Excitatory neuronal responses to dopamine in the cerebral cortex: involvement of D_2 but not D_1 dopamine receptors

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1   The technique of microelectrophoresis was used to evaluate the relative contribution of D_1 and D_2 dopamine receptors towards the mediation of the excitatory response of single neurones to dopamine in the somatosensory cortex of the rat.

2   The selective D_1 dopamine receptor agonist, SKF 38393, failed to excite any of the cells to which it was applied. In contrast, the selective D_2 dopamine receptor agonist, LY 171555, excited the majority of cells tested. The apparent potency of LY 171555 was significantly lower than that of dopamine.

3   When the mobilities of SKF 38393 and LY 171555 were assessed by an *in vitro* method, they were found to be at least as great as those of dopamine and phenylephrine, suggesting that the lack of effect of SKF 38393 and the lower apparent potency of LY 171555 compared to dopamine reflect genuine biological phenomena.

4   The α_1-adrenoceptor antagonist, prazosin, discriminated between excitatory responses to the α_1-adrenoceptor agonist, phenylephrine, and LY 171555: responses to phenylephrine were more susceptible to antagonism than were those to LY 171555. The dopamine receptor antagonist, haloperidol, produced the reverse discrimination: responses to LY 171555 were more affected than were those to phenylephrine. Neither antagonist reduced the response to the control agonist, acetylcholine.

5   When applied continuously with low ejecting currents, LY 171555 antagonized the excitatory response to dopamine while the response to phenylephrine was relatively preserved. The response to acetylcholine was unaffected. When similarly applied, SKF 38393 had no selective action on the response to dopamine.

6   These results suggest that D_2 dopamine receptors are involved in mediating the excitatory neuronal response to dopamine in the cerebral cortex, whereas D_1 dopamine receptors are unlikely to be involved. LY 171555 appears to act as a partial agonist at D_2 dopamine receptors in this test system.

Introduction

Single neurones in the somatosensory cerebral cortex of the rat can respond with both excitation and depression to noradrenaline and dopamine applied by microelectrophoresis (Bevan *et al.*, 1978). At least three different receptors have been implicated in the mediation of these responses: α_1- and β-adrenoceptors, respectively, in the case of the excitatory and depressant responses to noradrenaline (Bevan *et al.*, 1977) and 'excitatory dopamine receptors' in the case of the excitatory response to dopamine (Bradshaw *et al.*, 1983). Thus, the excitatory responses to these amines are amenable to pharmacological separation by means of selective α_1-adrenoceptor and dopamine receptor antagonists: the response to noradrenaline is more

susceptible to antagonism by phenoxybenzamine, while the response to dopamine is more susceptible to antagonism by haloperidol and α-flupenthixol (Bevan *et al.*, 1978).

It has become apparent in recent years that binding sites for dopamine and its congeners in the central nervous system do not represent a homogeneous population but, rather, can be resolved into at least four components (Seeman, 1981). Of these multiple binding sites the two most likely to subserve a physiological function have been termed D_1- (positively linked to adenylate cyclase activation) and D_2- (unlinked or negatively linked to adenylate cyclase activation) receptors (Kebabian & Calne, 1979). Alth-

ough both D_1- and D_2-receptors have been identified in the cerebral cortex (Thierry *et al.*, 1984), the possibility that one or both of these putative dopamine receptors may mediate the electrophysiological actions of microelectrophoretically applied dopamine has not been systematically explored.

In the present investigation we have used two selective dopamine receptor agonists (Kebabian *et al.*, 1984): SKF 38393 (D_1-receptor agonist) and LY 171555 (the active (−)-enantiomer of LY 141865, a D_2-receptor agonist), in an attempt to identify the sub-type of dopamine receptor involved in the excitatory neuronal response to dopamine in the rat cerebral cortex.

A preliminary account of the present work has been communicated to the British Pharmacological Society (Bradshaw *et al.*, 1985).

Methods

Male Wistar rats, weighing 230 to 270 g, were anaesthetized with halothane (3% in oxygen). Following induction the animals were transferred to a stereotaxic assembly and maintained under anaesthesia with halothane (0.8 to 1.0%) administered via a face mask. Preparation of the recording site (parietal cerebral cortex – stereotaxic coordinates according to König & Klippel (1963): A 4.8–6.5, L 0.9–2.4) has been described previously (Bradshaw & Szabadi, 1972). Rectal temperature was maintained between 37° and 38°C by means of a feedback-controlled heating blanket.

Six-barrelled micropipettes, drawn from glass fibre-containing capillary tubing, were filled with drug solutions immediately prior to use. Two barrels of each micropipette contained 4.0 M NaCl, one for the extracellular recording of action potentials, the other for current balancing. Unless otherwise stated, all drugs were dissolved in twice distilled water. The following drug solutions were used: (−)-phenylephrine HCl (0.05 M, pH 5.8 to 6.1); dopamine HCl (0.05 M, pH 5.4 to 6.1); acetylcholine Cl (0.05 M, pH 6.2 to 6.5); LY 171555 HCl (0.05 M, pH 6.2 to 6.5); SKF 38393 HCl (0.025 M, pH 5.6 to 5.8); prazosin HCl (0.001 M, pH;5.1 to 5.4); haloperidol (0.005 M dissolved in 0.005 M tartaric acid, pH 3.7 to 3.8). LY 171555 (*trans*-(−)-4aR-4,4a,5,6,7,8,8a,9-octa-hydro-5-propyl-2H-pyrazolo [3,4-g] quinoline) was a gift from Lilly Research Laboratories, Indianapolis, U.S.A., and SKF 38393 (7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine) was a gift from Smith Kline & French Laboratories, Philadelphia, U.S.A.

After filling, the micropipettes were broken back under microscopic control to yield tip diameters of 3.0 to 5.0 μm. Our methods for the extracellular recording of action potentials and for the microelectrophoretic

application of drugs have been described elsewhere (Bradshaw *et al.*, 1973a,b). Drug ions were released either by positive ejecting currents or by removal of the retaining current to facilitate diffusional release. Between successive applications of agonists retaining currents of − 10 nA were passed; retaining currents of − 25 nA were used for the antagonists. Electrodes were lowered through the cortex in steps of 2 to 4 μm until a suitable spontaneously active unit was encountered. The neuronal activity, bandpass-filtered in the range 100 Hz to 8 kHz, was continuously monitored on an oscilloscope. All spikes crossing a variable window discriminator were counted by a ratemeter (1 s time constant) and the ratemeter output, in spikes s^{-1}, was routed to a curvilinear chart recorder. When a suitable unit was found the agonists were applied in a regular cycle to standardize the effects of retaining current upon the subsequent electrophoretic release of drug (Bradshaw *et al.*, 1973b).

The agonistic actions of SKF 38393 were examined on cells that gave consistent excitatory responses to both phenylephrine and acetylcholine. A cell was considered to be unresponsive to SKF 38393 if no change in spontaneous firing rate was observed following application of this compound with ejecting currents of up to 200 nA for 1 min. The agonistic effects of LY 171555 were assessed by inclusion of this compound in an ejection cycle either with phenylephrine and acetylcholine, or with dopamine and acetylcholine. Cells were considered to be unresponsive to LY 171555 when no change in spontaneous firing rate was observed following application of LY 171555 with ejecting currents of up to 125 nA for 1 min. The relative potencies of LY 171555 and dopamine were established by comparing the plateau increase in firing rate produced by each of these agonists when applied with ejecting currents of 25 nA (equicurrent magnitude ratio: Bradshaw *et al.*, 1981a). A second parameter of the excitatory responses to LY 171555 and dopamine, the recovery time, was measured as the time taken for neuronal activity to return to baseline firing frequency following discontinuation of agonist application (Bradshaw *et al.*, 1973b).

The effects of antagonists were evaluated in the following way. When suitable control responses to the agonists had been obtained the antagonist was applied continuously, either by removal of the retaining current (allowing the drug to diffuse out from the micropipette), or by the passage of a small ejecting current (5 to 15 nA), and the time-course of the developing antagonism was followed. After a steady-state antagonism of the responses to the agonists had been obtained, the application of the antagonist was continued until a further response to the control agonist had been evoked. The application of the antagonist was then terminated and the time-course of

recovery was followed. Acetylcholine was used throughout as the control agonist. The degree of antagonism of responses to the agonists was expressed as the percentage change in the size of the response from the size of the control response, measured planimetrically directly from the ratemeter record (Bradshaw et al., 1973b). Values are expressed as mean ± s.e.mean. Statistical comparisons were made by the Student's t test.

The relative mobilities of dopamine, phenylephrine, SKF 38393 and LY 171555 were compared by the method of Bradshaw et al. (1981b). Six-barrelled micropipettes were prepared as described previously (Bradshaw et al., 1973a). Three barrels of each pipette were filled with a mixture of [methylene-^{14}C]-noradrenaline bitartrate (0.05 M, 1.0 mCi mmol^{-1}) and one of the following drugs (0.05 M): phenylephrine HCl (12 micropipettes), dopamine HCl (10 micropipettes), LY 171555 HCl (six micropipettes), SKF 38393 HCl (six micropipettes). In each pipette the efflux of radioactive material was measured during a series of 10 min periods. Initially the rate of spontaneous efflux was measured (two samples). Then the rate of efflux was measured during the passage of + 50 nA simultaneously through all three drug-containing barrels (four samples). Finally, spontaneous efflux was again measured (two samples). The transport number of noradrenaline, in the presence of each of the four added drugs, was determined as described previously (Bradshaw et al., 1981b). Statistical comparisons were made with Student's t test.

Results

Agonistic effects of SKF 38393 and LY 171555

Agonistic effects of SKF 38393 The effect of SKF 38393, applied with ejecting currents of up to 200 nA, was investigated on 17 neurones which gave consistent excitatory responses to phenylephrine and acetylcholine. On none of these cells could any excitatory effect of SKF 38393 be detected.

Agonistic effects of LY 171555 The effect of LY 171555 was investigated on 49 cells that gave consistent excitatory responses to phenylephrine and acetylcholine. Of these, 31 cells yielded an excitation to LY 171555. When tested on 9 neurones that gave consistent excitatory responses to dopamine and acetylcholine, LY 171555 produced excitation on 7 of these cells. However, on the remaining 18 phenylephrine- and 2 dopamine-sensitive cells, it was not possible to evoke any response to LY 171555 applied with ejecting currents of up to 125 nA for 1 min.
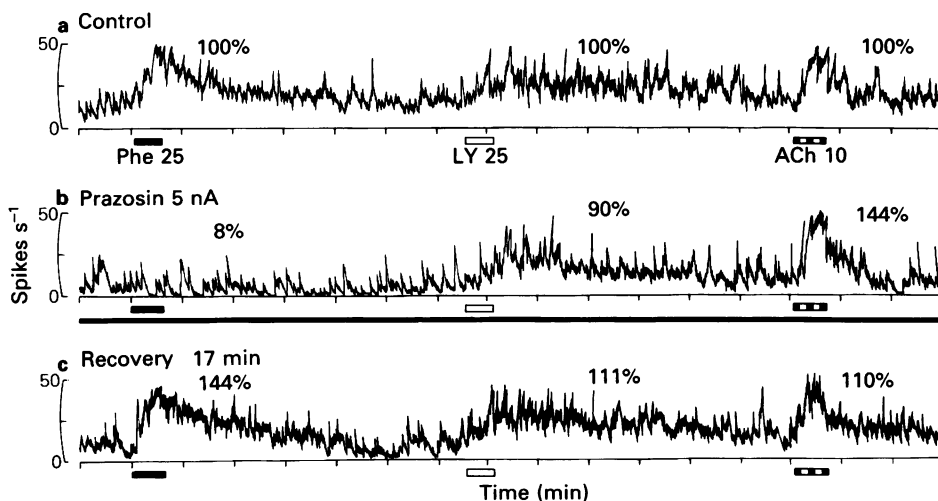

Figure 1   Effect of prazosin on excitatory responses to phenylephrine (Phe), LY 171555 (LY) and acetylcholine (ACh). Excerpts from the ratemeter recording of the firing rate of a single cortical neurone; ordinate scale: firing rate (spikes s^{-1}); abscissa scale: running time (min). Horizontal bars below the traces indicate microelectrophoretic drug applications; numbers refer to intensities of ejecting current (nA). Numbers above the traces indicate the sizes of the responses (total spike number, %), taking the size of the control response to each agonist as 100%. (a) Control responses to the agonists. (b) Responses to the agonists during the continuous application of prazosin (5 nA). At the start of trace (b) prazosin had been applied continuously for 18 min. The response to phenylephrine was reduced to a much greater extent than the response to LY 171555 while the response to acetylcholine was not diminished. (c) Recovery of the responses 17 min after the application of prazosin had been terminated.
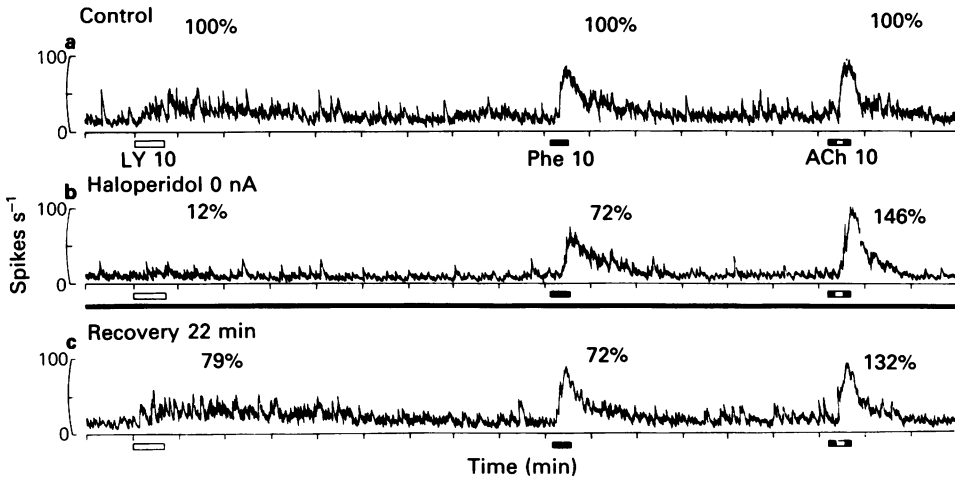
Figure 2 Effect of haloperidol on excitatory responses to LY 171555 (LY), phenylephrine (Phe) and acetylcholine (ACh). Excerpts from the ratemeter recording of the firing rate of a single cortical neurone (convention as in Figure 1). (a) Control responses to the agonists. (b) Responses to the agonists during the continuous diffusional application of haloperidol. At the start of trace (b) haloperidol had been applied continuously for 21 min. The response to LY 171555 was antagonized to a much greater degree than the response to phenylephrine. The response to acetylcholine was not diminished. (c) Partial recovery of the response to LY 171555 22 min after the application of haloperidol had been terminated.

Comparison of apparent potencies of LY 171555 and dopamine When applied with ejecting currents of 25 nA, LY 171555 and dopamine evoked equilibrium increases in firing rate of 13.1 ± 0.8 spikes s^{-1} (31 cells) and 18.4 ± 1.1 spikes s^{-1} (30 cells), respectively. These values were significantly different ($P < 0.001$) and yielded an equicurrent magnitude ratio of 0.71 (LY 171555:dopamine).
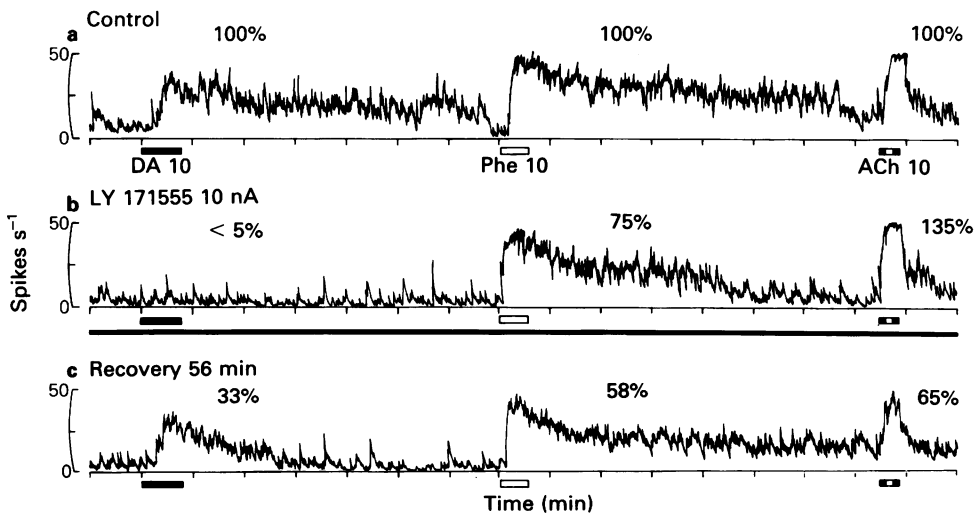

Figure 3 Effect of LY 171555 on excitatory responses to dopamine (DA), phenylephrine (Phe) and acetylcholine (ACh). Excerpts from the ratemeter recording of the firing rate of a single cortical neurone (convention as in Figure 1). (a) Control responses to the agonists. (b) Responses to the agonists during the continuous application of LY 171555 (10 nA). At the start of trace (b) LY 171555 had been applied continuously for 27 min. While the response to dopamine was abolished, the response to phenylephrine was only minimally reduced. The response to acetylcholine was not diminished. (c) Partial recovery of the response to dopamine 56 min after the application of LY 171555 had been terminated (note small decrease in sizes of responses to phenylephrine and acetylcholine).

Comparison of time-courses of responses to LY 171555 and dopamine The recovery times of the responses to LY 171555 and dopamine, each applied with an ejecting current of 25 nA, were 285.0 ± 12.0 s (31 cells) and 161.1 ± 9.8 s (30 cells), respectively. The recovery time of the response to LY 171555 was significantly longer than that to dopamine ($P < 0.001$).

Effects of prazosin and haloperidol on responses to phenylephrine and LY 171555

Effects of prazosin The antagonistic effects of prazosin (5 nA) were examined on 9 cells that gave

consistent excitatory responses to phenylephrine (10–25 nA), LY 171555 (25 nA) and acetylcholine (10–25 nA). Prazosin produced a significant reduction in the size of the responses to both phenylephrine and LY 171555 without affecting the response to acetylcholine. Moreover, there was a statistically significant difference between the degrees of antagonism of the responses to phenylephrine and LY 171555, the response to LY 171555 being less affected than the response to phenylephrine. An example of the effect of prazosin on one cell is illustrated in Figure 1 and the antagonistic actions of prazosin on all cells studied are summarized in Figure 4a. On some of the cells, the
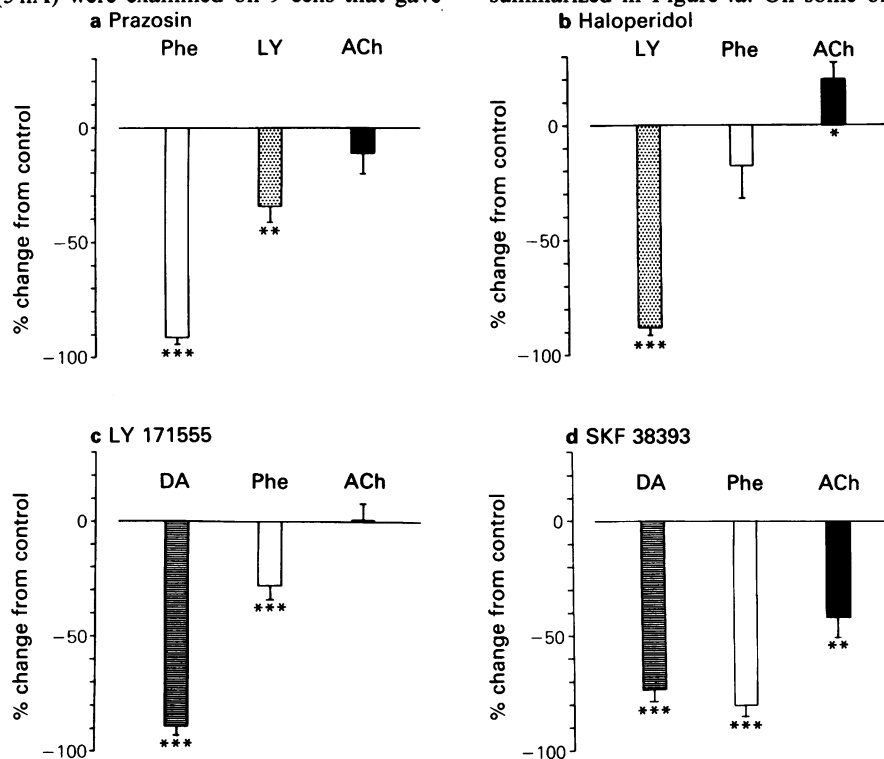

Figure 4 Summary of antagonistic effects of prazosin, haloperidol, LY 171555 and SKF 38393 on excitatory responses to phenylephrine (Phe), LY 171555 (LY), dopamine (DA) and acetylcholine (ACh). For each agonist the length of the column represents the mean percentage change from control of the size of the response (total spike number) in the presence of the antagonist; vertical bars indicate s.e.mean. Significant changes from control values: * $P<0.05$; ** $P<0.002$; *** $P<0.001$ (Student's t test, paired comparison). (a) Effect of prazosin on responses to phenylephrine, LY 171555 and acetylcholine (9 cells). Prazosin significantly antagonized the responses to phenylephrine and LY 171555 but had no significant effect on responses to acetylcholine. Prazosin had a significantly greater effect on responses to phenylephrine than on responses to LY 171555 ($P<0.001$; t test, paired comparison). (b) Effect of haloperidol on responses to LY171555, phenylephrine and acetylcholine (10 cells). Haloperidol significantly antagonized the response to LY 171555 but had no significant effect on the response to phenylephrine. The response to acetylcholine was not reduced. Haloperidol had a significantly greater effect on the response to LY 171555 than on the response to phenylephrine ($P<0.001$). (c) Effect of LY 171555 on responses to dopamine, phenylephrine and acetylcholine (14 cells). LY 171555 significantly antagonized the responses to dopamine and phenylephrine but had no significant effect on the response to acetylcholine. LY 171555 had a significantly greater effect on the response to dopamine than on the response to phenylephrine ($P<0.001$). (d) Effect of SKF 38393 on responses to dopamine, phenylephrine and acetylcholine (9 cells). SKF 38393 had no selective effect on the response to dopamine, responses to all 3 agonists being significantly diminished.

application of prazosin resulted in a small drop in the firing rate, and this was occasionally accompanied by an increase in the size of the response to acetylcholine (see, for example, Figure 1).

Effects of haloperidol The antagonistic effects of haloperidol (0–5 nA) were examined on 10 cells that yielded consistent excitations to LY 171555 (10–100 nA), phenylephrine (10–50 nA) and acetylcholine (10–35 nA). Haloperidol selectively and reversibly antagonized responses to LY 171555 without affecting responses to phenylephrine. Responses to the control agonist, acetylcholine, were not diminished. An example of the action of haloperidol on one cell is shown in Figure 2. The results from all cells studied are summarized in Figure 4b. On most of the cells, the application of haloperidol resulted in a small decrease in the firing rate of the cell, and this was accompanied by an increase in the size of the response to acetylcholine (see Figures 2 and 4b).

Antagonistic effects of LY 171555 and SKF 38393 on responses to dopamine and phenylephrine

Effects of LY 171555 On 14 cells that gave reproducible responses to dopamine (10–50 nA), phenylephrine (5–25 nA) and acetylcholine (5–15 nA), continuous application of LY 171555 (5–25 nA) produced a significant reduction in the size of the responses to dopamine and phenylephrine while the response to acetylcholine was unaffected. Furthermore, LY 171555 produced a significantly greater attenuation of the response to dopamine than of the response to phenylephrine. An example of this action of LY 171555 on one cell is illustrated in Figure 3 and a summary of the antagonistic effects of LY 171555 on all cells is shown in Figure 4c.

Effects of SKF 38393 The effects of SKF 38393 (5 nA) were examined on 9 cells that gave consistent excitations to dopamine (15–50 nA), phenylephrine (10–25 nA) and acetylcholine (10–25 nA). SKF 38393 had no selective action on responses to dopamine: responses to all 3 agonists were significantly diminished. The effect of SKF 38393 on all cells studied is summarized in Figure 4d.

Comparison of the mobilities of dopamine, phenylephrine, SKF 38393 and LY 171555

The transport number (mean ± s.e.mean) of noradrenaline in the presence of the added drugs was as follows: 0.126 ± 0.005 (phenylephrine HCl), 0.104 ± 0.004 (dopamine HCl), 0.080 ± 0.001 (LY 171555 HCl), 0.127 ± 0.004 (SKF 38393 HCl). The transport number of noradrenaline was not significantly different in the presence of phenylephrine

HCl and SKF 38393 HCl ($P > 0.1$). However, a significantly lower transport number was measured in the presence of both dopamine HCl and LY 171555 HCl ($P < 0.01$). Furthermore, the transport number of noradrenaline was lower in the presence of LY 171555 HCl than in the presence of dopamine HCl ($P < 0.01$).

Discussion

When applied by microelectrophoresis onto single cortical neurones SKF 38393, a selective D_1 dopamine receptor agonist (Setler *et al.*, 1978), and LY 171555, the active (−)-enantiomer of the selective D_2 dopamine receptor agonist, LY 141865 (Tsuruta *et al.*, 1981), had differential effects: while LY 171555 excited most neurones, SKF 38393 did not evoke any response. The lack of effect of SKF 38393 was unlikely to have been due to inadequate release of this compound from the micropipette since the transport number of SKF 38393 did not differ from that of phenylephrine. When excitatory responses to LY 171555 and dopamine, evoked by identical ejecting currents, were compared, the response to LY 171555 had a lower plateau and a longer recovery time than the response to dopamine. The lower plateau of the response to LY 171555 and thus the lower apparent potency of this compound, could not be attributed to a lower rate of release of LY 171555 from the micropipette since the electrophoretic mobility of LY 171555 was greater, when measured *in vitro*, than that of dopamine. The longer recovery time of the response to LY 171555 compared with that to dopamine is likely to reflect the slower rate of elimination of LY 171555 from the receptor sites (Szabadi & Bradshaw, 1974).

The excitatory response to LY 171555 could be antagonized both by the selective α_1-adrenoceptor antagonist, prazosin, and by the selective dopamine receptor antagonist, haloperidol. However, when the effects of these two antagonists on excitatory responses to phenylephrine and LY 171555 were compared, the antagonists produced contrasting effects: while the response to phenylephrine was preferentially antagonized by prazosin, the response to LY 171555 was more susceptible to antagonism by haloperidol. This observation is in agreement with earlier evidence for the existence of an excitatory dopamine receptor on cortical neurones which is pharmacologically distinct from the excitatory α_1-adrenoceptor (Bevan *et al.*, 1978; Bradshaw *et al.*, 1983). Moreover the selective antagonism of the excitatory responses to LY 171555 (present data) and dopamine (Bevan *et al.*, 1978; Bradshaw *et al.*, 1983) by haloperidol is consistent with the notion that the receptor mediating these responses belongs to the D_2-sub-type. Firstly, in

binding studies, haloperidol has at least a 200 fold greater affinity for D_2 than for D_1 dopamine receptors (Seeman, 1981; Christensen et al., 1984), and secondly, in a functional biochemical study, haloperidol has been reported to be approximately 900 times morpotent at the D_2- than at the D_1-receptor (Plantjé et al., 1984).

As SKF 38393 was without any agonistic potency and LY 171555 had a relatively low agonistic potency, it was possible to apply each of these drugs continuously with low ejecting currents without any appreciable effect on firing rate, and to study their effects on neuronal responses to dopamine and phenylephrine. While SKF 38393 had no specific effect on the responses to these amines, LY 171555 selectively antagonized the responses to dopamine, thus confirming an interaction between LY 171555 and dopamine at the same receptor. The relatively low agonistic potency of LY 171555 in comparison with dopamine and its ability to antagonize the response to dopamine suggest that LY 171555 interacts as a partial agonist with the neuronal D_2 dopamine receptor.

In conclusion, our results provide evidence for a role of D_2 dopamine receptors in mediating the excitatory response to dopamine in the cerebral cortex and fail to support a similar role for D_1 dopamine receptors. The physiological role of the D_2 dopamine receptors in the parietal cortex is not clear. It is unlikely that these receptors are activated by dopamine released from dopaminergic terminals since this area of cortex is hardly, if at all, innervated by dopaminergic fibres (Lindvall & Björklund, 1984). It is possible that these receptors are 'silent' under physiological conditions, or they might be activated by noradrenaline released from noradrenergic terminals which are abundant in the parietal cortex (Lindvall & Björklund, 1984).

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