.*, 1985, 1986). There is one published report which directly compares the cataleptogenic response produced by the D-1 antagonists SCH 23390 with that produced by haloperidol and other typical neuroleptic drugs (Undie and Friedman, 1988). The former effect was very much shorter-lived than the latter, a difference which could not be explained in pharmacokinetic terms. In addition it has been noticed that catalepsy produced by a single dose of haloperidol, and other typical neuroleptics may sometimes be quite long-lasting (with peak effects at 3–5 hr after injection) (Christensen *et al.*, 1984) whereas that produced by SCH 23390 peaks at 30–60 min (see also Calderon *et al.*, 1988). However the long-lasting catalepsy produced by haloperidol is affected by testing method: catalepsy is more likely to be short-lasting if the duration of the cut-off point in a single test is short (150 sec in Hillegaart *et al.* (1987)) rather than if it is long. The short-lived catalepsy produced by SCH 23390 (Undie and Friedman, 1988) was similar in duration to catalepsy produced by haloperidol under conditions of single testing with quite short cut-off points for each test (cf. Hillegaart *et al.*, 1987).

The "repeated measures effect" and the influence of the duration of the cut-off point in individual catalepsy tests on the duration of catalepsy, might be explicable in terms of a reward-mediated conditioning effect. If catalepsy represents co-activation of functionally antagonistic muscle pairs, it is likely that the striatal neurones which control it also show co-excitation, rather than mutual inhibition. According to the premise in Section 3.3, activity in striatal neurones which is accompanied by a "reward" effect (stimulation of D-1 receptor) will become strengthened by repetition of the concurrent events. Pure D-2 antagonists may produce catalepsy without impairing the "reward" process, consequent on tonic dopamine release. Indeed, since they enhance dopamine release by their action on autoreceptors, they may enhance the reward process, compared with the undrugged state. Therefore the motor signals in the striatum which generate catalepsy can become linked by this reward signal to the sensory conditions in which they habitually occur (the apparatus in which the drug is given, or the circumstances associated with drug injection). Any catalepsy produced by D-1 antagonists, however, could not be so conditioned, because the reward signal upon which the conditioning depends is abolished. The supposition that reward-mediated conditioning plays a role in these effects is strengthened by the finding of de Sousa Moreira *et al.* (1982) that after repeated testing of haloperidol-induced catalepsy, a saline injection alone can induce catalepsy 15 days later in animals tested in the environment of the earlier tests. Further support for this analysis comes from the evidence of Klemm (1985b) who found that mild catalepsy produced by haloperidol could be intensified and lengthened by concurrent administration of apomorphine (4 or 8 mg/kg), whose effect could have been exerted only at D-1 receptors. A similar effect has been seen with the D-1 specific agonist SKF 38393 and the D-2 antagonist raclopride (Ogren and Fuxe, 1988). Bromocriptine, a D-2 selective agonist, could not replicate this effect. The only reported exception to the "repeated measures effect" is from Costall *et al.* (1978b). However, in their experimental protocol, the maximum observation time at each test of catalepsy was 20 min, much longer than in any of the other reports. Catalepsy maintained for such lengthy periods (in many of their animals) could plausibly be regarded as allowing the conditioning effects usually found only in repeated tests to develop even in a single test. No further enhancement of catalepsy could then occur with repeated testing.

Although the empirical evidence does point to the involvement of a conditioning effect in the "repeated measures effect", two considerations make us suspect that the explanation offered above is not yet complete: (i) the doses at which the repeated measures effect (putatively a reward effect) has usually been seen are higher than the doses of the same drug which will *suppress* reward effects in other tests, hypothetically by an indirect effect on D-1 receptors (see Sections 5.9 and 5.13 later). (There are however no data which would allow a rigorous comparison of the dose/response relations for these two effects, so one cannot yet identify a definite contradiction here); (ii) in a simulation study (Wickens, unpublished) progressive increase of strength of the corticostriatal synapses (such as might be produced by a reward process) always led ultimately to increase of competition between the principal neurones, even when cholinergic tone was high. One possible additional factor in the repeated measures effect, which may resolve these discrepancies, is that the corticostriatal input to the cholinergic interneurones may also participate in conditioning processes. However, there is as yet no direct evidence for this.

5.7. Conditioned Reward

In this paradigm, the training stage involves a neutral stimulus (e.g. a tone) which is paired with reward (e.g. food, brain stimulation reward, or drug) and subsequently the animals are presented with the neutral stimulus alone, to assess whether it has acquired rewarding properties. Usually a chamber with two levers is used. In the training phase, pressing of one of these delivers both reward and a distinctive stimulus, the other delivers no reward and a different distinctive stimulus. In the test phase the reward is no longer delivered by pressing the first lever, but both of the distinctive stimuli continue as before. In normal circumstances, the lever producing the stimulus previously associated with reward is pressed more frequently than that producing the other stimulus. Since the response is identical for both levers, any

difference in pressing between the two levers during the test phase cannot be a performance effect, but a relatively pure measure of the relative rewarding propensity for the two stimuli.

According to the premises discussed in Section 3, one would expect that D-1 antagonists would abolish the differential pressing by blocking the rewarding effect of the reward-associated stimulus. D-2 antagonists would be expected to suppress performance on both levers, and although rewarding effects survive such treatment, differential lever pressing may not be observable simply because of the potent impairment of performance for either lever. D-1 agonists should abolish differential responding, by masking the reward effect of the reward-associated stimulus. D-2 agonists on the other hand would lead to activation of the dopamine neurones and would potentiate any rewarding effect exerted by these neurones on the unimpaired D-1 receptors. Differential responding on the reward-associated lever might therefore be expected to increase. (N.B. To sustain this argument it must be assumed that the effect of D-2 agonists is more powerful on neurones that are already *somewhat* active [i.e. at the time of the reward-associated stimulus] than on those that are not [i.e. at the time of the stimulus not associated with reward]. In other words the D-2 agonists should act as a *multiplier* of neural activity in the dopamine neurones, in a manner somewhat similar to amphetamine.)

No experiments have been carried out on the effects of receptor-selective dopamine antagonists on conditioned reward. However the effect of various dopamine agonists has been studied by Beninger *et al.* (1989). Apomorphine increases responding on both levers, without any differential effect. Presumably this is due to an indiscriminate enhancement of performance via the D-2 receptors, combined with a masking of any reward effect at the D-1 receptors. As expected, SKF 38393 prevents differential responding, and no non-differential increase in responding occurs either (presumably because the performance enhancement at D-2 receptors does not occur). On the other hand, bromocriptine or quinipirole produced enhanced responding specific to the reward-associated lever, again in accord with prediction.

5.8. PLACE PREFERENCE CONDITIONING

In this paradigm, animals are rewarded (with natural rewards, brain stimulation reward or a dopamine agonist) while enclosed in one side of a chamber. Subsequently, when the animals are free to explore both sides of the chamber they systematically spend more time in the side where they had previously been rewarded. It is established that dopamine is necessary for this type of learning (e.g. Spyraki *et al.*, 1982). According to the rationale of reward-mediated learning (whether seen in stimulus–response terms or as incentive learning) it would be expected that D-1 agonists, being the primary reward signal, should increase the linking of environmental cues to approach responses, and so should accentuate place-preference learning. (Animals should also show increased locomotor activity in the preferred side, as in the conditioned activity paradigm.) With D-2 agonists there should also be a rewarding effect (albeit by indirect means) and so these drugs should also promote a preference for the places in which such drugs are administered.

The actual experimental results are however, apparently paradoxical: a D-1 agonist (SKF 38393) mediates an *aversion* to the place in which it is administered (Hoffman and Beninger, 1988), while a D-2 agonist (quinpirole or bromocriptine) mediates the predicted place preference (Hoffman and Beninger, 1988; Hoffman *et al.*, 1988). The place aversion produced with a D-1 agonist is difficult to understand, though it appears to be a solid result, since it has been replicated by the original author and by N. M. White (personal communication). The result appears to indicate that, despite the presence of the drug which is masking any specific reward signal, there is intact another (presumably non-dopaminergic) system which can mediate aversion. This result, though unexpected, has some clinical significance, which will be discussed briefly later (Section 6.7).

5.9. LEVER PRESSING FOR FOOD OR WATER

This is a measure of a response learned by reward, but is also clearly influenced by performance capacity. Drugs acting at both D-1 and D-2 receptors should influence this measure therefore. D-1 agonists should mask the normal reward signal and lead to a drop in lever pressing. They should not enhance lever pressing, since this is a highly-specific selected response (rather than a more general one such as locomotion) whose rewarding consequences would be masked by the drug. D-2 agonists might enhance responding for food or water, via an effect on performance. However, this prediction is somewhat tentative, since dopamine agonists suppress the hunger motive (Gilbert and Cooper, 1985; Willner *et al.*, 1985) and also possibly suppress thirst (Ljungberg, 1987). When a rewarding event is withdrawn, gradual decline of previously-rewarded responding should occur (extinction). The same gradual decline should be observed when D-1 antagonists are administered. D-2 antagonists should cause a sudden drop in performance to a new steadily-maintained level. However, it is possible that these drugs could also reduce the activation of the dopamine neurones produced by the food reward, in which case an extinction-like decline would be evident, as with the D-1 antagonists. There is yet another possible way in which D-2 antagonists could reduce responding: just as the cataleptic effect of these drugs increases with repeated testing, an effect which apparently involves conditioning (the "repeated measures effect": see Section 5.6) it is also possible that some of the decline in responding is due to stiffness in the limbs produced by the D-2 antagonist becoming conditioned to environmental stimuli. It may be difficult to distinguish such an effect from a true extinction-like decline.

The only test of receptor-specific agonists on lever-pressing for food in normal animals is that of Hoffman and Beninger (1989). All varieties of dopamine agonist (D-1-selective, D-2-selective and non-selective) produced decreases in responding. Whether these are effects produced on reward or performance are uncertain. Plausibly they are all effects due to loss

of appetite, since both D-1 and D-2 receptor agonists can produce anorexia (Gilbert and Cooper, 1985; Willner *et al.*, 1985). There is one relevant report about the effect of the D-2 selective agonist LY-171555 in monkeys in which a Parkinsonian state had previously been produced by the neurotoxin MPTP. The D-2 agonist was effective in restoring normal motor function (i.e. relieving rigidity) but despite this could not restore operant responding (a reaching response, for a fruit-juice reward) (Schneider, unpublished; cited in Schneider *et al.*, 1988). It was also observed in this paper that the impairment on the operant tasks varied independently of the motor impairment.

Several studies have investigated the effects of receptor-selective antagonists on lever-pressing for food or water. Nakajima (1986) showed that D-1 antagonists, as predicted, blocked operant responding for food. At certain doses it was possible to impair responding for intermittent reward, while continuously-rewarded responding was maintained without impairment. This suggests that the effect was principally on reward rather than on performance. Sanger (1987) also found that SCH 23390 reduced the rate of lever pressing for food (on an FR-10 schedule), but saw no extinction-like decline. In another study Sanger (1986) showed that conventional neuroleptic drugs (i.e. mainly D-2 antagonists) suppressed lever-pressing on a similar schedule, and in this case the animals showed an extinction-like decline, suggesting that a reward component may have been impaired by the drugs. In addition Ljungberg (1987) found that D-2 antagonists suppressed lever pressing for water and showed an extinction-like decline. Beninger *et al.* (1987) found that in undrugged animals lever-pressing rates gradually increased throughout a session where reward was intermittently available. If reward was removed, rates progressively fell within and across sessions. If reward was available and a D-2 antagonist was given, rates failed to climb through the session, and showed a session-to-session decline. Thus, although the issue is not fully resolved, both D-1 and D-2 antagonists, in addition to performance effects, appear to lead to a decrease in effectiveness of reward in operant tasks.

5.10. Unconditioned Appetitive Responding

This is clearly influenced by the potency of the internal reward signal, but is also affected by other variables which determine the strength of the appetitive motive itself (hunger, thirst, etc.). Both D-1 and D-2 agonists should suppress food intake, the former by masking the reward signal, the latter by suppressing appetite. D-2 agonists might however increase water intake. Using receptor specific antagonists, it might be expected that unconditioned water intake would be less vulnerable to the performance-inhibiting effects of D-2 antagonists than to the reward-inhibiting effects of a D-1 antagonist. There is little data available on these matters, though Ljungberg (1987) has reported that D-2 antagonists impair lever-pressing for water in lower doses than they suppress unconditioned water intake, suggesting that such drugs have a more potent effect on performance. Gilbert and Cooper (1985) find that SCH 23390 reduces consumption of water or weak saline solution in thirsty rats, whereas sulpiride increases it. These results are compatible with the notion that D-1 blockade attentuates reward, while D-2 blockade leaves it intact.

5.11. Active Avoidance Acquisition and Performance

Avoidance learning and performance are traditionally very useful paradigms for detecting neuroleptic potency in drugs. *Acquisition* of an active avoidance response is thought to involve reward processes: absence of an expected aversive stimulus (or of a stimulus associated with it), consequent on a successful avoidance response, is held to be capable of rewarding that response (McKintosh, 1974). Consistent with this, acquisition of an active avoidance task is impaired in animals under the influence of dopamine-blocking drugs (Beninger *et al.*, 1983, 1989). *Maintenance* of responding for an already-acquired active avoidance response might be thought to be governed mainly by performance variables. However, when neuroleptic drugs are given to an animal which has previously acquired the avoidance response in an undrugged state, it can perform the avoidance task surprisingly well for a number of daily test sessions (Beninger *et al.*, 1983; Carey and Kenney, 1987). Over a number of days the vigour of the avoidance response declines slowly, an effect which seems like a slow extinction of a tenaciously-maintained habit. Thus one can conclude that the effect of neuroleptic drugs on maintenance of avoidance is more than merely an effect on performance: there appears to be a continuing requirement for a rewarding effect if responding is to be continued in the long-term without decrement (Beninger, 1989). Exactly which stimuli mediate the rewarding effect at their offset is a matter for some debate. It is unlikely that offset of the aversive stimulus *per se* mediates the reward, since the aversive stimulus is never initiated in an effective avoidance response. More likely is the possibility that stimuli previously associated with offset of the aversive stimulus (an explicit conditioned stimulus or the change in the apparatus cues which accompanies a successful response) can mediate a rewarding effect. This conjecture is supported by the experiments of Beninger *et al.* (1980). In the first stage of these experiments, animals were given avoidance training while drugged with a neuroleptic, and failed to acquire the response. They could however subsequently acquire responding if exposed to the same experimental procedure in the undrugged state, with the aversive stimulus switched off. Presumably this learning came about because stimuli previously associated with the aversive stimulus acquired some of its attributes whilst under the influence of the drug. Subsequently, it was these associated stimuli whose offset served to strengthen the avoidance response.

Apart from the reward element, avoidance tasks undoubtedly involve an important performance component. Several methods have been used to differentiate them. One method of assessing the integrity of performance capacity is to measure the vigour of escape responses. Results have shown that neuroleptic-treated animals failing to acquire avoidance

responses readily escape when shock is presented, suggesting that performance is relatively unimpaired. Another approach to this issue involves comparing the effects of neuroleptics on the acquisition of avoidance responding versus that on the maintenance of already acquired avoidance responses. As mentioned earlier the dopamine receptor blockers prevent acquisition. However, these drugs initially have little effect on pretrained avoidance responding, although performance eventually declines with repeated testing. These observations clearly show that the effects of neuroleptics on avoidance cannot simply be attributed to performance effects.

In the continuous (Sidman) avoidance task, pressing a lever is rewarded by delaying an aversive stimulus for a standard interval, and regular lever-pressing is required to avoid all shocks. The above arguments on the roles of reward and performance on acquisition and maintenance of avoidance probably also apply to this variety of avoidance learning as well as to the discrete trial variety (see discussion of this issue in McKintosh, 1974). In the following subsection, acquisition and performance of discrete-trial active avoidance, as well as Sidman avoidance performance will be considered together.

A few data are available on the relative effectiveness of D-1 and D-2 antagonists against active avoidance. Usuda *et al.* (1981) found that D-2 antagonists were of roughly equal potency in blocking a discriminated avoidance performance as they were at blocking other dopamine-related behaviours depending on active performance (e.g. apomorphine- or amphetamine-stimulated stereotyped behaviour). The effect of the D-1 antagonist SCH 23390 was studied by Iorio *et al.* (1983), who found that it was only slightly less effective in blocking active avoidance than in blocking apomorphine-induced stereotypy in rats. However, the typical neuroleptics haloperidol and perphenazine were much less potent against avoidance than against stereotypy. Bearing in mind that antagonism of drug-induced stereotypy may be a very sensitive measure of the performance-inhibiting capacity of neuroleptics (see Miller, 1987: Fig. 1E), this result seems to show that D-1 antagonists target the reward-related components as easily as the performance-related one, while D-2 antagonists are fairly specific for the performance-related task. Gerhardt *et al.* (1985), using squirrel monkeys, found that blockade of avoidance on the Sidman schedule could be achieved with lower doses of SCH 23390 than were required to produce dyskinesia. In contrast, haloperidol produced dyskinesia at doses lower than those needed to block Sidman avoidance. Again, the D-1 antagonist seems to be relatively selective for the task in which reward is more important. Sanger (1987) has also shown that SCH 23390 impaired responding on a one-way avoidance task. It is unclear whether this is an effect on reward or performance.

5.12. DRUG SELF-ADMINISTRATION

In this experimental design, the rewarding effects of a drug are assessed by allowing the animal to control administration of small quantities of the drug via an intravenous cannula. Animals can thus be trained to self-administer drugs such as stimulants. It would be expected that D-1-selective agonists should not be self-administered, because any reward signal associated with the self-administration response would be masked. On the other hand, D-2-selective agonists should be self-administered in this way, because they are rewarding by an indirect effect (the sudden loosening of the limbs). Thus far, these predictions are in accord with available results: D-2-selective agonists (like non-selective dopamine agonists) are self-administered by rhesus monkeys (Woolverton *et al.*, 1984) and rats (Yokel and Wise, 1978), while D-1-selective ones are not (Woolverton *et al.*, 1984).

However, the self-administration paradigm seems to be more complex than this brief analysis suggests. In studies where the dose of the dopamine agonist, or the ratio of responses to injections is varied it is found that lowering the dose (or raising the ratio) leads to a robust *increase* in responding (e.g. Pickens and Thompson, 1968; Wilson *et al.*, 1971). This suggests that animals which have acquired the self-administration habit are working to maintain a constant level of drug in their bloodstream. Thus, in some way, although the dopamine agonist is envisaged to be a mediator of reward, the animals' responding can increase when internal levels of the drug fall *below* optimal levels. When saline is substituted for the dopamine agonist in the intravenous cannula, responding again increases for a while, before extinction prevails (Pickens and Thompson, 1968; Yokel and Wise, 1975; Woolverton, 1986). The increased responding in this case may reflect a generalization from previous experiences of dose reduction.

Given these facts, the effects of receptor-selective antagonists are certainly complex, and predictions are not entirely clear. The following suggestions are given in rather tentative fashion: D-2 antagonists *in low or moderate doses* should reduce or prevent loosening of the limbs produced by administration of a D-2 agonist or a non-selective dopamine agonist. This should be in some ways similar to reduction of the dose of the agonist or the substitution of saline for active drug, so one might expect initial increase in responding, followed by extinction. The D-2 antagonist may also result in increased responding for another reason: since endogenous dopamine release would be intact, and even increased by the effect of the D-2 antagonist on autoreceptors, the reward function would still be intact. The effect of increased self-administration responding in preventing stiffening of the limbs could thus still be actively strengthened by the reward function. However, *with a large dose of the D-2 antagonist*, performance might be suppressed to such an extent that no increase in responding occurs, merely a rapid cessation of responding. With *D-1 selective antagonists* it is also possible that the animal would behave as it does with dose-reduction or with saline substitution for the active drug. If this effect were predominant initially there would be an increase of responding, followed by extinction. On the other hand, there would be a more selective reduction or blockade of the reward function than with D-2 antagonists. If this effect prevailed, only extinction-like effects would be seen. It is far from clear which of these two effects might be stronger. The question revolves around whether the increase in responding with a reduction of dose of a

non-selective dopamine agonist is determined by the reduced activation of D-1 or of D-2 receptors. This issue is not resolved at present. It is also probable that a number of other interacting variables determine which of the above two processes is predominant (for instance the precise dose of agonist and of antagonist, and the amount and nature of previous training with other doses of agonist, or with saline substitution).

The relevant experimental facts using receptor-selective antagonists are insufficient to evaluate these tentative predictions in a complete way. In experiments in which non-selective (cocaine) or D-2 selective (piribedil) dopamine agonists are self-administered by rhesus monkeys, the D-2-selective antagonist, pimozide, will increase self-administration if given in low doses, while in larger doses it suppresses self-administration (Woolverton, 1986). Potentiation of apomorphine self-administration by low doses of pimozide has been seen by Baxter *et al.* (1974) in rats (though only a small proportion of animals showed this effect) and likewise, cocaine self-administration by rats was increased by a small dose of spiperone (10 μg/gm), but decreased by a larger dose (20 μg/gm) (Koob *et al.*, 1987). This increase in self-administration has also been seen with the D-2 antagonists haloperidol, fluphenazine, sulpiride, pimozide, chlorpromazine and metoclopramide, as well as (though less strongly) with the atypical neuroleptic thioridazine (Roberts and Vickers, 1984).

Turning to D-1 selective antagonists the results are quite equivocal. Woolverton (1986) found that self-administration of cocaine by monkeys was not increased by injections of SCH 23390, and that of piribedil was increased in only one out of five monkeys. On the other hand, Koob *et al.* (1987) found in rats that SCH 23390 led consistently to an initial increase in cocaine self-administration. Two other results are relevant here: Yokel and Wise (1978) tested the neuroleptic butaclamol against self-administration of apomorphine. Enhancement of self-administration was not seen, the only effect being a suppression of self-administration. This result is relevant because butaclamol is equipotent as an antagonist at D-1 and D-2 receptors according to binding studies (Andersen *et al.*, 1986), so perhaps this experiment should be grouped along with the others using SCH 23390. Likewise, in the experiments of Roberts and Vickers (1984), the atypical drug clozapine showed only response-decreasing effects. As argued later (Section 6.3) this drug, although a mixed D-1/D-2 antagonist as assessed by dopamine receptor binding, may in practice owe most of its effects to D-1 blockade. These data may be construed as supporting our hypotheses, in that the increase in responding following administration of antagonists in this test is found more consistently with D-2 antagonists than with D-1 antagonists. However, the amount of data available for D-1 antagonists is small and there are inconsistencies which require clarification. Further work is clearly required in this area.

5.13. SELF-STIMULATION

Self-stimulation to obtain brain-stimulus reward is very well researched. It is now established that there are definite components of both performance and reward in the self-stimulation phenomenon as it is usually studied, and a variety of methods are available to study each component in isolation (Liebman, 1983). It would be predicted that D-1 agonists should mask the rewarding effect of brain stimuli, while D-2 agonists might potentiate it. D-1 antagonists should block the reward effect at source, and so suppress the reward component of self-stimulation. D-2 antagonists would certainly have the capacity to suppress performance. It is also possible that they might produce an effect similar to that in self-administration of dopamine agonists, an increase in lever pressing at low doses of the antagonist, with a decrease at higher doses. Whether this is actually observable depends on whether brain stimulus reward is actually potent enough to cause the "indirect" reward by loosening the limbs.

The available results are as follows: Nakajima and McKenzie (1986) have shown that SCH 23390 blocks lateral hypothalamic self-stimulation. This was shown to be an effect on reward rather than performance because the half-maximal stimulation parameters were increased by the drug, without a change in the performance ceiling. Kurumiya and Nakajima (1987) found that SCH 23390 (but not sulpiride) injected into the nucleus accumbens had a similar effect (using a similar method to ascertain that this effect was on reward rather than performance). D-2 antagonists also suppress self-stimulation, and several papers have linked this to an attenuation of the reward component, either by showing an extinction-like decline (Fouriezos and Wise, 1976; Fouriezos *et al.*, 1978; Ettenberg *et al.*, 1979; Atalay and Wise, 1983; Fenton and Liebman, 1982), a task-specific extinction (Gallistel and Davies, 1983), an elevation of current threshold (Esposito *et al.*, 1979) or an elevation on the half-maximal current strength without change in maximal performance rate (Franklin, 1978). According to present arguments, this should be an indirect blockade of reward processes, mediated by stiffening the limbs, and lowering the firing rate of dopamine neurones. The prediction from this (for which detailed data are not yet available) is that the apparent antireward effect of D-2 antagonist drugs should be lifted by muscarinic antagonists.

The idea that low doses of D-2 antagonists might *potentiate* lever-press responding for brain stimulus reward has never been mentioned in the literature, but some of the studies of extinction-like effects with pimozide give indications of a slight elevation of responding above control levels at the start of the test, followed by the more usual gradual extinction-like decline (Fouriezos and Wise, 1976 (especially some of the graphs for individual animals); Atalay and Wise, 1983 (graph for 0.5 mg/kg pimozide); Ettenberg *et al.*, 1979 (graph for 0.25 mg/kg pimozide)). This topic deserves more attention. It is predicted that the conditions in which an enhancement might be detected similar to those seen in drug self-administration studies would involve high current strength and/or stimulus frequency, with relatively low doses of the challenging D-2 antagonist. It is not clear whether D-1 antagonists would produce any enhancement of responding under the

same conditions (see discussion of the self-administration paradigm: Section 5.12).

5.14. STIMULUS PROPERTIES OF DOPAMINE AGONISTS

In Section 3.4 it was indicated that drugs which act at D-2 receptors should cause a characteristic change in proprioceptive feedback from the locomotor system. Any such change brought about by the corresponding drugs acting at D-1 receptors should be very much weaker, if it existed at all. This is relevant to another behavioural test used to evaluate psychoactive drugs, the drug discrimination paradigm. In this test, animals are first trained to produce one response when injected with the test drug and another when injected with saline. Subsequently, the trained animals can be used to test how far the internal cue (upon which drug discrimination depends) can generalize to other related drugs. In this way it is possible to evaluate the pharmacological receptor types which determine the "stimulus properties" of drugs. While there is little known about exactly how centrally acting drugs come to have such stimulus properties, in the present context, D-2-active drugs are clearly envisaged to owe much of their stimulus properties to effects produced on true sensory receptors, while for D-1-active drugs, this mechanism probably does not apply.

There are a number of experimental papers relevant to this issue. D-1- as well as D-2-selective agonists can be discriminated by trained animals (Kamien *et al.*, 1987). The stimulus properties of non-selective dopamine agonists rely mainly on activation of D-2 rather than D-1 receptors. For instance, the apomorphine cue generalizes to that of quinpirole (Tang and Franklin, 1987; Tang and Code, 1989), bromocriptine (Schechter and Greer, 1987) or piribedil (Woolverton *et al.*, 1987) but not to SKF 38393 (Woolverton *et al.*, 1985, 1987; Tang and Franklin, 1987; Tang and Code, 1989) or only partially to SKF 38393 (Schechter and Greer, 1987) and not to other, non-dopaminergic drugs. The piribedil cue (Kamien *et al.*, 1987) or the quinpirole cue (Weathersby and Appel, 1986) generalizes to that of apomorphine, but not that of SKF 38393. The SKF 38393 cue fails to generalize to either apomorphine or quinpirole (Cunningham *et al.*, 1985). There are also several results using antagonists in combination with agonists. The piribedil cue (Kamien *et al.*, 1987) or the apomorphine cue (Woolverton *et al.*, 1987) could be abolished by co-administration of the D-2 antagonist pimozide, but not that of SCH 23390 (Schechter and Greer, 1987). The quinpirole cue could be abolished by haloperidol (Weathersby and Appel, 1986). The SKF 38393 cue on the other hand was abolished by SCH 23390, but not by haloperidol (Cunningham *et al.*, 1985; Kamien *et al.*, 1987). There are a few more complex results using antagonists, whose significance is not yet clear. Tang and Code (1989) found that both D-1 and D-2 antagonists could abolish the apomorphine cue. Weathersby and Appel (1986) found that the D-1 antagonist SCH 23390 *generalized* to the D-2 agonist quinpirole. Despite these difficult results, the overall conclusion from these studies is that the stimulus properties of non-selective dopamine agonists depend more on D-2 receptor activation than on D-1 activation. Thus, while there is both a D-1 and a D-2 cue, the latter appears to be the stronger, a fact which may arise from the fact that it depends on true sensory messages.

5.15. DEVELOPMENTAL PSYCHOPHARMACOLOGY, IN RELATION TO THE MATURATION OF THE "CHOLINERGIC LINK"

In infantile rats (less than 2 weeks post-natal), the cholinergic component of the striatal matrix has not matured whereas the dopaminergic innervation is functional (McGeer *et al.*, 1971; Coyle and Campochiaro, 1976). Thus at this stage of development the D-1 receptors might be expected to mediate the reward function in a manner similar to that seen in adults, while the D-2 receptors should not be linked to the performance function as they are in adults. Therefore, in rats at this stage, one may obtain further evidence relevant to the hypotheses proposed here, by studying the role of D-1 and D-2 selective drugs on some of the behavioural tests discussed earlier. Shalaby and Spear (1980) found that apomorphine could increase locomotor activity at all ages tested. (In the very young rats this is envisaged to depend on its D-1 agonist properties). However, this drug could produce stereotyped sniffing only after 21 days of age. This may reflect the fact that only at this age can D-1 and D-2 receptors cooperate in the production of stereotypy. McDevitt and Setler (1981) found that in neonatal rats, bromocriptine failed to stimulate locomotion or produce stereotypy. SKF 38393, on the other hand, produced in these animals a syndrome that was like the full complement of stereotypy seen in the adult. This result can be interpreted as follows: in such young animals, since there is little cholinergic tone, a similar effect is produced as when a D-1 agonist is combined with D-2 receptor stimulation in the adult (suppression of cholinergic tone in the latter case being achieved by the action of the D-2 agonist). Catalepsy can be produced in very young rats using D-2 antagonists (Baez *et al.*, 1976; Burt *et al.*, 1982). This fact indicates either that in such young animals D-2 receptors have actions other than those on the cholinergic interneurones or that non-dopaminergic effects can contribute to catalepsy. Despite this, it is relevant to the ideas developed here that catalepsy, whether produced by D-2 antagonists (Burt *et al.*, 1982) or D-1 antagonists (Fitzgerald and Hannigan, 1989), is not lifted by muscarinic antagonists until 20 days post-natally.

5.16. CONCLUSION

With few exceptions, the explanatory framework put forward in Section 3 can account for the effects of D-1 and D-2 selective dopamine agonists and antagonists on a wide variety of experimental measures of dopamine-related reward and performance. Most of the evidence is, at least, compatible with the explanatory framework. Some parts of the evidence (for instance that pertaining to catalepsy, stereotypy and behavioural sensitization to dopamine agonists) constitute a compelling case for this, as opposed to

alternative explanations. There are still some areas of uncertainty (for instance the drug self-administration paradigm) and a number of tests that have not yet been performed, particularly of the interaction of dopamine D-2 effects on cholinergic tone. Further work needs to be carried out in these areas to provide additional and more decisive tests of the explanatory framework.

6. IMPLICATIONS FOR THE ANTIPSYCHOTIC ACTIONS OF NEUROLEPTIC DRUGS AND FOR OTHER ASPECTS OF PSYCHOTIC ILLNESS

6.1. Rival Explanations of the Time Course of Antipsychotic Therapy

When neuroleptic drugs are used in therapy of human psychotic disorders, *psychotic symptoms do not disappear suddenly: they abate gradually over a period of weeks or months* (Casey *et al.*, 1960; Cole and Davis, 1969; Davis and Garver, 1978). Since dopamine blockade is achieved within, at most, a few hours, this fact is a major constraint on hypotheses of how neuroleptic drugs might act. One possibility is that a slowly-changing biological parameter, resulting from dopamine blockade, is required to reach critical levels before therapy is achieved, the symptomatic improvement then following the biological parameter quite promptly. One example of this type of explanation for which there is some experimental support is that put forward by Pickar *et al.* (1984, 1986): prolonged administration of neuroleptic drugs to rats leads after a delay, to cessation of firing of most of the midbrain dopamine neurones (Bunney and Grace, 1978; Chiodo and Bunney, 1983; White and Wang, 1983a,b; Rompre and Wise, 1989). It has therefore been suggested that in humans undergoing neuroleptic therapy for acute psychosis, the delay in the "silencing" of midbrain dopamine neurones corresponds to the delay in symptomatic improvement (Pickar *et al.*, 1984, 1986). An alternative type of explanation is that the neuroleptic drugs have an immediate effect in correcting a disturbed biological parameter. As a consequence, the generation of further psychotic material and the continued elaboration of psychotic beliefs stored in memory is prevented. These memories are however durable, and are not dissipated immediately in the neuroleptic drugs. Instead, complex psychodynamic processes become possible to gradually resolve the conflicts between psychotic beliefs and more normal ones (Miller, 1984, 1987). Beninger (1983, 1988) has formulated similar ideas, in which the gradual process of recovery under the influence of neuroleptic drugs is likened to an extinction effect (of previously "learned" psychotic material).

In terms of the analysis of animal experiments presented earlier in this paper, the first class of explanation (e.g. Pickar *et al.*, 1984, 1986) corresponds to an effect of neuroleptic drugs on performance (actually the "performance of beliefs": see Section 6.4 later). The second class of explanation depends on the attenuation of the reward component which generates psychotic material, and this then allows other processes (extinction or "working through" the psychotic beliefs) to restore thought content gradually towards the normal range. According to this hypothesis, the process of therapy with neuroleptic drugs is quite closely similar to the effect of these drugs against avoidance performance, as studied in animals. In both cases a habit (of behaviour or of thought) is held with some tenacity, and much information processing is required before it is extinguished.

Both of these two types of explanation have strengths and weaknesses. The mechanism underlying the *"performance" explanation* (silencing of midbrain dopamine neurones) has support from animal studies. Clinical studies show that during neuroleptic therapy plasma homovanillic acid falls gradually in correlation with therapeutic improvement (Pickar *et al.*, 1984, 1985, 1986) which is compatible with the idea of delayed depolarization block in dopaminergic neurones. However, this idea does not explain the fact that patients under drug treatment for psychotic disorders do report a gradual "working through" of their psychotic beliefs, in order to reach less pathological beliefs. Moreover, if this explanation were the whole story (and without taking the separate role of different receptor subtypes into consideration), one would expect that alleviation of psychotic symptoms and production of Parkinsonian side effects should occur in parallel. In the early days of neuroleptic therapy these two were suspected to be inseparable: therapeutic benefit could not come about without producing motor side effects (Flugel, 1956; Deniker, 1960). Indeed in more recent years, attempts have been made to predict the dose of typical neuroleptic drugs required for each patient by using as a criterion the slight stiffening of the limbs produced by these drugs (e.g. McEvoy, 1986). This is a very plausible criterion, if it is assumed that D-2 receptors are the final site at which neuroleptic drugs achieve their therapeutic effects especially since there seem to be no D-2 receptors (other than those which produce the motor side effects) either in the striatum, or for that matter elswhere in the brain, which could mediate antipsychotic effect (see later). However, it is well known that the therapeutic effects and the side effects have quite different time courses, the therapeutic response growing gradually (see above), the side effects potentially occurring immediately (Sovner and DiMascio, 1978; Klein *et al.*, 1980), and then abating as tolerance to the drugs develops (Ayd, 1971; Shapiro, 1976; Keepers and Casey, 1986). This is difficult to explain by the depolarization block model.

The explanation based on extinction of reward-related learning accounts for the psychodynamic aspects of neuroleptic therapy and the great variability in rate and extent of response in drug treatment of acute psychosis. It is supported by the fact that the therapeutic potency of neuroleptic drugs is better predicted by their inhibition of reward-related learning measures than by a number of other measures of effects on dopamine-related behaviours (Miller, 1987). The fact that the therapeutic effects have a slow onset, whereas the side effects can have an immediate onset might be explained because performance and learning effects inevitably do have

different time courses, whether or not they are mediated by the same or different pharmacological receptor types.

However, other difficulties with the "extinction" explanation of antipsychotic action are presented by the relation between antipsychotic effects and Parkinsonian side effects. It is well established that, quite apart from differences in time course, these two are separable for the atypical drugs such as clozapine and thioridazine (see Section 6.3). However, if only one receptor type is involved, this is difficult to explain. It is also difficult to explain why, if only one receptor subtype is involved, tolerance develops to the extrapyramidal side effects (Orlov *et al.*, 1971) of neuroleptic drugs, while the antipsychotic effects are maintained without fall in drug potency.

6.2. D-1 RECEPTORS AS THE FINAL TARGET OF ANTIPSYCHOTIC THERAPY

In earlier reviews (Miller, 1984, 1987), it was believed that the antipsychotic and the antireward effects were produced by blocking D-2 receptors, although in different parts of the brain from the D-2 receptors which mediate the Parkinsonian side effects. However, the analysis presented so far in this paper shows that it is more plausible to suggest that the primary receptor-subtype at which reward effects are produced, namely the D-1 receptor, is different from that at which motor side effects are produced, the D-2 receptor. This leads to another conclusion: *since the antipsychotic and the antireward effects appear to correlate well, the antipsychotic effects of neuroleptic drugs should also ultimately be a function of the D-1 receptor*. However, to sustain this conclusion, much more evidence about neuroleptic therapy needs to be re-evaluated.

The original idea that antipsychotic effects of neuroleptic drugs are a function of D-2 receptors stems mainly from the fact that the clinical potency of a range of neuroleptic drugs correlates fairly well with their affinity for the D-2 receptor (Seeman, 1980, 1987; Peroutka and Snyder, 1980; Miller, 1987 (Fig. 1A)). However, with this as the first point of action, it is possible to see how D-1 receptors may also in consequence receive less activation. In part this might come about because of the immediate aversive effect of "stiffening the limbs". In addition, the animal experiments referred to above show that prolonged administration of neuroleptic drugs can eventually silence midbrain dopamine neurones.

6.2.1. *Depolarization or deafferentation block by neuroleptics?*

There is a complicating factor here. The electrophysiological evidence that chronic regimes of neuroleptic drugs lead, after a delay, to the silencing of midbrain dopamine neurones is generally interpreted as indicating "depolarization inactivation" of those neurones (Bunney and Grace, 1978; White and Wang, 1983a; Chiodo and Bunney, 1983). This is a process that occurs as a result of such intense excitation that neurones are depolarized beyond the level at which action potentials can be generated. A variety of evidence is compatible with this interpretation: intracellular studies show that the silenced neurones are depolarized (Grace and Bunney, 1986). Silenced neurones can be reactivated by hyperpolarization produced by current injection (Grace and Bunney, 1986), GABA delivered iontophoretically (Bunney and Grace, 1978; Chiodo and Bunney, 1983), or intravenous apomorphine (Bunney and Grace, 1978; Grace and Bunney, 1986). Administration of excitatory influences (glutamate or CCK delivered iontophoretically; depolarizing current pulses) can silence the firing of midbrain dopamine neurones in acute experiments (Grace and Bunney, 1986).

The idea of delayed depolarization block is similar in *net effect* to the process proposed here. However, the process by which depolarization block is produced—excess activity—is diametrically opposed to that proposed here—a reduction of afferent drive to these neurones as the limbs are stiffened. There is thus an issue which is not yet resolved. A possible mechanism (as an alternative to depolarization block due to overactivation) by which the dopamine neurones could be silenced is that the suppression of firing seen in dopamine neurones after prolonged regimes of neuroleptics is a change consequent on effective "deafferentation". Precedents for such an action can be found in denervated skeletal muscle, in which the membrane potential drops (Albuquerque and Thesleff, 1968; Albuquerque and McIsaac, 1970) and there may be silencing of the muscle fibre (Albuquerque and Thesleff, 1968) or spontaneous contractions of the mucle fibre (fibrillation: see Nastuk, 1974). In some studies of partially deafferentated central neurones irregular burst-like spontaneous discharge has also been described (Loeser and Ward, 1967; Anderson *et al.*, 1971; Kjerulf *et al.*, 1973). Much of the evidence on the silenced dopamine neurones is compatible with either the "overactivity" or the "deafferentation" explanations: (i) In dopamine neurones which are not completely silenced after chronic regimes of neuroleptics, irregular burst-like firing may be seen (White and Wang, 1983a). This could be a consequence of depolarization produced by either excess activity or as a result of deafferentation. (ii) Lesions of the striatum (Bunney and Grace, 1978) or the striatal outflow pathways (Chiodo and Bunney, 1983) can prevent the silencing of the midbrain dopamine neurones. If performed in acute experiments in which previous drug administration has led to these neurones being silenced, such lesions can reactivate the dopamine neurones. These outflow pathways could be involved either in feedback processes which produce overactivity, or in the production of the characteristic proprioceptive activity which reduced afferent drive to the dopamine neurones. (iii) In acute experiments, neuroleptic drugs such as haloperidol, given in low doses, have been seen to accelerate firing, an effect attributable to actions at autoreceptors. In higher doses the same drug silences the neurones acutely (Hand *et al.*, 1987). This could be regarded as a consequence of overactivation, an acute "depolarization inactivation". On the other hand, it may reflect the fact that neuroleptics in sufficient dose to stiffen the limbs may lower the afferent drive to such an

extent that it *overrides* the autoreceptor-mediated activation.

The mechanism which produces the depolarization inactivation clearly requires further investigation. One clear difference between the rival explanations of the reduced activity of the dopamine neurones is that the depolarization block model arises from studies in anaesthetized or paralyzed preparations (used in all of the relevant electrophysiological work). On the other hand, the "deafferentation" explanation has its first application to the free-moving animal. The relevance of most of the available electrophysiological evidence is thus somewhat uncertain. Experiments in free-moving animals may contribute to a resolution of this issue. If a neuroleptic drug could be shown to silence the midbrain dopaminergic neurones acutely in the free-moving animal, at the same time as catalepsy developed, it would support the hypothesis proposed here. By the "overactivation" explanation, neuroleptic doses sufficient to cause catalepsy should have no necessary correlation with silencing of midbrain dopamine neurones: such doses might sometimes produce autoreceptor-mediated activation of these neurones, at the same time as catalepsy is produced by a post synaptic action within the striatum.

In summary, although the details of the mechanism are as yet unresolved, there certainly are processes in operation by which drugs whose common property is to block D-2 receptors could nevertheless reduce dopamine neurone firing and consequent activation of D-1 receptors. These processes may involve a delay. Thus the long time course of neuroleptic action with such D-2 antagonists may depend partly on the delay in producing depolarization or deafferentation block. However, regardless of this unresolved issue, the long therapeutic latency with neuroleptic drugs is also certainly substantially dependent on the lengthy psychodynamics involved in resolving psychotic beliefs, once the factors promoting active generation of such beliefs are no longer in operation.

6.2.2. *D-2 receptors not linked to cholinergic neurones as the mediators of the antipsychotic effects?*

The above argument has been constructed on the assumption that D-2 receptor antagonists can reduce activation of D-1 receptors via the cholinergic link, the D-1 receptors being the true target for antipsychotic actions. It might be suggested that the receptors which mediate the antipsychotic effects *are* still D-2 receptors, but not linked to cholinergic neurones. However the only such receptors which are definitely known in the neostriatum are the autoreceptors, activation of which *increases* dopamine release, an effect unlikely to be responsible for antipsychotic effects. In the limbic striatum, it has been suggested that the "cholinergic link" (found for dopamine receptors in the neostriatum) is absent (Lloyd *et al.*, 1973; Stadler *et al.*, 1975; Consolo *et al.*, 1977; de Belleroche and Gardiner, 1983), pointing to the limbic striatum as important for the therapeutic actions of neuroleptic drugs. However, the balance of more recent evidence is against this suggestion (Marco *et al.*, 1976; Mao *et al.*, 1977; Stephens and Herberg, 1979; Murzi and Herberg, 1982; Bluth *et al.*, 1985). Outside the striatum, there are dopaminergic systems in the prefrontal and other cortical areas. It has previously been suggested that this was the site of therapeutic action of neuroleptic drugs, due to fact that tolerance does not develop to the antipsychotic effects of neuroleptic drugs, and likewise does not develop to a biochemical action of them in these cortical regions (see: Miller, 1984, and summary in Section 6.5 later). However there appear to be very few dopamine D-2 receptors at all in these cortical regions in humans (de Keyser *et al.*, 1985; Farde *et al.*, 1987). Thus it is difficult to account for the main therapeutic actions of dopamine blocking drugs if one adheres to the idea that any known D-2 receptors are responsible for all actions.

6.2.3. *D-1 selective antagonists in antipsychotic therapy*

Thus, an important implication of these arguments is that selective D-1 antagonists should have good antipsychotic potency. If the explanation of the long time course of neuroleptic action based on extinction (of psychotic beliefs acquired by a reward-like process) is correct, these D-1 selective drugs should also have a lengthy time course of action for the reasons put forward by Miller (1984, 1987) and Beninger (1983, 1988). However, delayed depolarization or deafferentation block of the midbrain dopamine neurones would not be needed for their action, and it is therefore possible that the start of the therapeutic process (although not its full course) would be somewhat accelerated compared with standard neuroleptic drugs.

There is at present little experimental data to test these predictions. However the drug fluperlapine, which has three-fold higher affinity for D-1 than for D-2 receptors (Anderson *et al.*, 1986) is an effective antipsychotic drug (Woggon *et al.*, 1984; Fischer-Cornelssen, 1984). Clinical tests with the more specific D-1 antagonists such as SCH 23390 are therefore awaited eagerly.

If the therapeutic effects and the side effects are produced at different receptor subtypes, their different time courses, and their different susceptibility to development of tolerance, can be explained. It would also be predicted that D-1 antagonists should be non-cataleptogenic antipsychotic drugs. This prediction is made somewhat tentatively, since in animals SCH 23390 is certainly cataleptogenic (see earlier) though less potently and with shorter duration than D-2 antagonists. Nevertheless, the prediction receives some support from recent data on Parkinson's disease, which is well treated by D-2 selective agonists, while D-1-selective drugs appear to be of little value (Braun *et al.*, 1987). The idea that D-1 antagonists might be non-cataleptogenic in human therapy has been suggested several times by empirically-minded researchers (e.g. Chipkin *et al.*, 1988) and this appears to be true for fluperlapine (Woggon *et al.*, 1984; Fischer-Cornelssen, 1984). The present arguments give these conjectures and empirical results a theoretical basis. Clinical trials with D-1 selective antagonists will soon resolve this issue.

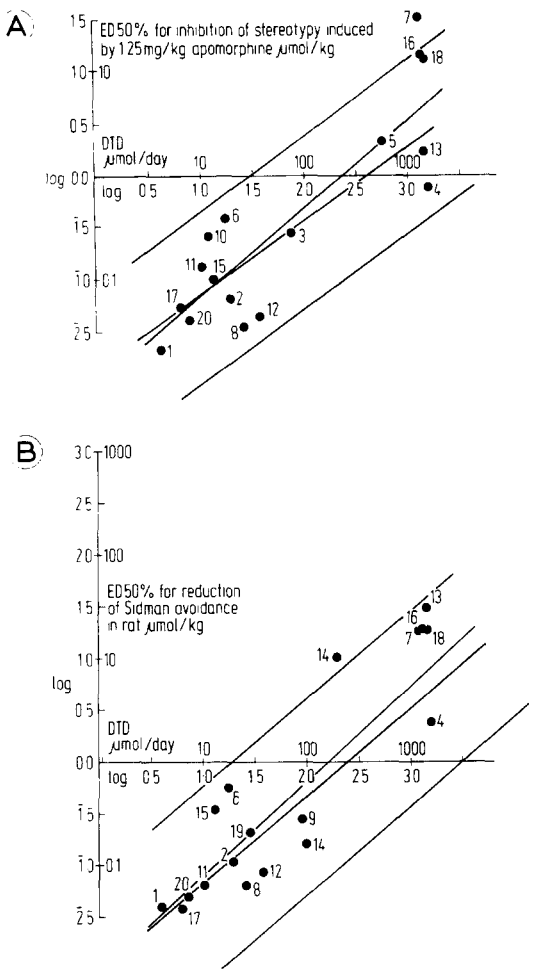

FIG. 4. A and B are log/log plots, for a variety of neuroleptic drugs, of therapeutic potency in treatment of schizophrenia (*horizontal axes*) versus potency in two behavioural tests used for identifying neuroleptic activity (*vertical axes*). Therapeutic potency (Seeman and Lee, 1975; Wyatt, 1976; Seeman, 1977; Stanley *et al.*, 1980; Martindale, 1982) is expressed as μmole/day. *Vertical axis* in A represents ED50 for inhibition of stereotypy in rats induced by 1.25 mg/kg apomorphine (μmole/kg) (Leysen *et al.*, 1978). *Vertical axis* in B represents ED50 for reduction of Sidman avoidance performance in rats (μmole/kg) (Niemegeers, 1974; Maj *et al.*, 1974; Wauquier, 1979; Dubinsky *et al.*, 1982; Hori *et al.*, 1983). Three parallel lines indicate main regression lines ± 2 s.d. (of residual errors) for all points except the two atypical drugs (clozapine and thioridazine). The fourth line is drawn showing the regression of all points (including these two atypical drugs). In Fig. 4A, the point for clozapine is right outside the 2 s.d. limit, while that for thioridazine is close to this limit. In Fig. 4B, the points for both drugs are well within the 2 s.d. limit. *Tests of significance*: in t-test comparisons of the slope of the fourth line with that of the other three, a highly significant difference ($P = 0.00137$) is found in A, while the difference is of only marginal significance ($P = 0.0605$) in B. Key to drugs—1: benperidol; 2: bromperidol; 3: +butaclamol; 4: chlorpromazine; 5: chlorprothixene; 6: clothiapine; 7: clozapine; 8: droperidol; 9: fluanisone; 10: alpha-flupenthixol; 11: fluphenazine; 12: haloperidol; 13: metoclopramide; 14: moperone; 14: perphenazine; 15: pimozide; 16: pipamperone; 17: prochlorperazine; 18: thioridazine; 19: trifluoperazine; 20: metiapine.

6.3. ATYPICAL NEUROLEPTIC DRUGS: THIORIDAZINE AND CLOZAPINE

A few of the currently-used neuroleptic drugs have drawn attention to themselves as having an antipsychotic potency, with little tendency to cause motor side effects. There may be a variety of ways in which this fortunate combination of properties can come about. However, amongst these atypical drugs, are two whose unusual profile can be explained in terms of the present hypotheses. These two are thioridazine and clozapine. Both possess significant antimuscarinic potency (Miller and Hiley, 1974; Snyder *et al.*, 1974). At dopamine receptors both have affinities for the D-1 and D-2 receptor subtypes which are roughly equivalent. (Clozapine has a slightly greater affinity for D-1 than for D-2 receptors, and thioridazine has only slightly lower affinity at D-1 than at D-2 receptors (Andersen *et al.*, 1985, 1986)). The prediction to be made about drugs with this combination of receptor affinities is that the D-2 blocking effects would be effectively neutralized by the antimuscarinic actions, so that in practice such drugs would be effectively D-1 selective antagonists.

Bearing in mind the hypotheses about the relation of reward and performance variables to the two receptor subtypes, the profile of these drugs in animal experiments gives some support to the idea that they are effectively D-1 antagonists. Their *cataleptogenic potency* in rats is much less than would be predicted on the basis of their clinical potency (see Miller, 1987: Fig. 1C). Even at high doses their maximum cataleptic effects are weaker than those of standard neuroleptic agents, and are qualitatively different. In particular, these drugs cannot produce prolonged catalepsy (Costall and Naylor, 1975). From Section 5.6, this could be explained by the fact that prolonged catalepsy requires reward effects acting on catalepsy, which is impossible when D-1 receptors are blocked. These two drugs are also less potent in blocking *stereotypy* induced by amphetamine (Miller, 1987: Fig. 1E; see also Bentall and Herberg, 1980) or apomorphine (Fig. 4A) than would be predicted from their clinical potency. From the above discussion of stereotypy (Section 5.2) this is what would be expected of a D-1 antagonist, since actions of a non-selective dopamine agonist at D-2 receptors alone (for instance after administering a D-1 antagonist) are greater than at D-1 receptors alone (as after administering a D-2 antagonist). There is actually some evidence that thioridazine and clozapine can *enhance* the stereotypy seen after amphetamine administration (Robertson and McDonald, 1984; Robertson *et al.*, 1986), which might reflect the fact that doses were used where the anticholinergic effect of these neuroleptic drugs was most prominent, and cooperated with the agonist in lowering cholinergic tone. A recent paper of Tschantz and Rebec (1989) supports these interpretations with phenomenological detail. Clozapine and thioridazine failed to suppress locomotion induced by a low dose of amphetamine. However clozapine suppressed the oral aspects of stereotypy at both doses tested. Thioridazine did so at the higher doses tested. Head bobbing was suppressed by clozapine at some doses. Haloperidol on the other hand suppressed all aspects

of stereotypy. Bearing in mind that locomotor activation appears to be related mainly to D-2 receptor stimulation, while oral stereotypy requires combined D-1 and D-2 stimulation, these results give some support to the idea that clozapine and thioridazine are effective D-1 antagonists. Another paradigm in experimental animals in which these drugs are of low potency compared with clinical potency is in the *inhibition of lateral hypothalamic self-stimulation* (Miller, 1987: Fig. 1D). While self-stimulation has both reward and performance components, as discussed earlier, the routine self-stimulation paradigm used in these experiments emphasizes performance rather than reward. Thus in three paradigms in which performance variables predominate, these atypical drugs are of lower potency than would be predicted from clinical efficacy.

Positive evidence for the selective action of clozapine and thioridazine against reward components of instrumental behaviour has been discussed previously (Miller, 1987): in contrast to the catalepsy and anti-stereotypy paradigms, potency of these drugs in antagonizing active avoidance behaviour (Miller, 1987: Fig. 1F) and Sidman avoidance (Fig. 4B) corresponds well with clinical potency. Making a similar point, Iorio *et al.* (1983) find that clozapine and thioridazine (like SCH 23390) are almost as effective in blocking active avoidance behaviour as in blocking apomorphine-induced stereotypy. Haloperidol on the other hand was far less effective in the first of these tests. In addition, several studies of self-stimulation behaviour in which the reward component was assessed (Atrens *et al.*, 1976; Schaefer and Michael, 1980; Gallistel and Davis, 1983) have shown that these two atypical drugs have a higher potency against reward (relative to performance) than do typical neuroleptic drugs such as haloperidol (Miller, 1987). The same point can be made for instrumental tasks dependent on natural rewards (Miller, 1987: Table 1). Furthermore the two atypical neuroleptic drugs are similar to SCH 23390 in another paradigm using dopamine agonists: cage climbing in mice, induced by apomorphine (see Section 5.4) is blocked more effectively by these two drugs (as by SCH 23390) than is stereotyped behaviour. For typical neuroleptics on the other hand stereotypy is blocked at lower doses than climbing (Gerhardt *et al.*, 1985; Vasse *et al.*, 1988). Finally there are two further studies (Chipkin and Latranyi, 1987; Altar *et al.*, 1988) which point out some features of empirical similarity between these atypical neuroleptics and SCH 23390, although the theoretical significance of these features is not yet clear.

In summary, these two drugs have many similarities to true D-1 antagonists in animal studies. That they are also non-cataleptogenic antipsychotic drugs in human therapy therefore gives some support to the prediction in Section 6.2.3 that D-1 antagonists should be non-cataleptogenic antipsychotic agents. The idea that the receptors which are the final target in neuroleptic therapy are the D-1 receptors, and different from those that mediate the motor effects (putatively the D-2 receptors) fits the correlation between antireward and antipsychotic processes: it can explain the different time courses of the therapeutic and side effects; it can explain the fact that tolerance develops only to the motor side effects but not to the therapeutic effects; and it helps to understand the clinical and psychopharmacological differences between typical and atypical drugs.

6.4. Acquisition Versus Performance of Psychotic Beliefs

The psychotic beliefs which determine symptoms have hitherto been assumed to be *acquired* gradually by reward-like processes, and dissipated gradually by extinction-like processes. It may be asked whether there is anything corresponding to "*performance*" of these beliefs, once they have been acquired. Such a possibility would be supported if it could be shown that under some circumstances, psychotic symptomatology could be changed by drugs (for better or worse) in a rapid step-like manner as shown in Fig. 1A, these changes being superimposed on the slower learning or extinction-like effects (Fig. 1B). Two bodies of evidence show such effects.

Several studies have shown that small single doses of apomorphine can produce short-lived improvement in psychotic symptoms (Corsini *et al.*, 1977; Smith *et al.*, 1977; Tamminga *et al.*, 1978, 1981; Hollister, 1981; Del Zompo *et al.*, 1981, 1986; Levy *et al.*, 1984). The same effect has also been seen with another direct dopamine agonist, *N*-propylnorapomorphine (Tamminga *et al.*, 1981, 1986). These papers made the suggestion that this apparently paradoxical effect is achieved by activation of autoreceptors on dopaminergic neurones, resulting in a reduction of dopamine release from their terminals. These effects are quite different from the actions of conventional neuroleptics, and are not maintained with longer-term administration of direct dopamine agonists, due, probably, to the development of tolerance (Tamminga *et al.*, 1986).

Cholinergic agonists such as arecoline and physostigmine can also produce short-lived improvements ("lucid intervals") in schizophrenia (Pfeiffer and Jenney, 1957; Janowsky *et al.*, 1973a) and mania (Davis and Berger, 1978). In two of the above reports (Janowsky *et al.*, 1973a; Davis and Berger, 1978) the short-lived benefits in psychotic symptoms were accompanied by dysphoria or (for mania) reduction in euphoria. On the other hand cholinergic antagonists have been found to interrupt the normal course of therapeutic improvement if given concomitantly with conventional neuroleptic drugs (Singh and Kay, 1975; Johnstone *et al.*, 1983). In the paper of Singh and Kay (1975) benztropine's adverse effect started and stopped rather abruptly with start and stop of the drug administration. In the paper of Johnstone *et al.* (1983) it was found that the exacerbation of psychotic symptoms matched the amelioration of the extrapyramidal symptoms quite well.

These facts can be fitted quite well into the conceptual framework proposed here. The reward and extinction processes for psychotic information can be regarded as applying to underlying belief structures. In addition, however, the *expression* of these beliefs as symptoms may be linked to the behaviour maintained by performance variables, in a reward-mediated task. This is not necessarily referring to the actual *motor* programming necessary for their

expression, but probably to a more abstract and internalized performance or "rehearsal" of an already acquired thought. The fact that the effects of apomorphine, acting on autoreceptors to suppress dopamine release, consist of short-lived lucid intervals of an hour or two suggests that the performance or rehearsal of psychotic thoughts is prevented by this action, without affecting the underlying beliefs. From this, one would also predict that there be another difference between D-1 and D-2 antagonists in antipsychotic therapy. The antipsychotic action exerted by D-2 antagonists would be expected firstly to prevent performance or "rehearsal" of the psychotic beliefs, and only later, when the firing of dopaminergic neurones falls, would the extinction-like process begin, which allows the psychotic beliefs themselves to be resolved. The D-1 antagonists on the other hand may apparently have a lesser immediate impact on symptomatology, because the effect on expression of beliefs is less. However, there should be a more direct and perhaps quicker effect on the underlying belief structures which maintain the symptoms. Finally, if it is true that conventional neuroleptic drugs achieve their effect in part via a cholinergic link, one would expect that cholinergic drugs should also exert short-lived effects on the expression ("performance") of psychotic symptoms. The evidence cited above shows that this is true: for both cholinergic agonists and antagonists there are step-like effects of the drug on symptom intensity, compatible with an enhancement or curtailment of the rehearsal of psychotic thoughts for the duration of the drug's action.

6.5. IMPLICATIONS FOR THE LOCUS OF ACTION OF NEUROLEPTIC DRUGS IN HUMAN THERAPY

The site of therapeutic action of neuroleptic drugs has been much debated. The issue is still unresolved, partly because there is little to correspond in animals with the brain structures underlying human cognitive functions disturbed in psychotic illness. While most of the brain's dopamine is in the neostriatum, this structure has not been considered a likely site of action, because it has generally been regarded as being involved in motor rather than cognitive functions. In addition most of the known actions of dopamine in the neostriatum exhibit tolerance, unlike the processes involved in neuroleptic therapy. Furthermore the "cholinergic link" is a very important part of neostriatal functions, whereas it has usually been thought that there is no such link in the therapeutic actions of antipsychotic drugs. (The previous subsection shows that this may not be so: the conventional view may have arisen from the fact that cholinergic agonists would be very poor therapeutic agents, on account of their manifold side effects.) The limbic striatum (principally the nucleus accumbens in animals) has been much studied as an alternative site for antipsychotic action (e.g. Anden, 1972; Crow *et al.*, 1977). It seems to have the same cholinergic link as the neostriatum (see earlier). However, the fact which is often overlooked by animal researchers is that the limbic striatum is a very small structure in the human brain (Spokes, 1979), whose very identity has been a source of some controversy for neurochemical pathologists studying schizophrenia (Bird *et al.*, 1979). In view of this, arguments have been presented by various groups that the dopamine-rich areas of the cortex are the target of antipsychotic drugs during therapy. One of the best arguments for this is that one of the biochemical effects of neuroleptic drugs (elevation of dopamine metabolites) does not show tolerance (with repeated doses corresponding roughly to therapeutic doses) for metabolites obtained from the cortical regions (Bacopoulos *et al.*, 1978, 1979; Miller, 1984). On the other hand tolerance does develop to the change in these metabolites in other dopamine-rich areas of the brain (reviewed in Miller, 1984). Processes occurring in the dopamine-rich cortical areas thus seem to correspond best to the process of antipsychotic therapy. However, according to traditional views that D-2 receptors mediate the therapeutic actions, this site of action also becomes implausible, because there are exceedingly few D-2 receptors in the human dopamine-rich cortical areas (De Keyser *et al.*, 1985; Farde *et al.*, 1987). There thus exists a very inconclusive situation on the locus of therapeutic action of antipsychotic drugs. When the D-1 receptor is identified as the target of antipsychotic drug therapy, various other possibilities are permitted which might help to resolve this issue.

When D-1 receptors are identified as the final target of neuroleptic drugs as used in therapy, the possibility that the relevant receptors are in the cortex remains open. This agrees with traditional views that the prefrontal cortex is important in cognitive processes such as language and thought (Luria, 1973; Fuster, 1980), which appear to be disturbed in psychosis. On the other hand there is growing evidence that the striatum and associated circuitry are also involved in these processes and in psychosis. Alexander *et al.* (1986) demarcated a variety of homologous circuits involving different parts of the striatum and the cortex. The implication of their review is that different parts of the striatum perform logically similar operations on different input pathways, there being a number of different resulting striatal functions, each centred on a different part of the striatum. The impairment of motor control seen in Parkinson's disease is known to result from dopamine depletion in relatively small parts of the striatum—the putamen (Nyberg *et al.*, 1983; Kish *et al.*, 1988)—and presumably corresponds to only one of these functions. There remain large areas of striatum which presumably have non-motor functions, which could well include the cognitive functions of language and thought (Crosson, 1984) apparently underlying acute psychosis. There is also more direct evidence for the involvement of the basal ganglia in psychotic disturbances (DeLisi *et al.*, 1985; Volkow *et al.*, 1986; Crosson and Hughes, 1987; Early *et al.*, 1987; Musalek *et al.*, 1989).

The relationships depicted in Figs 2 and 3 are all envisaged to occur in the same structure and are compatible with the cytology and neurochemistry of the striatum. While they were originally conceived as applying to the acquisition and performance of reward-mediated overt responses, it is possible that the same sort of circuitry operating in specific parts of the human striatum could govern the acquisition (by reward) and subsequent utilization of *thoughts* that

in some way are rewarding. It is thus quite plausible to think that the D-1-mediated reward mechanism underlying the thought disorder of psychosis could be located in a specific subregion of the striatum. The evidence cited in the previous subsection, that there may be a cholinergic link involved in the expression of psychotic beliefs, is compatible with this idea.

It was pointed out earlier that tolerance does not develop to the antipsychotic effects of neuroleptic drugs, nor is supersensitivity psychosis on sudden withdrawal of these drugs a very common event. Hence, if the therapeutic effect of neuroleptic drugs does depend ultimately on actions at D-1 receptors in a striatal subregion, it might be expected that chronic regimes of neuroleptics, corresponding to clinical doses, would not elicit a proliferation of D-1 receptors, or a tolerance to D-1 antagonists in the striatum, as they do for D-2 receptors and D-2 antagonists. Some evidence on this is available (Murugaiah *et al.*, 1983; Hess *et al.*, 1986; McKenzie and Zigmond, 1985; Savasta *et al.*, 1988; Hyttel, 1986; Memo *et al.*, 1987a,b; Vaccheri *et al.*, 1987; Barone *et al.*, 1988), showing in some cases tolerance to D-1 antagonists or proliferation of D-1 receptors, and in other cases, absence of these effects. One specific result is worth mentioning: Hornykiewicz and Kish (1985) found that in the striatum from Parkinsonian patients there was no D-1 receptor proliferation, although D-2 receptors had increased in association with the disease. On the whole these data are difficult to interpret at present, since one does not yet know what is the therapeutic dose range for SCH 23390 or related compounds in man, let alone its equivalent in animals. In addition it is unclear whether the activity of the dopamine-stimulated adenyl cyclase or the binding to the D-1 receptors itself is the more relevant measure in these studies, which is important because the two measures do not vary in parallel in some studies (Murugaiah *et al.*, 1983; Hess *et al.*, 1986). Further work will undoubtedly clarify this issue before long.

6.6. Implications for the Pathology of Schizophrenia and Other Endogenous Psychoses

A recurrent theme throughout this paper is that a drug which acts directly on one of the dopamine receptor types may nevertheless require active release of dopamine and stimulation of the other receptor subtype for full expression of the drug's effects. In the case of the behavioural sensitization produced by chronic regimes of dopamine agonists, available evidence suggests that there develops an increased firing of midbrain dopamine neurones, either spontaneously or more usually when activated by stimulant drugs. It was argued that the lowering of the dose threshold for many behavioural effects of stimulants, after chronic regimes, was due to the increased enhancement of dopamine release by stimulants in the sensitized animal. In patients who are prone to psychotic episodes, it has also been observed that the threshold dose for induction of psychotic changes by stimulants is very much lower than in normal persons, or in patient groups whose psychosis has been well stabilized (Janowsky *et al.*, 1973b; Janowsky and Davis, 1976; Segal and Janowsky, 1978). *It is therefore suggested that this sensitization in humans is also a result of increased firing of dopamine neurones and increased dopamine release.* If this process occurs in the striatum as a whole, it is likely that efflux of dopamine metabolites from the CNS as a whole (as detected in CSF or blood plasma) would be elevated in a psychotic or prepsychotic state and would fall during the course of drug therapy. These ideas therefore are compatible with the data of Pickar *et al.* (1984, 1985, 1986), Davis *et al.* (1985), Bowers *et al.* (1986) and Bowers and Swigar (1987) on increased plasma homovanillic acid levels in schizophrenic patients. These data are difficult to understand if only cortical dopaminergic mechanisms (which are a quantitatively small fraction of dopamine efflux) are involved in psychosis. The evidence cited in the previous subsection, that apomorphine and similar drugs in doses that act preferentially on autoreceptors, can have a short-lived antipsychotic effect, is also relevant to the idea that there is increased dopamine release in an active psychotic state: if dopamine release is very low, as it may be under normal circumstances, autoreceptor activation could do little to suppress dopamine release. If it is high, autoreceptor activation can have more powerful effects.

There are many possible initial causes of this sensitized state: superabundant dopaminergic innervation in the striatum has been detected in striatal structures (Bird *et al.*, 1977; Crow *et al.*, 1978; MacKay *et al.*, 1982) and supersensitive D-2 receptors in the striatum in schizophrenia have been much discussed (Owen *et al.*, 1978; Crow *et al.*, 1978; Lee and Seeman, 1980; MacKay *et al.*, 1982). In addition there is some evidence for "hyperconnectivity" in some part of the forebrain which might influence firing of dopamine neurones (discussed in Miller, 1989a). A further possibility is that there might be some actual toxic substance (e.g. an antibody; see Knight, 1982) which has pharmacological actions similar to the stimulant drugs. Lastly there is the intriguing finding of Memo *et al.* (1983) that the dopamine-stimulated adenyl cyclase (a D-1 receptor function) shows greater activity in striatal tissue from the brains of schizophrenic patients than from those of controls. All of these possible abnormalities, combined with the feedback processes described in this paper could lead to increased activity of midbrain dopamine neurones. Therefore the present paper does not allow any definite statement to be made about these initiating pathological mechanisms. There need not be a single initial cause: the syndrome of acute psychosis may be a state reached after a variety of different precipitants, both biological and psychological, singly or in combination. Nevertheless, *it is suggested here, as a major conclusion of the argument, that a common feature of the active psychotic state, whatever its precipitating cause, is increased neural activity in dopaminergic fibres. When this takes place, positive feedback processes are set in motion (a possibility depicted in Fig. 3), which may make it difficult to escape from the psychotic state without pharmacological intervention. While the state of increased tonic neural activity in dopamine neurones is present, the*

increased dopamine release has a double action: (i) it allows the generation of new psychotic material, to be stored in memory (this storage not actually being under dopaminergic control); (ii) in addition it facilitates the rehearsal of already acquired psychotic thoughts. Short-term amelioration of psychotic symptoms can be produced by drugs which reduce the impulse traffic in dopamine neurones, by an effect limited to the latter of these two processes.

6.7. RELEVANCE OF PRESENT IDEAS FOR UNDERSTANDING PSYCHOTIC SYMPTOMS

The relationship between these ideas and the detailed phenomenology of the acute psychotic state is a very large subject. Some discussion of this is given by Miller (1984, 1989b). It will not be discussed in detail here. However, before summarizing and concluding our argument, two suggestions are relevant: (i) Many of the positive psychotic symptoms may arise because the rewarding value of thoughts has been enhanced. This comment seems to apply mainly to initial stages of a psychotic breakdown, in which the symptoms may have a rather "seductive" quality for the patient; (ii) At a later stage, much more complex processes may be set in motion, whose net effect can hardly be equated with excessive reward. For instance, it is commonly observed that patients suffering from psychosis show social withdrawal and other symptoms that seem to be an escape from a too-threatening reality. One aspect of the animal evidence discussed above offers an insight into this aspect of psychosis. In animal experiments, the D-1 agonists, far from mediating place-preference (as might be predicted) mediated place aversion. While this effect is not understood at present, it seems to have some similarity to the social withdrawal seen in psychosis and may be mediated by similar mechanisms. Although we know of no direct evidence to support this speculation, one finding may be relevant. Steiner *et al.* (1969) trained rats to self-stimulate and recorded the pattern of responding. When the rats were subsequently given free stimulation according to the same pattern that they themselves had previously generated, they readily escaped from the situation. This finding suggests that the same stimulation that may be rewarding under some circumstances can be aversive under others.

7. CONCLUDING REMARKS

The main thrust of the argument in this paper is as follows: dopamine's effects in animals include separate reward and performance components. The former appears to be mediated via D-1 receptors, the latter via D-2 receptors and the "cholinergic link". However, although D-2 receptors principally affect performance, they also have motivational consequences ("stiffening or loosening of the limbs") which result in alterations in firing of the midbrain dopamine neurones. As a result, many of the effects of non-selective dopamine agonists can be mimicked by either D-1 or D-2 selective dopamine agonists only if there is some level of tonic dopamine release to activate the alternate receptor type. These relationships also make possible complex positive feedback processes which can further accentuate the behavioural pathology seen in animals.

In man the same processes may also apply. The psychotic state can be regarded as having distinct reward and performance components, which can be modulated separately. We postulate that the D-1 receptors are the final target for antipsychotic effects of neuroleptic drugs. D-1 antagonists should preferentially block the reward processes which generate psychotic thought-material, without producing motor side effects. D-2 antagonists can reduce activation of the D-1 receptors only indirectly by way of the "cholinergic link" in the striatum and the stiffening of the limbs which follows this. Indeed some of our arguments may even be construed as providing a theoretical basis for the use of other means of reducing motor activity, such as physical restraint, in the treatment of acute psychotic states (though we are not recommending a return to such practices). If these conclusions are correct, D-1 antagonists should have several advantages over D-2 antagonists. Since the effect of D-2 antagonists depends on a loop with the potentiality for positive feedback, it may be easier to titrate drug dosage to obtain optimum therapeutic effects with D-1- than with D-2-blocking drugs. Short-term reduction of dopaminergic tone (by autoreceptor activation or cholinergic agonists) appears to improve aspects of the psychotic state by preferential reduction of performance (or "rehearsal") of psychotic thoughts already formed. Hyperactive dopaminergic tone, maintained by positive feedback processes, seems to be an important component in maintaining the psychotic state, whatever aetiological factors may initiate such states in the first place. A final conclusion made here is that an important and perhaps the crucial locus of action of neuroleptic drugs is in some subregion of the striatum rather than in dopamine-rich cortical areas.

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APPENDIX: CLASSIFICATION OF DRUGS MENTIONED IN THE TEXT OF THIS REVIEW

Dopamine agonists mainly acting on D-2 receptors
- Quinpirole (LY171555)
- Bromocriptine
- Piribedil
- Lisuride
- PHNO ([+]-4-propyl-9-hydroxynaphthoxazine)

Dopamine agonists mainly acting on D-1 receptors
- SKF 38393

Mixed D-1/D-2 dopamine agonists
- Apomorphine
- L-DOPA

Indirect dopamine agonists (mixed D-1/D-2)
- Amphetamine
- Cocaine

Dopamine antagonists mainly acting on D-2 receptors
- Chlorpromazine
- Pimozide
- Haloperidol
- Metoclopramide
- Sulpiride
- Raclopride
- Perphenazine
- Spiperone
- Fluphenazine

Dopamine antagonists mainly acting on D-1 receptors
- SCH 23390

Mixed D-1/D-2 receptor antagonists
- Thioridazine (see Section 6.3)
- Clozapine (see Section 6.3)
- Butaclamol
- Fluperlapine

Catecholamine synthesis inhibitor
- alpha-methyl-para-tyrosine

Monoamine depletor
- Reserpine

Anticholinergic (antimuscarinic) agents
- Atropine
- Benztropine
- Scopolamine

NOTE ADDED IN PROOF

Since submitting this manuscript a few relevant papers have appeared, whose conclusions are summarized below: (i) Vezina and Stewart (1989) showed that SCH 23390 blocks the development of behavioural sensitization with repeated doses of amphetamine, while the D-2 antagonist pimozide does not. This result confirms the interpretation of behavioural sensitization to dopamine agonists put forward in Section 5.5. (ii) Esposito and Bunney (1989) find that delayed inactivation of midbrain dopamine neurones does not occur with chronic administration of SCH 23390 (either in the A9 or A10 cell groups), although it does with conventional neuroleptic drugs. This result supports the argument of the present paper, because the D-1 blocker, having no tendency to stiffen the limbs, will have no tendency to reduce the tonic afferent input to these neurones. (iii) Meltzer (1989) found that a proportion of schizophrenic patients who were resistant to treatment with conventional neuroleptic drugs, would respond to clozapine, with a very long latency (as much as 6 months in some cases). If the conjecture advanced in Section 6.3, that clozapine is effective because of its dopamine D-1 blocking properties, is true, one may see this result as an example of the pure anti-reward action of neuroleptics in human therapy, completely divorced from the anti-performance action ("preventing *rehearsal* of psychotic thoughts"), which conventional neuroleptic drugs are suggested to show.

We would also like to offer an alternative explanation for the delay in the silencing of midbrain dopamine neurones when conventional neuroleptic drugs are give to experimental animals: in Section 5.6 it was described how catalepsy was conditionable (the "repeated measures" effect). It is possible that, during the course of a chronic regime of conventional neuroleptic drugs, some similar conditioning process produces a gradual increase in the effects of these drugs on the locomotor system. If this were the case, the complete abolition of afferent drive to the midbrain dopamine neurones would not occur until some time had elapsed after the start of the chronic regime. Further work is clearly required to evaluate whether this (or either of the other explanations discussed in Section 6.2.1) is the best account of the delayed silencing of the dopaminergic neurones. All these explanations are potentially relevant to the

early stages of neuroleptic therapy, but none is an argument against the anti-reward (extinction-like) process which resolves psychotic beliefs more slowly.

Finally we would like to add two points in qualification of details of the argument of this paper. First, the drug SKF 38393 is not a full D-1 agonist but a partial agonist. This may affect the interpretation given in this paper for some of its behavioural effects. The validity of these interpretations must therefore be tested further using drugs which are full D-1 agonists. Secondly, in Section 6.5, it was assumed that tolerance to neuroleptic drugs and supersensitivity to dopamine agonists did not occur during chronic neuroleptic treatment in man. However this assumption may be incorrect: tolerance to these drugs has been described, as well as "supersensitivity psychosis" when these drugs are withdrawn abruptly (Chouinard *et al.*, 1978). Thus to provide a consistent account of the pharmacology of neuroleptic actions in man it may not be necessary to discover a dopamine receptor type which does not proliferate during prolonged blockade.

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