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EFFECTS OF DESIPRAMINE ON NEURONAL RESPONSES TO DOPAMINE, NORADRENALINE, 5-HYDROXYTRYPTAMINE AND ACETYLCHOLINE IN THE CAUDATE NUCLEUS OF THE RAT

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1 The sensitivity of single neurones to microelectrophoretically applied dopamine, noradrenaline (NA), 5-hydroxytryptamine (5-HT) and acetylcholine (ACh) was investigated in the caudate nucleus of the rat, anaesthetized with halothane. Both excitatory and depressant responses could be observed to each of the agonists. There was a high correlation between the direction of responses to dopamine and noradrenaline, whereas there was no significant correlation between the direction of responses to dopamine and ACh.

2 The effect of desipramine was studied on both excitatory and depressant responses to dopamine, NA and 5-HT, and on excitatory responses to ACh. Both potentiation and antagonism of neuronal responses to monoamines and ACh could be observed after a brief application of desipramine.

3 Excitatory responses to glutamate were not affected by desipramine.

4 The observation that responses to dopamine and NA can be potentiated by desipramine in the caudate nucleus suggests that uptake blockade is not a prerequisite for potentiation.

5 It is suggested that the potentiation of neuronal responses to dopamine by desipramine may be responsible for the therapeutic efficacy of desipramine in Parkinson's disease.

Introduction

It is generally believed that the symptomatology of Parkinson's disease is caused by the selective degeneration of the dopamine-containing nigrostriatal pathway, which leads to an impaired balance between dopaminergic and cholinergic inputs in the striate nucleus (Barbeau, 1962; Klawans, 1968). Drugs effective in the treatment of Parkinson's disease are thought to act either by inhibiting the effects of acetylcholine (e.g. atropine), or by enhancing the effects of dopamine (e.g. L-DOPA) (Klawans, 1968; Yahr & Duvoisin, 1972).

It has been reported that desipramine, a tricyclic antidepressant drug, is effective in the treatment of Parkinsonism (Laitenen, 1969). The basis for the anti-Parkinsonian efficacy of desipramine, however, is not known. Although the cholinolytic effects of desipramine are well documented (Atkinson & Ladinsky, 1972), it is not likely that this is the sole explanation for the anti-Parkinsonian efficacy of the drug, since the therapeutic effectiveness of desipramine is greatly enhanced by the concurrent administration of another cholinolytic drug (Yahr & Duvoisin, 1972). Another possibility could be that desipramine potentiates the effects of dopamine in the caudate nucleus. Such an effect, however, could not be predicted on the basis of the well known 'uptake blockade hypothesis of potentiation' (Iversen, 1974), since desipramine is almost completely ineffective in blocking the uptake of dopamine in the caudate nucleus (Ross & Renyi, 1967; Horn, Coyle & Snyder, 1971).

We have reported earlier that desipramine has a dual effect on neuronal responses to noradrenaline (NA), 5-hydroxytryptamine (5-HT), and acetylcholine (ACh) in the cerebral cortex: both antagonism and potentiation of the responses can be observed (Bradshaw, Roberts & Szabadi, 1974; Bevan, Bradshaw & Szabadi, 1975a). In the experiments described here we used the technique of microelectrophoresis in order to examine how neuronal responses to dopamine, NA, 5-HT and ACh can be affected by desipramine in the caudate nucleus of the rat.

Some of the results presented here have been communicated to the British Pharmacological Society (Bevan, Bradshaw & Szabadi, 1975b).

Methods

Male albino Wistar rats, weighing between 250 and 300 g were used. Anaesthesia was induced with halothane (3.0%), and maintained with halothane (0.5-1.0%) delivered from a temperature and flow-rate compensated vapouriser (Fluotec Mk 3, Cyprane Ltd). All animals respired spontaneously via a tracheal cannula. ECG and EEG were monitored continuously throughout the experiment. Rectal temperature was maintained between 37° C and 38° C with a heating pad controlled by a thermosensitive rectal probe.

The head of the animal was held rigidly in a stereotaxic frame. A small hole was prepared in the skull (coordinates: A: 8 mm; L: 2.4 mm; König & Klippel, 1963), and a small area of the cortex exposed according to the method of Bradshaw & Szabadi (1972). A six-barrelled micropipette was then introduced into the brain, under microscopic control, and slowly lowered through the cortex into the caudate nucleus.

Six-barrelled glass micropipettes were constructed and filled as described by Bradshaw, Roberts & Szabadi (1973). Two barrels of each micropipette contained 4 M NaCl, one barrel for recording action potentials, the other for use in current balancing. The remaining barrels contained drug solutions. The following drug solutions were used: dopamine hydrochloride (0.2 M, pH 4.0-4.5), noradrenaline bitartrate (0.2 M, pH 3.0-3.5), 5-hydroxytryptamine bimaleate (0.2 M, pH 3.5), acetylcholine chloride (0.2 M, pH 3.6), sodium glutamate (0.05 M, pH adjusted to 8.5 by the addition of 0.1 M NaOH), and desmethylimipramine hydrochloride (0.15 M, pH 7.5).

The techniques for recording action potentials, and for the electrophoretic application of drugs, were as described by Roberts & Straughan (1967). A cumulative record of the total number of action potentials was obtained via a Grass UI-1 unit integrator.

All the neurones studied were spontaneously active. All the drugs were applied by microelectrophoresis. Repeated responses to an agonist were compared before and after a brief application of desipramine. In order to ensure that standard ejecting current pulses gave rise to standard pulses of drug ejection (Bradshaw, Szabadi & Roberts, 1973), the intervals between drug applications were kept constant by means of a sequential timing device (Bevan & Bradshaw, 1973). Cells were excluded from drug interaction studies if the variation in the size of the control responses to an agonist exceeded ± 10% (see Bradshaw *et al.*, 1974).

The magnitude of a response was measured by calculating the difference between the number of spikes generated during the response and the number of spikes generated during an equivalent period when no drug was applied ('total spike number', see Bradshaw *et al.*, 1974).

Results

Responses to monoamines and acetylcholine

The effects of dopamine, NA, 5-HT and ACh were studied on 208 spontaneously active neurones in the caudate nucleus. Three types of responses could be observed: (1) excitation; (2) depression; (3) biphasic responses, consisting of an initial depressant phase followed by an excitatory phase. Table 1 shows the frequency of occurrence of these effects in our material. In eight cells a 'spontaneous reversal' of the response to the monoamine was observed: the cell first responsed with either a clear excitation or a depression to the monoamine; later, however, the same monoamine evoked an opposite response (four cells with dopamine, two cells with NA, two cells with 5-HT). Cells showing 'spontaneous response reversal' were not used for drug interaction studies.

In 48 cells responses to dopamine and to another agonist (NA, 5-HT, ACh) were compared. (In a number of cells responses to dopamine and to two other agonists were tested.) Table 2 shows the correlation between the direction of the response (excitation or depression) to dopamine and the direction of the response to the other agonist. It is apparent that there was a highly significant correlation between the effects of dopamine and NA, whereas there was no significant correlation between the effects of dopamine and 5-HT. Furthermore, there was no significant correlation between responses to dopamine and ACh.

Effect of desipramine on neuronal firing

The direct effect of desipramine on the firing rate was studied on 65 cells. The dose of antidepressant applied was 30-100 nA passed for 30-80 seconds. In six cells (9%) the firing rate was increased during the application of desipramine, whereas in 19 cells (29%) the firing rate was decreased. There was no significant correlation between the dose of desipramine applied and the effect on neuronal firing. The response was always of a temporary nature, and the original base line firing rate recovered within a minute after the application of desipramine had been terminated.

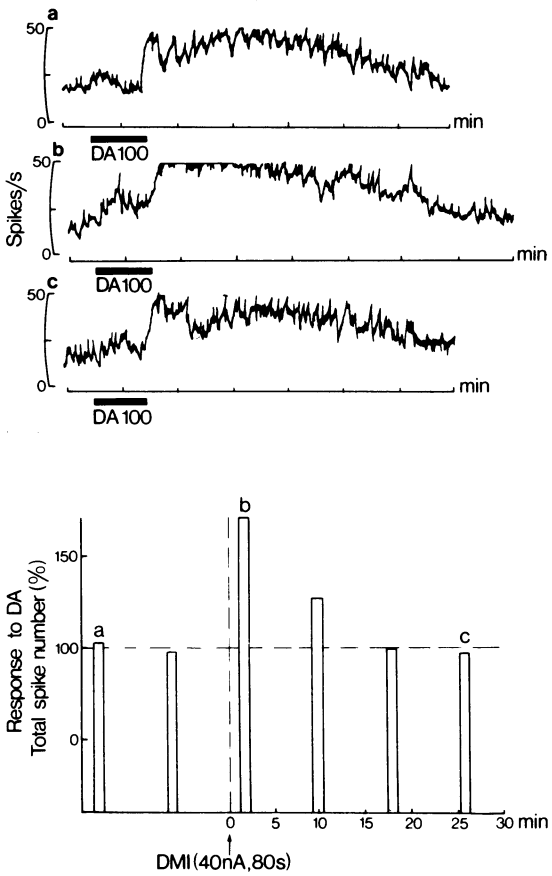

Figure 1 Potentiation of excitatory responses of a single caudate neurone to dopamine (DA) by desipramine (DMI). Top of the figure shows excerpts from the ratemeter recording of the firing rate of the neurone. Horizontal bars indicate applications of dopamine; numbers refer to the intensity of the ejecting current (nA). (a) Control response to dopamine; (b) potentiated response to dopamine 1 min after a brief application of desipramine (40 nA; 80 s); (c) recovery of control response 25 min after the application of desipramine. The graph at the bottom shows the time course of the entire study. The sizes of the responses to dopamine are expressed as a percentage of the mean of the control responses. Each column represents a single response. Letters above the graph indicate responses illustrated in the rate-meter tracings above.

Effect of desipramine on responses to dopamine

Excitatory responses Both potentiation and antagonism of excitatory responses to dopamine could be observed after a brief application (30-100 nA for 30-80 s) of desipramine.

Potentiation of the response was seen in five cells. A response was regarded as potentiated if there was more than 20% increase over the size of the mean control response (Bradshaw *et al.*, 1974). An example of potentiation is shown in Figure 1. Antagonism of the response to dopamine was seen in six cells. A response was regarded as antagonized if there was more than 20% decrease in the size of the response compared to the mean

Table 1 Responses of caudate neurones to monoamines and acetylcholine

	Response (number of cells)		
Agonist	*Excitation*	*Depression*	*Biphasic*
Dopamine	33 (53%)	21 (34%)	8 (13%)
Noradrenaline	32 (50%)	26 (41%)	6 (9%)
5-Hydroxytryptamine	32 (64%)	12 (24%)	6 (12%)
Acetylcholine	52 (91%)	4 (7%)	1 (2%)

Table 2 Correlation between the effects of dopamine and of other agonists on caudate neurones

		Direction of responses to the two agonists		*Significance of correlation*
*Agonists compared**		*Same*	*Opposite*	*(χ^2 test)*
Dopamine, noradrenaline	(33)	91%	9%	$P < 0.001$
Dopamine, 5-hydroxytryptamine	(19)	79%	21%	NS
Dopamine, acetylcholine	(17)	71%	29%	NS

* Figures in parentheses indicate number of cells on which comparisons were made.

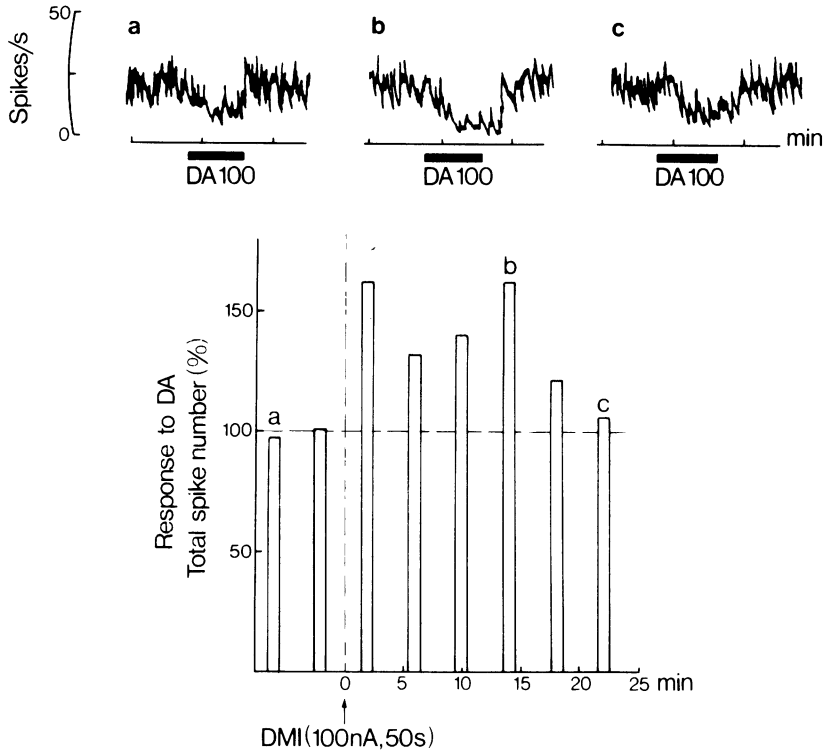

Figure 2 Potentiation of depressant responses of a single caudate neurone to dopamine (DA) by desipramine (DMI). Top of the figure shows excerpts from the ratemeter recording of the firing rate of the neurone (as in Figure 1). (a) Control response to dopamine; (b) potentiated response to dopamine 13 min after a brief application of desipramine (100 nA; 50 s); (c) recovery of the control response 21 min after the application of desipramine. Graph at the bottom shows the time course of the entire study (as in Figure 1).

of the control responses. In three of the cells in each group, both potentiation and antagonism were observed. The response was first antagonized following the application of desipramine; this antagonism was followed later by potentiation, and finally by recovery of the control response. In two cells no significant change in the size of responses could be observed after the application of desipramine. The degrees of potentiation or antagonism seen in each cell are summarized in Figure 5.

In another three cells the excitatory response was reversed into depression following the application of desipramine.

Depressant responses Both potentiation and antagonism of depressant responses to dopamine could be observed after a brief application of desipramine. Potentiation was seen in six cells, antagonism was seen in three cells. In one cell included in each group both antagonism and potentiation were observed. An example of the potentiation of the depressant response to dopamine by desipramine is shown in Figure 2. In one cell no significant change in the size of responses could be observed after the application of desipramine. The degrees of potentiation or antagonism seen in each cell are summarized in Figure 5.

In six other cells, the depressant response to dopamine was reversed into excitation following the application of desipramine.

Effect of desipramine on responses to noradrenaline

Excitatory responses Both potentiation and antagonism of excitatory responses to NA could be observed after a brief application of desipramine. Potentiation was observed in four cells, antagonism was seen in six cells. In one cell included in each group both antagonism and

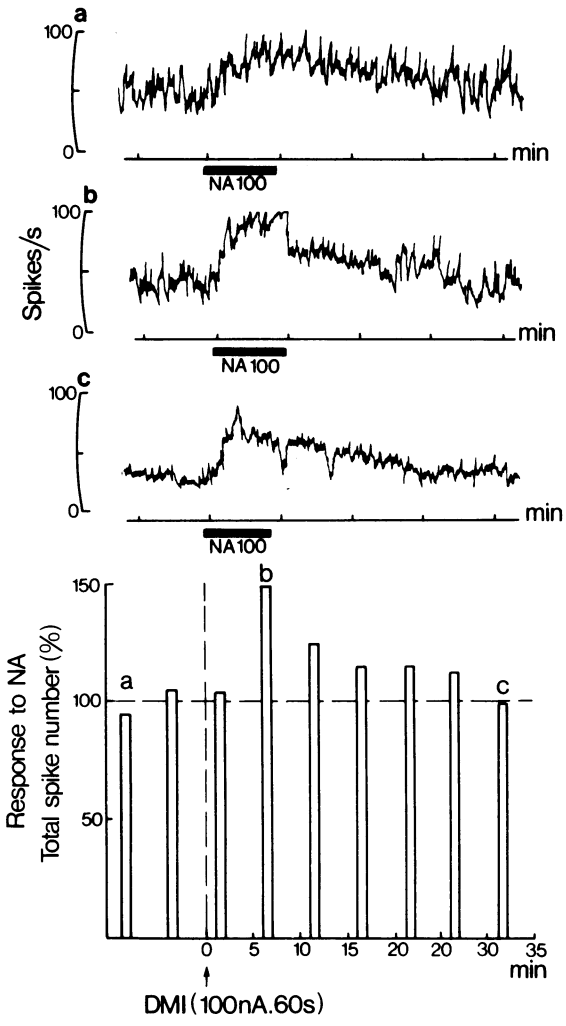

Figure 3 Potentiation of excitatory responses of a single caudate neurone to noradrenaline (NA) by desipramine (DMI). Top of the figure shows excerpts from the ratemeter recording of the firing rate of the neurone (as in Figure 1). (a) Control response to NA; (b) potentiated response to NA 6 min after a brief application of desipramine (100 nA; 60 s); (c) recovery of the control response 31 min after the application of desipramine. Graph at the bottom shows the time-course of the entire study (as in Figure 1).

potentiation were observed, the antagonism preceding the potentiation. An example of the potentiating effect of desipramine on responses to NA is shown in Figure 3. In one cell no significant change in the size of responses could be observed after the application of desipramine. The degrees of potentiation or antagonism seen in each cell are summarized in Figure 5.

In one further cell the excitatory response to NA was reversed into a depression following the application of desipramine.

Depressant responses Potentiation was seen in six cells depressed by NA, antagonism was observed in four cells. Both effects were seen in two cells included in both groups. In two cells no effect of desipramine could be observed. Figure 5 summarizes the degrees of potentiation or antagonism observed in each cell.

In another four cells the depressant response to noradrenaline was reversed into an excitatory one following the application of desipramine.

Effect of desipramine on responses to 5-hydroxytryptamine

Excitatory responses Potentiation was observed in four cells excited by 5-HT, antagonism was seen in three cells. In two cells in each group both antagonism and potentiation were seen; the antagonism preceded the potentiation. On two cells no effect of desipramine could be observed. The data are summarized in Figure 5.

Depressant responses In one cell, the depressant response to 5-HT was reversed into an excitation, following the application of desipramine.

Effect of desipramine on responses to acetylcholine

Both potentiation and antagonism of excitatory responses to ACh could be observed after a brief application of desipramine. Potentiation was observed in four cells, antagonism was seen in four cells. In one cell included in each group both antagonism and potentiation were seen; the antagonism preceded the potentiation. An example of the potentiating effect of desipramine on responses to ACh is shown in Figure 4. In two cells desipramine had no significant effect. The data are summarized in Figure 5.

Effect of desipramine on responses to glutamate

The effect of desipramine on excitatory responses to glutamate was studied in 10 cells. The effects of glutamate on the firing rate were studied for 20-30 min following the application of desipramine. In none of the cells could any significant change be observed in the size of the responses to glutamate after the application of desipramine (See Figure 5).

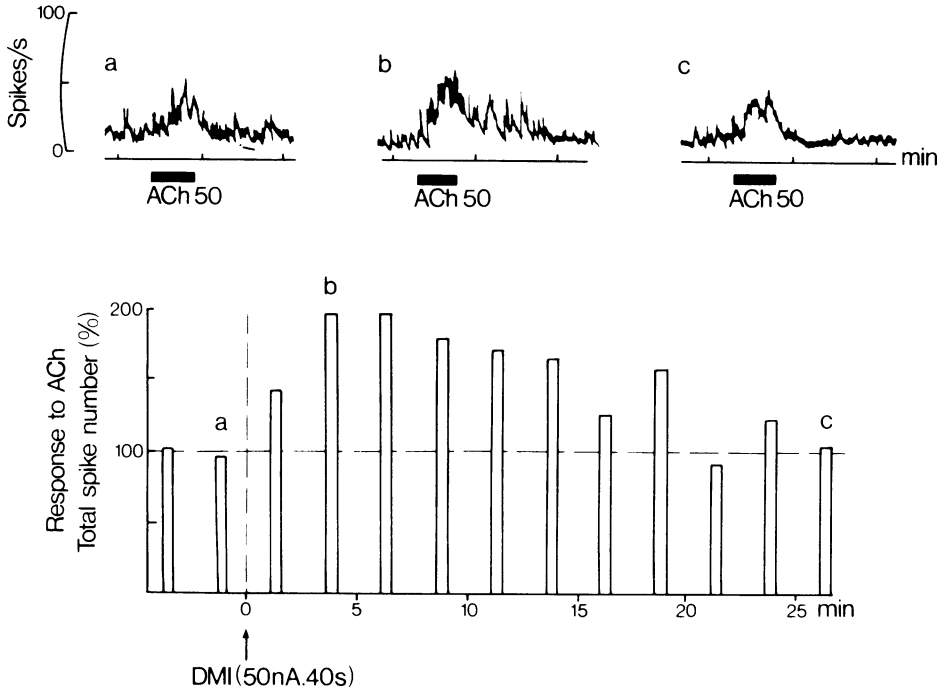

Figure 4 Potentiation of excitatory responses of a single caudate neurone to acetylcholine (ACh) by desipramine (DMI). Top of the figure shows excerpts from the ratemeter recording of the firing rate of the neurone (as in Figure 1). (a) Control response to ACh; (b) potentiated response to ACh 4 min after a brief application of desipramine (50 nA; 40 s); (c) recovery of the control response 26 min after the application of desipramine. Graph at the bottom shows the time course of the entire study (as in Figure 1).

Discussion

The results presented in this paper were obtained on spontaneously firing single neurones in the caudate nucleus of the rat. There have been some recent reports concerning the effects of dopamine (Gonzalez-Vegas, 1974; Woodruff, Elkhawad, Crossman & Walker, 1974; Siggins, Hoffer & Ungerstedt, 1974; Spencer & Havlicek, 1974) and of NA and ACh (Spencer & Havlicek, 1974) in this structure and in this species. Although Woodruff *et al.* (1974) reported only depressant responses to dopamine in cells activated by homocysteic acid, other authors described the occurrence of both excitatory and depressant responses to DA (Gonzalez-Vegas, 1974; Siggins *et al.*, 1974; Spencer & Havlicek, 1974) and to NA (Spencer & Havlicek, 1974). We observed both excitatory and depressant responses to dopamine, NA, and 5-HT. Similarly, both excitatory and depressant responses to the monoamines have been described in the striate nucleus of the cat (Salmoiraghi & Stefanis, 1965; Bloom, Costa & Salmoiraghi, 1965; McLennan & York, 1967; York, 1970). A fair proportion of neurones in our material responded in a biphasic fashion to the monoamines (see Table 1). Biphasic responses to dopamine have been described in the striate nucleus of the cat (York, 1970), and of the monkey (York, 1972). The presence of biphasic responses and the observation of 'spontaneous response reversal' may suggest that both excitatory and inhibitory receptors to the same monoamine can co-exist on the same cell (Szabadi & Bradshaw, 1974). The high correlation between both the excitatory and depressant effects of dopamine and NA (compared to the lack of correlation between the effects of dopamine and 5-HT) (see Table 2) suggests that dopamine and NA may act at similar receptors on caudate neurones. Indeed, it is known that dopamine stimulates α-adrenoceptors in the periphery (Rossum, 1965).

ACh had a predominantly excitatory effect in our experiments. When responses to dopamine and ACh were compared on the same neurones, no significant correlation, either positive or negative,

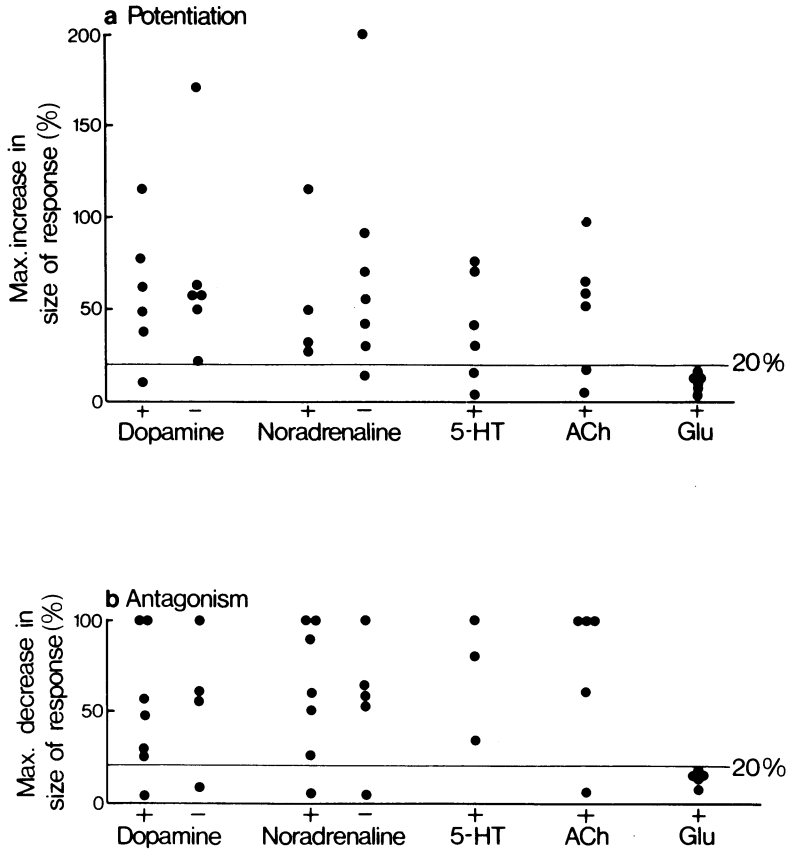

Figure 5 Summary of the effects of desipramine on neuronal responses to dopamine, noradrenaline, 5-hydroxytryptamine (5-HT), acetylcholine (ACh), and glutamate (Glu).
(a) Potentiation: each point shows the maximum potentiation observed on one individual cell (e.g. response b in Figure 1). +: excitatory responses; −: depressant responses. A response was regarded as potentiated if there was more than 20% increase over the size of the control response (see text).
(b) Antagonism: each point shows the maximum degree of antagonism observed on one individual cell. A response was regarded as antagonized if there was more than 20% decrease over the size of the control response (see text).

could be found (see Table 2). This would argue against the claim that dopamine and ACh have opposite effects in the caudate nucleus (Klawans, 1968; Yahr & Duvoisin, 1972).

Desipramine applied by microelectrophoresis had a dual effect on responses to monoamines and ACh: both antagonism and potentiation of the responses could be observed. Responses to glutamate were not affected. A dual effect of desipramine on responses to NA and 5-HT (Bradshaw *et al.*, 1974) and on responses to ACh (Bevan *et al.*, 1975a) has been described in the cerebral cortex of the cat.

The antagonism of responses to NA could be interpreted on the basis of the α-adrenoceptor blocking effect of desipramine (Türker & Khairallah, 1967). Since it is known that dopamine can stimulate peripheral α-adrenoceptors (Rossum, 1965), an α-receptor blocking action might explain the antagonism of responses to dopamine. The antagonism of responses to 5-HT may be explained on the basis of the anti-5-HT action of the antidepressants (Domenjoz & Theobald, 1959), whereas the antagonism of responses to ACh may reflect the antimuscarinic action of these drugs (Atkinson & Ladinsky, 1972).

It is more difficult to interpret the potentiating effects of desipramine. In the case of 5-HT, the most plausible explanation is uptake blockade.

There is indirect evidence that 5-HT terminals reach the caudate nucleus (Gumulka, Ramirez del Angel, Samanin & Valzelli, 1970), and that desipramine inhibits the uptake of 5-HT into brain tissue (Ross & Renyi, 1969). Uptake blockade, however, cannot explain the potentiation of responses to dopamine and NA by desipramine. It is known that both dopamine and NA are accumulated by an active uptake process in the striatum (Horn *et al.*, 1971); this uptake, however, is almost entirely unaffected by desipramine (Ross & Renyi, 1967; Horn *et al.*, 1971). An alternative explanation for potentiation could be that it reflects the blockade of masked, and functionally opposite, receptors on the post-synaptic neurone (Szabadi & Bradshaw, 1974; Bradshaw *et al.*, 1974). The blockade of masked receptors could also account for the prolongation of the recovery time of the potentiated responses often seen in our experiments (e.g. Figure 1), since the activation of the masked receptors may contribute to the termination of the response (Szabadi & Bradshaw, 1974). Our observation that the response to a monoamine was occasionally reversed after the application of desipramine can also be interpreted by this model. In this case, desipramine would block the dominant receptors selectively and thus reveal the effect of the masked receptors. However, since response reversal occurred spontaneously in a few cells, the causal relationship between the application of desipramine and the subsequent reversal of the response remains inconclusive.

It has been suggested that the potentiation of responses to ACh by desipramine could also be explained in terms of post-synaptic receptor blockade (Bevan *et al.*, 1975a). The occurrence of both excitatory and depressant responses to ACh in the caudate nucleus suggests the existence of two opposing receptor populations to ACh on caudate neurones, and thus the selective blockade of masked inhibitory receptors may account for the potentiation of excitatory responses. Moreover, there is evidence that the inhibition of cholinesterase cannot explain the potentiation of neuronal responses to ACh by desipramine (Bevan *et al.*, 1975a).

The results presented here show that desipramine can potentiate neuronal responses to dopamine in the caudate nucleus. It is possible that this action is responsible for the therapeutic efficacy of desipramine in Parkinson's disease. However, responses to ACh can also be potentiated by desipramine, and this might counteract the anti-Parkinsonian effect of desipramine. This may explain why a small dose of a potent cholinolytic drug has to be administered concurrently with desipramine in order to obtain the full therapeutic benefit from the anti-depressant in Parkinsonism (Yahr & Duvoisin, 1972).

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References

ATKINSON, J. & LADINSKY, H. (1972). A quantitative study of the anticholinergic action of several tricyclic antidepressants on the rat isolated fundal strip. *Br. J. Pharmac.*, **45**, 519-524.

BARBEAU, A. (1962). The pathogenesis of Parkinson's disease: a new hypothesis. *Canad. Med. Ass. J.*, **87**, 802-807.

BEVAN, P. & BRADSHAW, C.M. (1973). A simple low-cost circuit for the programmed application of ejecting and retaining currents in microelectrophoresis experiments. *Br. J. Pharmac.*, **48**, 365-366P.

BEVAN, P., BRADSHAW, C.M. & SZABADI, E. (1975a). The effect of tricyclic antidepressants on cholinergic responses of single cortical neurones. *Br. J. Pharmac.*, **53**, 29-36.

BEVAN, P., BRADSHAW, C.M. & SZABADI, E. (1975b). Tricyclic antidepressants and monoamines: the relationship between uptake blockade and potentiation of neuronal responses. *Br. J. Pharmac.*, **53**, 459P.

BLOOM, F.E., COSTA, E. & SALMOIRAGHI, G.C. (1965). Anesthesia and the responsiveness of individual neurons of the caudate nucleus of the cat to acetylcholine, norepinephrine, and dopamine administered by microelectrophoresis. *J. Pharmac. exp. Ther.*, **150**, 244-252.

BRADSHAW, C.M., ROBERTS, M.H.T. & SZABADI, E. (1973). Kinetics of the release of noradrenaline from micropipettes: interaction between ejecting and retaining currents. *Br. J. Pharmac.*, **49**, 667-677.

BRADSHAW, C.M., ROBERTS, M.H.T. & SZABADI, E. (1974). Effects of imipramine and desipramine on responses of single cortical neurones to noradrenaline and 5-hydroxytryptamine. *Br. J. Pharmac.*, **52**, 349-358.

BRADSHAW, C.M. & SZABADI, E. (1972). A technique for achieving greater stability of the brain for microiontophoretic studies of single cortical neurones. *Br. J. Pharmac.*, **45**, 185-186P.

BRADSHAW, C.M., SZABADI, E. & ROBERTS, M.H.T. (1973). The reflection of ejecting and retaining currents in the time course of neuronal responses to microelectrophoretically applied drugs. *J. Pharm. Pharmac.*, **25**, 513-520.

DOMENJOZ, R. & THEOBALD, W. (1959). Zur

Pharmakologie des Tofranil (N-(3-dimethylamino-propyl)-iminodibenzyl-hydrochlorid). *Arch. Int. Pharmacodyn. Thér.*, **120**, 450-489.

GONZALEZ-VEGAS, J.A. (1974). Antagonism of a dopamine-mediated inhibition in the nigro-striatal pathway: a mode of action of some catatonia-inducing drugs. *Brain Res.*, **80**, 219-228.

GUMULKA, W., RAMIREZ del ANGEL, A., SAMANIN, R. & VALZELLI, L. (1970). Lesion of substantia nigra: biochemical and behavioural effects in rats. *Eur. J. Pharmac.*, **10**, 79-82.

HORN, A.S., COYLE, J.T. & SNYDER, S.H. (1971). Catecholamine uptake by synaptosomes from rat brain. Structure activity relationships of drugs with differential effects on dopamine and norepinephrine neurones. *Mol. Pharmac.*, **7**, 66-80.

IVERSEN, L.L. (1974). Uptake mechanisms for neurotransmitter amines. *Biochem. Pharmac.*, **23**, 1927-1935.

KLAWANS, H.L. (1968). The pharmacology of Parkinsonism. *Dis. Nerv. Sys.*, **29**, 805-816.

KÖNIG, J.F.R. & KLIPPEL, R.A. (1963). *The rat brain. A stereotaxic atlas of the forebrain and lower parts of the brain stem.* Baltimore: Williams & Wilkins.

LAITENEN, L. (1969). Desipramine in treatment of Parkinson's disease. *Acta Neurol. Scand.*, **45**, 109-113.

McLENNAN, H. & YORK, D.H. (1967). The action of dopamine on neurones of the caudate nucleus. *J. Physiol.*, **189**, 393-402.

ROBERTS, M.H.T. & STRAUGHAN, D.W. (1967). Excitation and depression of cortical neurones by 5-hydroxytryptamine. *J. Physiol.*, **193**, 269-294.

ROSS, S.B. & RENYI, A.L. (1967). Inhibition of the uptake of tritiated catecholamines by antidepressant drugs and related agents. *Eur. J. Pharmac.*, **2**, 181-186.

ROSS, S.B. & RENYI, A.L. (1969). Inhibition of the uptake of 5-hydroxytryptamine into brain tissue. *Eur. J. Pharmac.*, **7**, 270-277.

ROSSUM, J.M. van (1965). Different types of sympathomimetic α-receptors. *J. Pharm. Pharmac.*, **17**, 202-216.

SALMOIRAGHI, G.C. & STEFANIS, C.N. (1965). Patterns of central neurons responses to suspected transmitters. *Arch. Ital. Biol.*, **103**, 705-724.

SIGGINS, G.R., HOFFER, B.J. & UNGERSTEDT, U. (1974). Electrophysiological evidence for involvement of cyclic adenosine monophosphate in dopamine responses of caudate neurones. *Life Sci.*, **15**, 779-792.

SPENCER, H.J. & HAVLICEK, V. (1974). Alterations by anaesthetic agents of the responses of rat striatal neurons to iontophoretically applied amphetamine, acetylcholine, noradrenaline and dopamine. *Can. J. Physiol. Pharmac.*, **52**, 808-813.

SZABADI, E. & BRADSHAW, C.M. (1974). The role of physical and biological factors in determining the time-course of neuronal responses. *Neuropharmacology*, **13**, 537-545.

TÜRKER, R.K. & KHAIRALLAH, P.A. (1967). Desmethylimipramine (desipramine), an α-adrenergic blocking agent. *Experientia*, **23**, 252.

WOODRUFF, G.N., ELKHAWAD, A.O., CROSSMAN, A.R. & WALKER, R.J. (1974). Further evidence for the stimulation of rat brain dopamine receptors by a cyclic analogue of dopamine. *J. Pharm. Pharmac.*, **26**, 740-741.

YAHR, M.D. & DUVOISIN, R.C. (1972). Drug therapy of Parkinsonism. *New Eng. J. Med.*, **287**, 20-24.

YORK, D.H. (1970). Possible dopaminergic pathway from substantia nigra to putamen. *Brain Res.*, **20**, 233-249.

YORK, D.H. (1972). Dopamine receptor blockade – a central action of chlorpromazine on striatal neurones. *Brain Res.*, **37**, 91-99.

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