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Actions of dopamine antagonists on stimulated striatal and limbic dopamine release: an *in vivo* voltammetric study

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1 Fast cyclic voltammetry at carbon fibre microelectrodes was used to study the effects of several dopamine antagonists upon stimulated dopamine release in the rat striatum and nucleus accumbens.

2 In both nuclei, stimulated dopamine release was increased by D_2-receptor-selective and mixed D_1/D_2-receptor antagonists. The D_1-selective antagonist SCH 23390 had no effect.

3 Striatal and limbic dopamine release were elevated by *cis*- but not *trans*-flupenthixol.

4 The 'atypical' neuroleptics (clozapine and thioridazine) did not cause a selective elevation of dopamine release in the limbic terminal region, whereas the non-antipsychotic drug metoclopramide increased dopamine release more in striatum than nucleus accumbens.

5 We conclude from this study that striatal and limbic dopamine release are under the control of a stereoselective dopamine D_2-autoreceptor on the nerve terminal and that atypical neuroleptics do not show a limbic-selective effect at this receptor after acute administration.

Introduction

Since the first description of the antipsychotic effects of chlorpromaxine (Lehmann & Hanrahan, 1954), clinical experience has shown that most neuroleptics alleviate psychosis only at the expense of extrapyramidal side-effects. While the antipsychotic effect is often considered to be mediated by dopamine receptor blockade in the limbic system (Crow *et al.*, 1977), extrapyramidal side-effects are the result of actions in the striatum. More recently, however, it has become clear that certain neuroleptics, particularly clozapine and thioridazine, have a lower incidence of extrapyramidal side-effects. Because of this property, these neuroleptics have been called 'atypical' to distinguish them from the therapeutic profile of the 'classical' antipsychotics (Creese, 1983). Interestingly another drug, metoclopramide, seems to possess the opposite profile. The drug causes dystonic reactions (Reid, 1977) yet does not have any antipsychotic potency except at much higher doses (Stanley *et al.*, 1980). The dissociation of antipsychotic and extrapyramidal effects observed with these drugs has focussed attention on the nigrostriatal and mesolimbic pathways. In order to probe the mechanisms responsible, several recent studies have compared aspects of dopamine function in the nigrostriatal and mesolimbic systems *in vitro* and *in vivo* (Bartholini, 1976; De Belleroche & Neal, 1982; White & Wang, 1983).

Neuroleptics have several possible pre- and postsynaptic sites of action within the basal ganglia (Kebabian & Calne, 1979). However, despite the number of studies, the anatomical sites mediating selectivity are not firmly established. Recordings of unit activity in the substantia nigra and ventral tegmental area show a selective action of clozapine and thioridazine upon ventral tegmental cells, while metoclopramide acts only upon nigral units (White & Wang, 1983). This implies that dopamine receptors at the cell body level may be responsible for selective actions. Conversely behavioural studies have shown that clozapine blocks the hyperactivity induced by injection of dopamine into the nucleus accumbens but not the striatum. Metoclopramide only prevents the hyperactivity due to intrastriatal dopamine injection (Costall *et al.*, 1978). From these studies one might conclude that postsynaptic sites in

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the nucleus accumbens and striatum mediated selectivity.

The purpose of the present study was to focus upon the presynaptic dopamine autoreceptor on the nerve terminals to see if selectivity was observable at this level. Therefore, we measured the effects of the neuroleptics upon the release of dopamine in striatum and nucleus accumbens. Dopamine release was evoked by electrical stimulation of the ascending axons in the median forebrain bundle. The presence of a stimulating electrode between cell body and terminals meant that action potential flow was controlled by the stimulus, thus minimizing the interference due to changes in cell firing rate. Dopamine release was measured using fast cyclic voltammetry (Millar *et al.*, 1985; Stamford *et al.*, 1986).

Methods

Preparation of animal

All experiments were performed in male Sprague–Dawley rats (250–350 g) anaesthetized with chloral hydrate (400 mg kg^{-1} i.p.). Further smaller doses of anaesthetic (50 mg kg^{-1}) were given every 30 min to abolish corneal and hind limb withdrawal reflexes. Core temperature was maintained at 36–37°C using a rectal probe and homeothermic blanket placed under the rat. With the cranium held in a stereotaxic frame according to Pellegrino *et al.* (1979), holes (3 mm diameter) were drilled in the skull immediately behind and ahead of bregma. The dura was carefully drawn back using a hooked microsyringe needle and the exposed cortex was thenceforth bathed in saline.

Carbon fibre microelectrodes were implanted, using a dual electrode carrier, into the nucleus accumbens (AP: +3.3, L: +1.3, V: −6.5) and striatum (AP: +1.8, L: +2.8, V: −4.5). These coordinates, in millimetres, are relative to bregma (AP, L) and the cortical surface (V). Subsequent histology revealed the tips of the accumbens electrodes to be located at the same depth and slightly medial to the anterior comissure. Typically, dopamine release was detectable in more than 95% of cases. In the few animals where limbic release could not be detected the most common cause was location of the working electrode in the anterior comissure. Striatal electrode tips were located centrally within the striatum. The silver-silver chloride (Ag/AgCl) reference was positioned in a small dip drilled into the left side of the skull while a stainless steel auxiliary electrode was inserted into the neck muscle.

A standard concentric bipolar stimulating electrode (Rhodes SNE-100) was positioned in the region of the median forebrain bundle (AP: −2.2, L: +1.2, V: c −8 mm) as previously described (Ewing *et al.*, 1983; Millar *et al.*, 1985). The stimulating electrode was lowered with continuous stimulation until dopamine release was detected in both striatum and nucleus accumbens (Kuhr *et al.*, 1986). The stimulator was then disconnected for ten minutes to allow recovery before commencing the experiment.

Electrodes and electrochemistry

Single carbon fibre microelectrodes (8 μm diameter) were prepared as previously described (Armstrong James & Millar, 1979). The carbon fibre protruding beyond the glass insulation was cut to a length of 20 μm under micromanipulator control. No electrochemical pretreatments of the electrodes were performed. Before implantation *in vivo* the microelectrodes were immersed in phosphate buffered saline for one hour. This resulted in effective 'wetting' of the surface and was necessary for a fast electrode response time (J.A. Stamford, unpublished observations).

Dopamine release was measured using fast (high speed) cyclic voltammetry (Armstrong James & Millar, 1984). Figure 1 shows the data generation and presentation format. The input voltage waveform to the potentiostat consisted of 1.5 cycles of a 75 Hz triangular waveform (−1.0 to +1.0 V vs Ag/AgCl, 300 Vs^{-1}) scanning initially in the cathodic direction (Figure 1a). The waveform was applied alternately to the two working electrodes at a rate of 20 scans per electrode per second. At a sufficiently high voltage dopamine is electrochemically oxidised and gives rise to an oxidation peak. On reversal of the voltage scan the dopamine is then reduced again. Figure 1b shows typical current signals from an electrode in the striatum. Current at the dopamine oxidation peak potential (+600 mV vs Ag/AgCl) was monitored using sample-and-hold circuits (Figure 1c). The output from this circuit was then displayed directly onto a chart recorder. This provided, in essence, a direct record of dopamine release. Figure 1d shows the sample and hold record during a typical experiment. The 'spikes' on the trace correspond to the release of dopamine by the stimulus train. Haloperidol (0.5 mg kg^{-1}) caused a marked increase in stimulated release, observable upon the first post-drug stimulation.

Electrical stimulations

Electrical stimulations (50 Hz sinusoidal current, 100 ± 10 μA r.m.s., 2 s train duration) were applied to the MFB at intervals of 5 min throughout the experiment. The first 6 stimulations served as a control period. Dopamine release due to these stimulations was averaged and expressed as 100%. All drugs were administered immediately after stimu-

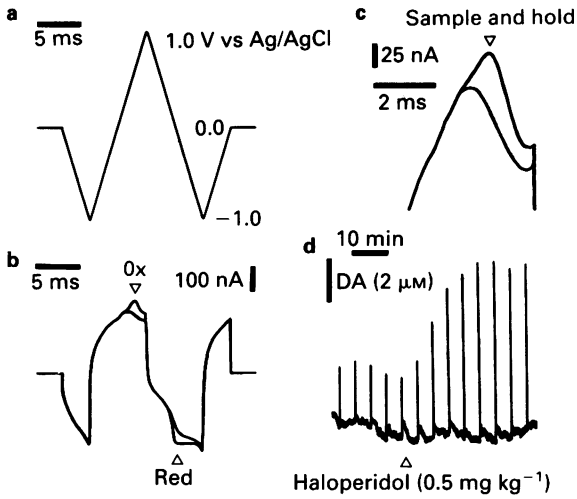

Figure 1 Data generation and presentation with fast cyclic voltammetry. (a) Input voltage waveform to the potentiostat (1.5 cycles of a 75 Hz triangular waveform scanning from −1.0 to +1.0 V vs Ag/AgCl at 300 Vs^{-1}). (b) Resultant current output from a carbon fibre microelectrode implanted in the striatum. Two signals, taken before and after stimulation of dopamine release, are shown superimposed. The signals are identical except for the oxidation (Ox) and reduction (Red) current due to the released dopamine. The remaining non-faradaic charging current does not change with dopamine release. (c) The oxidation region of the bottom left trace at higher amplification. A sample-and-hold circuit is set to monitor the current at the dopamine oxidation peak potential. the output from this circuit can be displayed directly onto an oscilloscope or chart recorder. (d) The sample-and-hold output from an electrode in the striatum. Electrical stimulation of the median forebrain bundle was performed every 5 min. Haloperidol (0.5 mg kg^{-1}) caused an increase in the amount of dopamine (DA) released by the stimulation.

lation 6 and their effects monitored for a further 1.5–3 h depending on their duration of action.

Data presentation and statistics

All drug-induced alterations in stimulated dopamine release were expressed as percentage change relative to the vehicle controls. Changes in dopamine release in the controls were subtracted from those in test animals to give the net drug-induced effect. This was done for each individual stimulation, as well as for the mean drug effect over the entire post-drug experimental period. The Mann–Whitney U test was used to compare dopamine release in drug- and vehicle-treated animals. Comparison of responses between striatum and nucleus accumbens was made by paired t test.

Terminology

Throughout this paper the term 'release' is used to denote the amount of dopamine that overflows from the synapse into the extracellular fluid where it is measured at the working electrode. This represents the difference between the amounts released by the neurones and that taken up again from the synapse before reaching the extracellular fluid. In all cases dopamine 'release' was recorded as the peak extracellular concentration attained during the stimulus train. The words 'striatum' and 'striatal' are taken to mean the neostriatum (or caudate-putamen complex), while 'limbic' is used here to describe the nucleus accumbens portion alone (i.e. excluding the olfactory tubercle).

Drugs and dosing

The following drugs were used at the doses stated: metoclopramide hydrochloride (Beechams, 10 mg kg^{-1}), *cis*- and *trans*-flupenthixol dihydrochloride (Lundbeck, 1 mg kg^{-1}), thioridazine hydrochloride (Sandoz, 10 mg kg^{-1}), haloperidol (Searle, 0.5 mg kg^{-1}), clozapine (Sandoz, 20 mg kg^{-1}), chlorpromazine hydrochloride (Sigma, 5 mg kg^{-1}), pimozide (Janssen, 1 mg kg^{-1}), sulpiride (Sigma, 100 mg kg^{-1}) and SCH 23390 (R-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol maleate: Schering, 1 mg kg^{-1}). The drugs were dissolved in 1% w/v tartaric acid and administered intraperitoneally in a dose volume of 0.33 ml 100 g^{-1} body weight. All drug doses refer to the base. Control animals received vehicle alone.

Results

Using the stimulating electrode co-ordinates described, peak evoked dopamine release for a standard stimulation (2 s train, 100 ± 10 μA r.m.s., 50 Hz) was greater ($P < 0.02$, paired t test) in striatum (2.90 ± 0.25 μM, mean ± s.e.mean, $n = 67$) than in nucleus accumbens (2.25 ± 0.18 μM). Preliminary experiments failed to reveal any correlation between pre-drug levels of dopamine release and the response to subsequent neuroleptic administration. Therefore all drug effects were calculated as percentages.

The vehicle controls were interspersed with drug-treated animals in order to minimize any external sources of variation. In the controls the release of dopamine declined slightly on successive stimulations over the course of the experiment. The rate of decline was constant and a little faster in striatum (17.6 ± 3.3% per hour, mean ± s.e. mean, $n = 8$) than nucleus accumbens (10.8 ± 1.5% per hour).

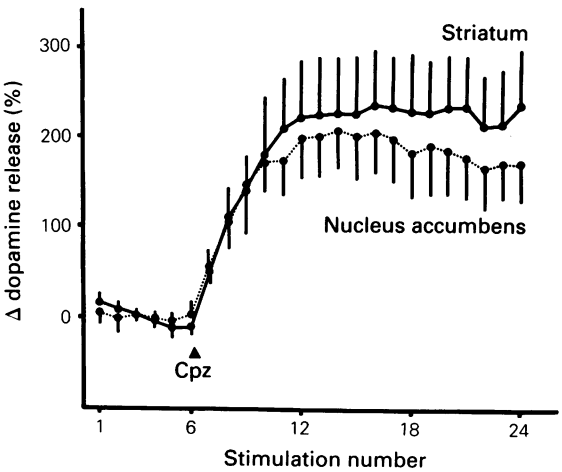

Figure 2 The effect of chlorpromazine (Cpz 5 mg kg^{-1} i.p.) upon stimulated dopamine release in the striatum (solid line) and nucleus accumbens (stippled line) expressed as the percentage change in release relative to the control period (stimulations 1–6). Each point is mean ($n = 6$) of the difference between drug and vehicle; vertical lines indicate s.e. mean. All values (stimulation 7 onward) in both nuclei are significantly different from vehicle-treated controls. ($P < 0.05$ to $P < 0.001$, Mann-Whitney U-test).

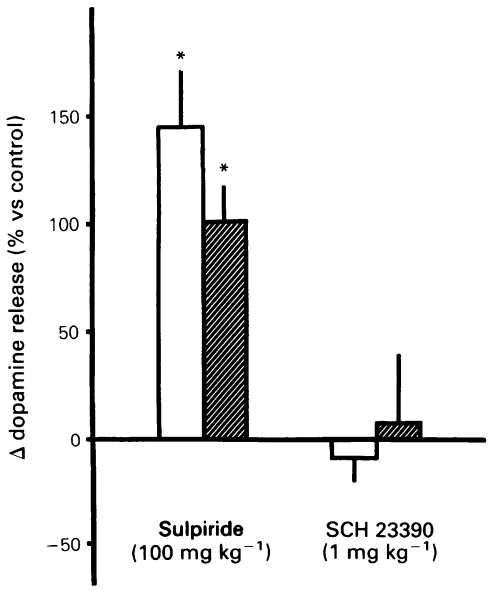

Figure 3 The effect of sulpiride (100 mg kg^{-1} i.p.) and SCH 23390 (1 mg kg^{-1} i.p.) upon stimulated dopamine release in striatum (open columns) and nucleus accumbens (hatched columns) expressed as the mean percentage change in release over stimulations 7–42 relative to vehicle-treated controls. Each column represents the mean, $n = 5$ or 8; vertical lines indicate s.e. mean. *$P < 0.001$ vs vehicle controls.

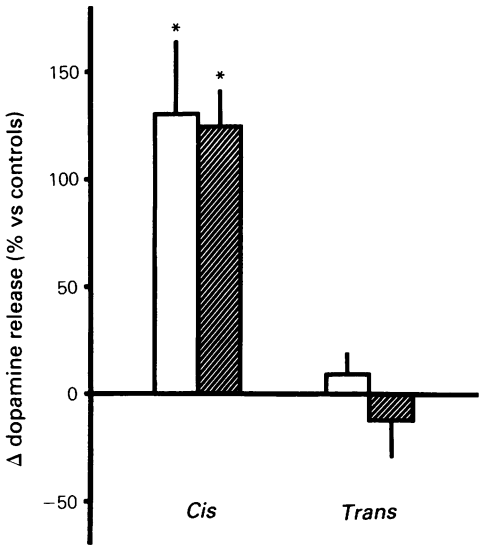

Figure 4 The effect of *cis*- and *trans*-flupenthixol (1 mg kg^{-1} i.p.) upon stimulated dopamine release in striatum (open columns) and nucleus accumbens (hatched columns) expressed as the mean percentage change in release over stimulations 7–42 relative to vehicle-treated controls. Each column represents the mean, $n = 4$ or 7; vertical lines indicate s.e. mean. *$P < 0.001$ vs vehicle controls.

Figure 2 shows the effect of chlorpromazine (5 mg kg^{-1}) upon dopamine release. Release was significantly elevated in both nuclei from the first post-drug stimulation onward, consistent with blockade of dopamine-mediated self inhibition of release. The maximum effect in the striatum (+ 237 ± 61%, mean ± s.e. mean, $n = 6$) was not significantly different from that in the nucleus accumbens (+ 207 ± 42%).

Chlorpromazine is a non-selective drug acting upon both D_1- and D_2-receptors (Clement-Cormier *et al.*, 1974; Andersen *et al.*, 1985). In an effort to define the receptor type involved in control of dopamine release, the effects of SCH 23390 and sulpiride were compared. SCH 23390 and sulpiride are highly selective blockers of dopamine D_1- and D_2-receptors, respectively (Jenner & Marsden, 1979; Hyttel, 1983). Figure 3 shows that sulpiride (100 mg kg^{-1}) significantly ($P < 0.001$) elevated release in both striatum (+ 143 ± 27%, mean ± s.e. mean, $n = 8$) and nucleus accumbens (+ 100 ± 16%), whereas SCH 23390 (1 mg kg^{-1}) had no effect in either nucleus.

The thioxanthene derivative flupenthixol exists as two isomers, *cis* and *trans*. Their separate effects upon release were compared (Figure 4). *cis*-

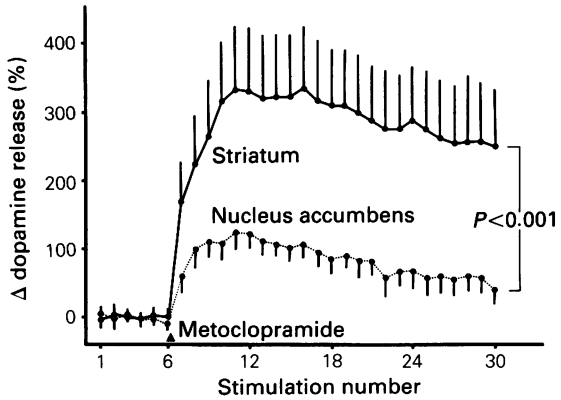

Figure 5 The effect of metoclopramide (10 mg kg^{-1} i.p.) upon stimulated dopamine release in the striatum (solid line) and nucleus accumbens (stippled line) expressed as the percentage change in release relative to the control period (stimulations 1–6). Each point is mean ($n = 8$) of the difference between drug and vehicle-treated groups; vertical lines indicate s.e. mean. All striatal values (stimulation 7 onward) are significantly ($P < 0.001$, Mann-Whitney U-test) different from vehicle-treated controls. Values in nucleus accumbens: $P < 0.001$ (stimulations 8–19, 21), $P < 0.01$ (stimulations 7, 20), $P < 0.05$ (stimulations 23, 24, 28, 29). All other values were not significantly different. The effect in the striatum was significantly greater than that in the nucleus accumbens ($P < 0.001$, paired t test).

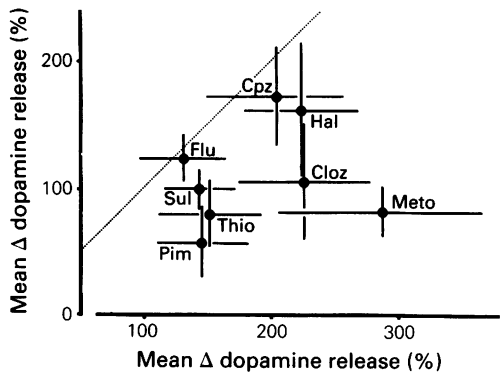

Figure 6 Comparative effects of neuroleptics upon stimulated dopamine release in the striatum (horizontal axis) and nucleus accumbens (vertical axis). Each point is the averaged percentage change in release over the entire post-dosing period (mean ± s.e. mean, $n = 6$–8). The stippled line represents the position of equal effect in both nuclei. Drugs are *cis*-flupenthixol (Flu), 1 mg kg^{-1}; sulpiride (Sul), 100 mg kg^{-1}; pimozide (Pim), 1 mg kg^{-1}; thioridazine (Thio), 10 mg kg^{-1}; chlorpromazine (Cpz), 5 mg kg^{-1}; haloperidol (Hal), 0.5 mg kg^{-1}; clozapine (Cloz), 20 mg kg^{-1}; metoclopramide (Meto), 10 mg kg^{-1}.

Flupenthixol (1 mg kg^{-1}) significantly increased stimulated dopamine release ($P < 0.001$) in striatum (+ 131 ± 33%, mean ± s.e. mean, $n = 7$) and nucleus accumbens (+ 124 ± 16%). The *trans*-isomer had no effect, indicating stereoselectivity of the receptor.

Metoclopramide is a selective D_2-receptor antagonist almost devoid of antipsychotic properties, but nevertheless causes extrapyramidal side-effects (Reid, 1977) implying an action in the nigrostriatal system. Figure 5 shows the effect of metoclopramide upon stimulated dopamine release. Release was significantly ($P < 0.001$) elevated in both nuclei. However, the effect was greater ($P < 0.001$) in the striatum (+ 334 ± 94%, mean ± s.e. mean, $n = 8$) than in the nucleus accumbens (+ 123 ± 21%).

Thioridazine and clozapine are atypical antipsychotics in that they have a low tendency to cause extrapyramidal side-effects (Simpson *et al.*, 1978; Gerlach & Simmelsgaard, 1978). Figure 6 shows the effects of these and other neuroleptics upon dopamine release in the striatum (horizontal axis) and nucleus accumbens (vertical axis). The stippled line shows the region of equal effect in both nuclei. None of the drugs showed greater effect in the nucleus accumbens than striatum. Indeed, throughout the group the trend was toward a greater effect in striatum. Only chlorpromazine and *cis*-flupenthixol showed equal effect in the two regions.

Discussion

Several studies, *in vitro* and *in vivo*, have shown differences in the effects of neuroleptics in the mesolimbic and nigrostriatal systems. At the cell body level it has been shown that atypical neuroleptics enhance the firing of cells in the ventral tegmental area (A10) without effect in the substantia nigra (A9) (White & Wang, 1983; Hand *et al.*, 1987a,b). Other neurochemical studies have shown that these drugs elevate dopamine release selectively in the mesolimbic terminals (Bartholini, 1976). However, it is unclear from these studies whether or not the elevation of dopamine release is due to blockade of dopamine receptors on the nerve terminals. It is possible that an elevation of cell firing rate may be responsible, at least in part, for the observed changes.

In order to test this hypothesis it is necessary to investigate the effects of the neuroleptics in a preparation where the action potential traffic can be decided by the experimenter and is not under the control of the cell body. One popular means of achieving this has been stimulated brain slice.

However, field stimulation or potassium, as commonly used, are rather crude means of causing transmitter release. Firstly, they cause direct depolarization of the nerve terminals without necessarily evoking action potential traffic. Secondly, they are unlikely to cause a selective release of the transmitter of interest, in this case dopamine. It is highly likely that many other transmitters present in the striatum (acetylcholine, glutamate and γ-aminobutyric acid (GABA)) would be released simultaneously.

The alternative approach used here is to place a stimulating electrode in the region of the ascending dopaminergic axons in the intact animal. Thus it is possible to stimulate dopamine release from the terminals by the passage of action potentials. In addition, other neurotransmitter systems are unaffected, except indirectly as a consequence of dopamine release.

The presence in our experimental regime of a stimulating electrode between cell body and nerve terminal means that action potential traffic was primarily controlled by the stimulation itself. Although there is a reciprocal striatonigral pathway (Dray, 1979) to the substantia nigra (Nauta & Domesick, 1984) and ventral tegmental area (Scheel Kruger, 1986), any actions of the neuroleptics upon this feedback loop are unlikely to be detected in our experimental protocol.

The variety of structural classes of the neuroleptics used in this study makes it unlikely that the observed effects are a chemical artefact. The phenothiazines (chlorpromazine, thioridazine), butyrophenones (haloperidol), thioxanthenes (flupenthixol), benzamides (metoclopramide, sulpiride, pimozide) and dibenzodiazepines (clozapine) have little structural similarity. At the receptor level it is apparent that many neuroleptics block receptors other than those for dopamine. Some inhibit binding to adrenoceptors (α) and 5-hydroxytryptamine (5-HT_2) receptors in addition to their effects at dopamine receptors (Seeman, 1981). Others have actions at muscarinic receptors (Jenner & Marsden, 1979). Often these properties are peculiar to the individual chemical class of the drug. However, dopamine receptor blockade is a property shared by all of the drugs used in this study (Seeman & Grigoriadis, 1987). One cannot, nevertheless, unequivocally exclude the possibility that all of the drugs share actions at another non-dopamine receptor type that influences dopaminergic neurotransmission.

The drugs used in the present study covered the entire range of D_1/D_2-receptor selectivity, based on *in vitro* binding studies. SCH 23390 is the most selective D_1-blocker (Hyttel, 1983) with a selectivity ratio, determined by K_i values, greater than 5000 (Andersen *et al.*, 1985). *cis*-Flupenthixol, thioridazine, clozapine and chlorpromazine show broadly similar potency at D_1- and D_2-sites whereas metoclopramide, pimozide and sulpiride are highly selective D_2-receptor blockers (Jenner & Marsden, 1979). Uniquely, SCH 23390 had no effect on dopamine release in either nucleus. SCH 23390 reputedly retains D_1-selectivity in rats at doses up to $3\,mg\,kg^{-1}$ (Meller *et al.*, 1985) and, when used at the same dose as in the present study ($1\,mg\,kg^{-1}$), causes no change in striatal tyrosine hydroxylase activity or L-DOPA accumulation after NSD 1015 (Onali *et al.*, 1985). Studies with cerebral dialysis have shown that SCH 23390 blocks the SKF 38393-induced depression of striatal dopamine release without itself affecting dopamine release (Zetterstrom *et al.*, 1986).

Dopamine D_1-receptors are found at high concentrations in the nucleus accumbens and striatum as well as the substantia nigra (Dawson *et al.*, 1985; Scatton & Dubois, 1985), where very low levels are found in the ventral tegmental area (Dawson *et al.*, 1986). Within the nigrostriatal system they are found only postsynaptically within the striatum (Filloux *et al.*, 1987) and presynaptically in the substantia nigra (Altar & Hauser, 1987). The absence of effect of SCH 23390 on stimulated (this study) or basal dopamine release (Zetterstrom *et al.*, 1986) indicates that dopamine does not influence its own release via D_1-receptors under normal circumstances.

The evidence of the present study is consistent with the view that dopamine release *in vivo* is under the control of D_2-but not D_1-receptors (Boyar & Altar, 1987). *In vitro* studies also imply that dopamine release is under D_2-receptor control (Lehmann *et al.*, 1981; Herdon *et al.*, 1987). Within the brain, D_2-receptors are present at a high concentration in the striatum and nucleus accumbens (Gehlert & Wamsley, 1985) as well as the cell body regions (Stoof & Kebabian, 1984). In the present study, for the reasons already argued, it seems likely that the observed effect is due solely to those actions in the terminal fields.

The autoreceptor in both striatum and nucleus accumbens shows stereoselectivity, as previously found for striatum (Arbilla & Langer, 1981; Heikila *et al.*, 1983). *cis*-Flupenthixol elevated dopamine release whereas the *trans*-isomer at the same dose had no effect. This is consistent with *in vitro* data showing that *cis*-flupenthixol is at least forty times as potent at D_2-receptors as the *trans*-isomer (Fleminger *et al.*, 1983; Andersen *et al.*, 1985).

One major finding of the present study is the absence of any selective effect of the atypical neuroleptics on dopamine release in the nucleus accumbens. A conflicting picture is apparent from various other studies of the nigrostriatal and mesolimbic systems *in vivo*. The early study of Bartholini (1976) first drew attention to a selective enhancement of

limbic dopamine release by clozapine. At the nerve cell body level it has been shown that clozapine and thioridazine increase the number of spontaneously active cells in the ventral tegmental area without an effect in the substantia nigra (White & Wang, 1983). Thioridazine and clozapine also selectively elevate the firing rate of A10 but not A9 cells (Hand *et al.*, 1987a,b), although others have failed to observe this effect (Chiodo & Bunney, 1983). Conversely, studies of dopamine metabolites generally fail to reveal any limbic selectivity of atypical neuroleptics (Stawarz *et al.*, 1975; Elliott *et al.*, 1977; Maidment & Marsden, 1986) in agreement with the present release study. This would seem to indicate a dissociation of dopamine release and metabolism from neuronal cell firing.

It seems likely that the purported changes in basal limbic dopamine release after atypical neuroleptics stem, in part at least, from the parallel elevation of cell firing rate observed. The present study, in which actions at the terminal are recorded without significant interference from the cell body firing rate, reveals no limbic selectivity of the atypical neuroleptics. We cannot exclude the possibility that limbic selectivity occurs only in a very narrow dose range beyond those selected for this investigation. However, the dose of clozapine used in the present study was the same as that shown by White & Wang (1983) to cause selective activation of A10 neurones. The thioridazine dose here was half of that used by White & Wang (1983). It seems improbable that a two fold change in dose can reverse the selectivity of a drug. Thus, we conclude that after acute administration there is no selective effect of the atypical neuroleptics upon dopamine autoreceptors in the nucleus accumbens.

Conversely, the actions of metoclopramide do appear to match the profile of this drug. Behavioural (Costall *et al.*, 1978) and electrophysiological (White & Wang, 1983) studies indicating a nigrostriatal selectivity of this drug are matched by the present work in which metoclopramide potentiated dopamine release more in striatum than nucleus accumbens. Thus, in contrast to the atypical neuroleptics, the selectivity of metoclopramide does seem to be manifested at the nerve terminal level.

One cannot, of course, rule out a contribution of general anaesthesia to the results obtained in the present study. A recent study (Ford & Marsden, 1986) showed that chloral hydrate attenuated the effects of apomorphine and haloperidol upon striatal dopamine metabolism. Nevertheless, the experiments of White & Wang (1983), which showed limbic selectivity at the cell body level for clozapine and thioridazine, were also conducted in chloral hydrate-anaesthetized rats. Further experiments in conscious animals are nonetheless necessary to remove this potential source of concern.

In conclusion, the present study shows that striatal and limbic dopamine release is controlled by stereoselective D_2-autoreceptors at the level of the nerve terminal. No effects of D_1-receptor blockade were observed. We were unable to demonstrate any limbic selectivity of the atypical neuroleptics at these nerve terminal autoreceptors. We therefore conclude that other sites in the nigrostriatal and mesolimbic circuitry mediate the proposed limbic selectivity of the atypical antipsychotics.

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