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EFFECTS OF IPRINDOLE ON RESPONSES OF SINGLE CORTICAL AND CAUDATE NEURONES TO MONOAMINES AND ACETYLCHOLINE

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1 The technique of microelectrophoresis was used to study the effects of iprindole on single neurones in the cerebral cortex and caudate nucleus of the rat.

2 Iprindole, when applied for a brief period, did not affect the firing rate of the vast majority of neurones tested.

3 Both potentiation and antagonism of neuronal responses to noradrenaline, dopamine, and 5-hydroxytryptamine could be observed after a brief application of iprindole. Potentiation and antagonism often occurred after the same application of iprindole, antagonism always preceding potentiation.

4 Responses to acetylcholine were affected by iprindole similarly: both potentiation and antagonism of the responses could be observed.

5 Responses to glutamate were not affected by iprindole.

6 It is concluded that the potentiation of responses to monoamines by iprindole cannot be explained on the basis of uptake blockade; this potentiation may be due to the blockade of masked receptors on the post-synaptic cell.

7 It is suggested that the common pharmacological action of the tricyclic antidepressants may be the ability to block both monoamine and acetylcholine receptors in the brain.

Introduction

According to the monoamine theory of affective disorders, the tricyclic antidepressant drugs exert their antidepressant effect by potentiating the pharmacological actions of monoamines at postsynaptic receptor sites in the brain (Schildkraut, 1965; Davis, 1970). It is generally believed that the monoamine potentiating effect of the tricyclic antidepressants is due to their ability to block the uptake of monoamines into monoamine-containing nerve terminals (Iversen, 1974). Previous reports on imipramine and desipramine seem to confirm this hypothesis. It has been shown that these antidepressants block the uptake of noradrenaline (NA) and of 5-hydroxytryptamine (5-HT) into brain tissue (Ross & Renyi, 1967; 1969), and that they also potentiate neuronal responses to NA and 5-HT (Bradshaw, Roberts & Szabadi, 1974). However, there are reports suggesting that the 'uptake blockade hypothesis' of potentiation may not apply to another antidepressant, iprindole.

Iprindole is a tricyclic antidepressant drug with a similar structure and clinical antidepressant efficacy to imipramine (Imlah, Murphy & Mellor, 1968; Rickels, Chung, Csanalosi, Sablosky & Simon, 1973). Like imipramine, iprindole potentiates the peripheral effects of NA (Gluckman & Baum, 1969). However, in contrast to imipramine and other tricyclic antidepressant compounds, iprindole does not block the uptake of NA into sympathetically innervated tissues (Gluckman & Baum, 1969; Lahti & Maickel, 1971). It has also been reported that, in contrast to imipramine and desipramine, iprindole is ineffective in blocking the uptake of NA (Ross, Renyi & Ögren, 1971; Rosloff & Davis, 1974), dopamine and 5-HT (Ross *et al.*, 1971) into brain tissue. However, it is not known how pharmacological responses to the monoamines are affected by iprindole in the brain.

We have reported earlier that the tricyclic antidepressants imipramine and desipramine have a dose-dependent dual effect on responses of single cortical neurones to NA, 5-HT and acetylcholine (ACh): smaller doses potentiate, and bigger doses antagonize the responses (Bradshaw *et al.*, 1974; Bevan, Bradshaw & Szabadi, 1975a). In the experiments described here we used the technique

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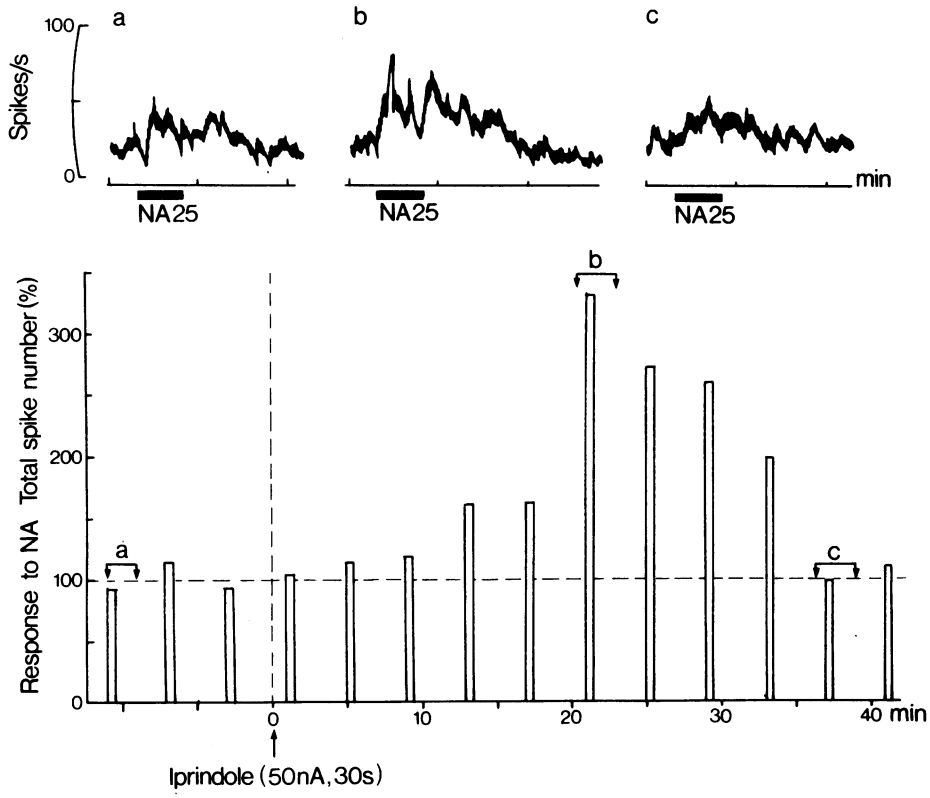

Figure 1 Potentiation of excitatory responses of a single cortical neurone to noradrenaline (NA) by iprindole. Top of the figure shows excerpts from the ratemeter recording of the firing rate of the neurone. Horizontal bars indicate applications of NA; numbers refer to the intensity of the ejecting current (nA). (a) Control response to NA. (b) Potentiated response to NA 21 min after a brief application of iprindole (50 nA; 30 seconds). (c) Recovery of control response 37 min after the application of iprindole. The graph below shows the time course of the entire study. The sizes of the responses to NA are expressed as a % of the mean of the control responses. Each column represents a single response. Letters above the graph indicate responses illustrated in the ratemeter tracings above.

of microelectrophoresis in order to investigate how responses of single cortical and caudate neurones to NA, dopamine, 5-HT and ACh can be modified by iprindole.

Some of these results 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 vapourizer (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. Neurones were studied both in the cerebral cortex and in the underlying caudate nucleus, using the same electrode track.

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: noradrenaline bitartrate (0.1 M, pH 3.0-3.5), dopamine hydrochloride (0.1 M, pH 4.0-4.5), 5-hydroxytryptamine bimaleate (0.1 M, pH 3.5), acetylcholine chloride (0.1 M, pH 3.6), sodium glutamate (0.05 M, pH adjusted to 8.5 by the addition of 0.1 M NaOH), and iprindole hydrochloride (0.1 M, pH 4.6).

Standard techniques were used for recording action potentials, and for the electrophoretic application of drugs. A cumulative record of the total number of action potentials was obtained as described by Bradshaw, Szabadi & Roberts (1973).

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 iprindole. In order to ensure that standard ejecting current pulses gave rise to standard pulses of drug ejection (Bradshaw *et al.*, 1973), the intervals between drug applications were kept constant by the use of a sequential timing device (Bevan & Bradshaw, 1973). A retaining current of 25 nA was passed between drug ejections. Cells were excluded from drug interaction studies if the variation in the size of 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

Cerebral cortex

Direct effect on neuronal firing The effect of iprindole on the firing rate was studied in 68 cells. The dose of iprindole applied was 30-100 nA passed for 30-60 seconds. Four cells responded with a clear increase in firing rate to the application of iprindole, whereas 18 cells were depressed. There was no significant correlation between the dose of iprindole applied and the effect on neuronal firing. The excitation or depression was always of a temporary nature, and the original base-line firing rate recovered within a minute after the application of iprindole had been terminated. On 46 cells iprindole did not affect the firing rate. On occasions a reduction in spike amplitude was observed; such cells were not used for drug interaction studies.

Effect on responses to noradrenaline

Excitatory responses Both potentiation and antagonism of excitatory responses to NA could be observed after a brief application (30-100 nA for 30-60 s) of iprindole.

Potentiation was seen in 6 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. On one cell, the response was first reduced in size following the application of iprindole; this antagonism was followed later by potentiation, and finally by recovery of the control response. (A response was regarded as antagonized if there was more than 20% decrease in the size of the response compared to the mean of the control responses). On 2 cells no significant change in the size of responses could be observed after the application of iprindole. The degrees of potentiation and antagonism seen in each cell are summarized in Figure 6.

Depressant responses Both potentiation and antagonism of depressant responses to NA could be observed after a brief application of iprindole. Potentiation was seen in 10 cells, antagonism was seen in 3 cells. In 2 cells both antagonism and potentiation could be observed; in both cases antagonism preceded potentiation. An example of the potentiation of the depressant response to NA by iprindole is shown in Figure 2. In 2 cells no significant change in the size of responses could be observed after the application of iprindole. The results are summarized in Figure 6.

Effect on responses to dopamine

Excitatory responses Both potentiation and antagonism of excitatory responses to dopamine could be observed after a brief application of iprindole. Potentiation was seen in 5 cells, antagonism was seen in 4 cells. In 3 cells both antagonism and potentiation of the response could be observed; antagonism always preceded potentiation. Figure 3 shows an example of antagonism followed by potentiation. In one cell no significant change in the size of responses could be observed after the application of iprindole. The results are summarized in Figure 6.

Depressant responses Potentiation was seen in 3 cells depressed by dopamine; antagonism was observed in one cell. In one cell no effect of iprindole could be observed. Figure 6 summarizes the results.

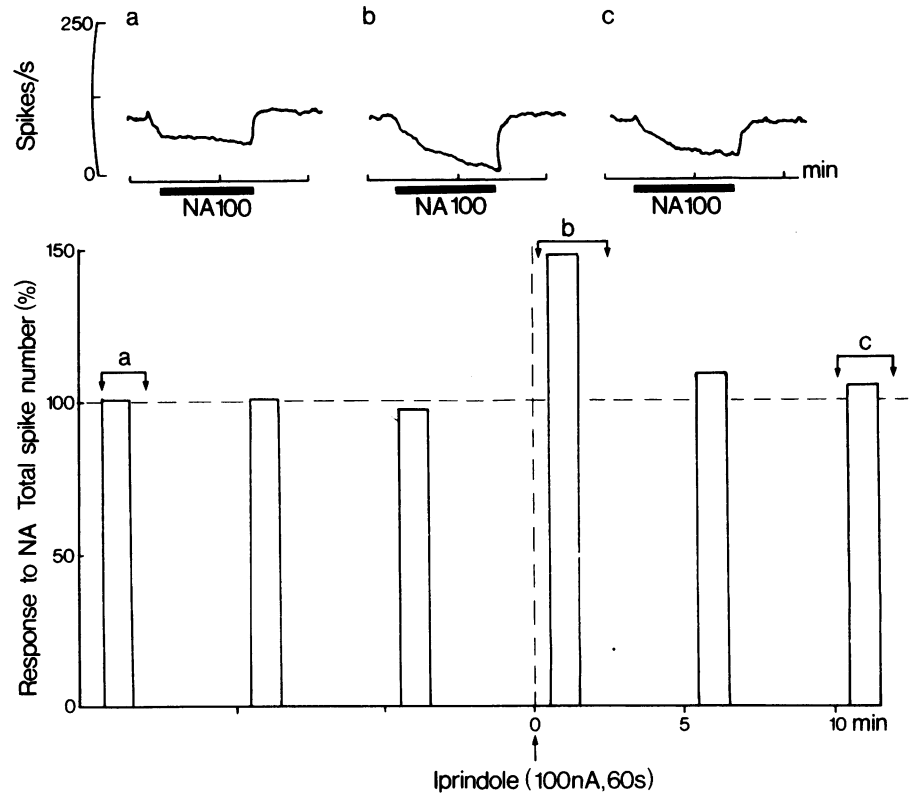

Figure 2 Potentiation of depressant responses of a single cortical neurone to noradrenaline (NA) by iprindole. Top of the figure shows excerpts from the ratemeter recording of the firing rate of the neurone (as in Figure 1). (a) Control response to NA. (b) Potentiated response 1 min after a brief application of iprindole (100 nA; 60 seconds). (c) Recovery of the control response 11 min after the application of iprindole. Graph below shows the time course of the entire study (as in Figure 1).

Effect on responses to acetylcholine Both potentiation and antagonism of excitatory responses to ACh could be observed after a brief application of iprindole. Potentiation was observed in 3 cells, antagonism was seen in 5 cells. In 3 cells both antagonism and potentiation could be seen; the antagonism always preceded the potentiation. An example of antagonism followed by potentiation is shown in Figure 4. In one cell, iprindole had no significant effect. The data are summarized in Figure 6.

Effect on responses to glutamate The effect of iprindole 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 iprindole. In none of the cells could any significant change be observed in the size of the response to glutamate after the application of iprindole (see Figure 6).

Caudate nucleus

The direct effect of a brief application of iprindole was tested in 18 neurones: 3 cells were excited, 2 cells were depressed, whereas in 13 cells there was no change in the firing rate. The effect of iprindole was also examined on neuronal responses to NA, dopamine and 5-HT. The same patterns of drug interaction could be observed as described above for the cerebral cortex. Following a brief application of iprindole, both antagonism and potentiation of excitatory responses to NA (2 cells), dopamine (3 cells) and 5-HT (3 cells) could be observed. Similarly, both antagonism and potentiation of depressant responses to NA (3 cells) and dopamine (5 cells) were seen. Excitatory responses to glutamate (3 cells) were not affected by iprindole. Figure 5 shows an example of the potentiation of depressant responses to dopamine by iprindole in the caudate nucleus.

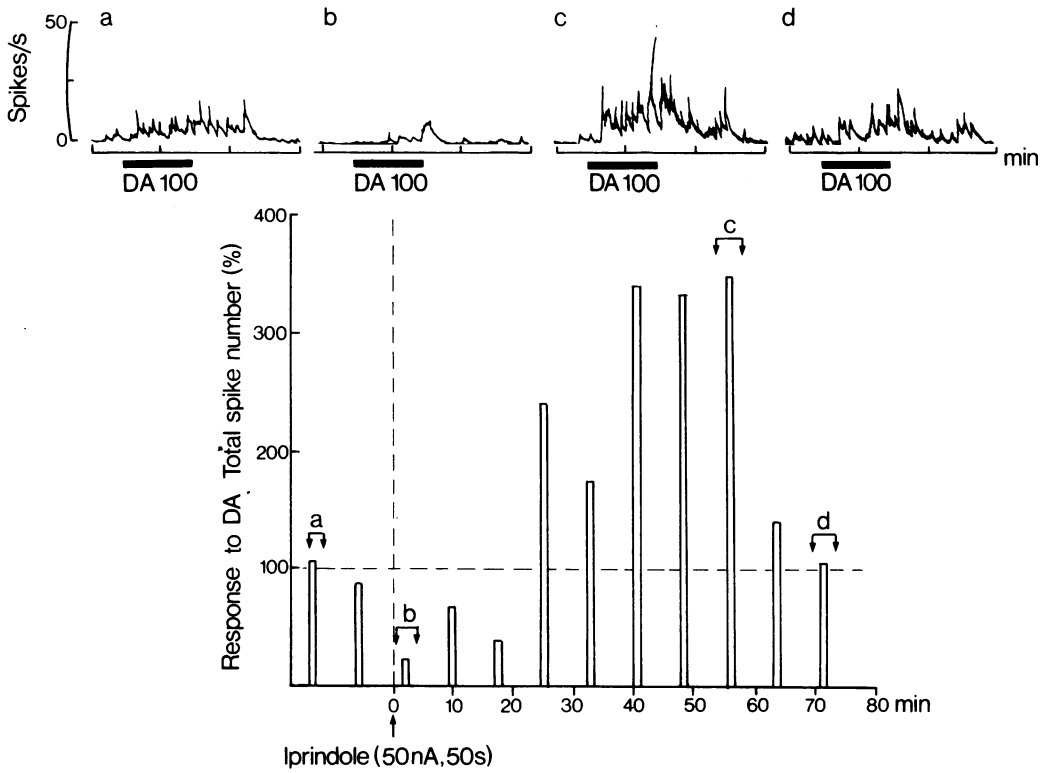

Figure 3 Antagonism and potentiation of excitatory responses of a single cortical neurone to dopamine (DA) by iprindole. Top of the figure shows excerpts from the ratemeter recording of the firing rate of the neurone (as in Figure 1). (a) Control response to DA. (b) Antagonized response, 1 min after a brief application of iprindole (50 nA; 50 seconds). (c) Potentiated response, 55 min after the application of iprindole. (d) Recovery of the control response 71 min after the application of iprindole. Graph below shows the time course of the entire study (as in Figure 1).

Discussion

A brief application of iprindole did not affect the firing rate of the majority of neurones tested in the cerebral cortex and in the caudate nucleus. However, in a small number of cells a response to iprindole was observed. A possible explanation for this effect of iprindole itself could be that it reflects the interaction between endogenously released monoamine transmitters and iprindole. As responses to ACh are also affected by iprindole, an interaction with ACh released by cholinergic inputs to the neurone should also be considered. Like iprindole, imipramine and desipramine can also evoke both excitatory and depressant responses in spontaneously firing cortical neurones (Bradshaw *et al.*, 1974). In a few cells, a reduction in spike amplitude was observed in response to iprindole. This probably reflects the local anaesthetic action of tricyclic antidepressant drugs (Domenjoz & Theobald, 1959).

We have found that iprindole can cause both antagonism and potentiation of the responses of cortical and caudate neurones to monoamines (NA and dopamine in the cerebral cortex; NA, dopamine and 5-HT in the caudate nucleus). When both antagonism and potentiation of the response occurred after a single application of iprindole, antagonism invariably preceded the development of potentiation (see Figure 3). After a brief ejecting pulse, the concentration of iprindole probably rises quickly to a peak, and then gradually declines (Bradshaw *et al.*, 1974) so that antagonism of the response to the monoamine is likely to reflect a higher, and potentiation a lower concentration of the antidepressant (see Bradshaw *et al.*, 1974).

The most plausible explanation for antagonism

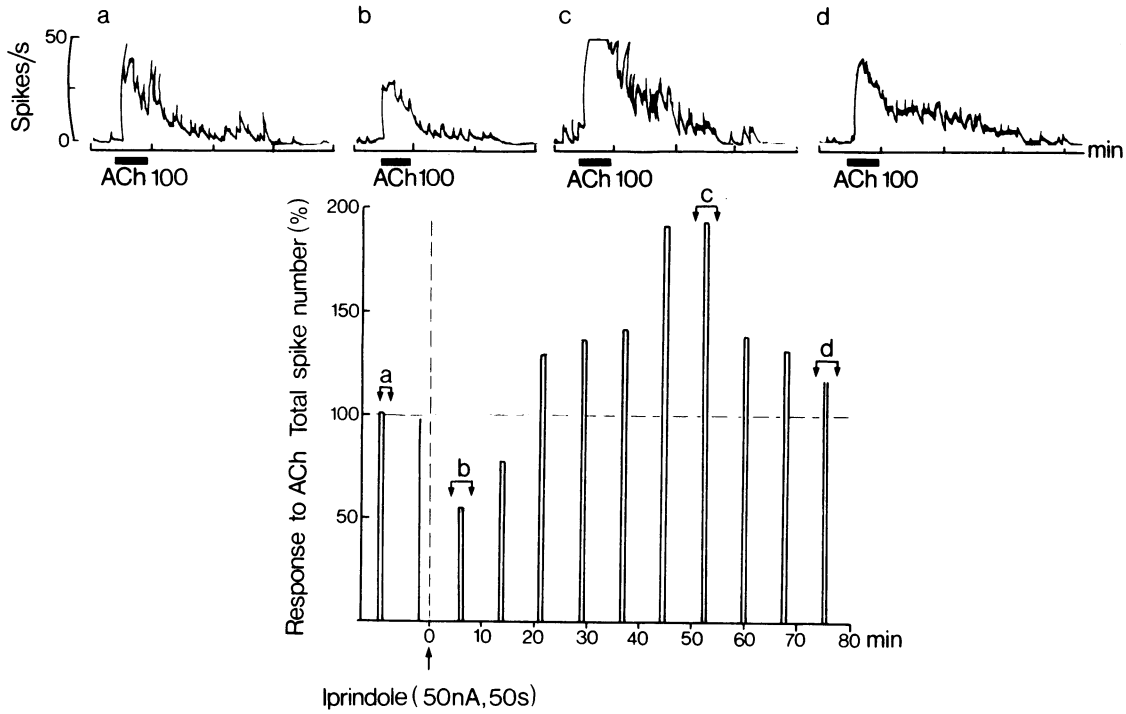

Figure 4 Antagonism and potentiation of excitatory responses of a single cortical neurone to acetylcholine (ACh) by iprindole. Top of the figure shows excerpts from the ratemeter recording of the firing rate of the neurone (as in Figure 1). (a) Control responses to ACh. (b) Antagonized response, 6 min after a brief application of iprindole (50 nA; 50 seconds). (c) Potentiated response, 52 min after the application of iprindole. (d) Recovery of the control response 75 min after the application of iprindole. Graph below shows the time course of the entire study (as in Figure 1).

is the blockade of monoamine receptors on the post-synaptic neurone. This would indicate that iprindole probably shares the α-adrenoceptor blocking and anti-5-HT actions of other tricyclic antidepressants (Domenjoz & Theobald, 1959; Callingham, 1966).

It is more difficult to interpret the potentiation of neuronal responses to monoamine by iprindole. As iprindole is ineffective in blocking the uptake of NA, dopamine and 5-HT into brain tissue (Ross *et al.*, 1971), uptake blockade cannot be an explanation for the potentiation observed in our experiments. It is possible that not only antagonism, but also potentiation is due to a post-synaptic effect of iprindole. We have proposed earlier that the dose-dependent dual effect of peripheral monoamine antagonists (e.g. methysergide, sotalol) (Bevan, Bradshaw & Szabadi, 1974; Bevan, Bradshaw, Roberts & Szabadi, 1974), and of tricyclic antidepressants (e.g. imipramine, desipramine) (Bradshaw *et al.*, 1974) may be due to the selective blockade of one or both of two opposing receptor populations on the post-synaptic neurone (Szabadi & Bradshaw, 1974). According to this hypothesis, a smaller concentration of the antagonist (or antidepressant) would block selectively the more sensitive masked (opposite) receptors on the cell, thus causing potentiation of the response, whereas a higher concentration of the antagonist (or antidepressant) would block the dominant receptors as well, thus causing antagonism of the response (Szabadi & Bradshaw, 1974; Bradshaw *et al.*, 1974). The dual effect of iprindole on neuronal responses to monoamines may also be interpreted by this model.

We have found that iprindole has a dual effect not only on responses to monoamines, but also on responses to ACh: both antagonism and potentiation can be observed. As the appearance of antagonism invariably precedes the development of potentiation, it is likely that antagonism reflects a higher, and potentiation a lower concentration of iprindole (see above, and Bevan

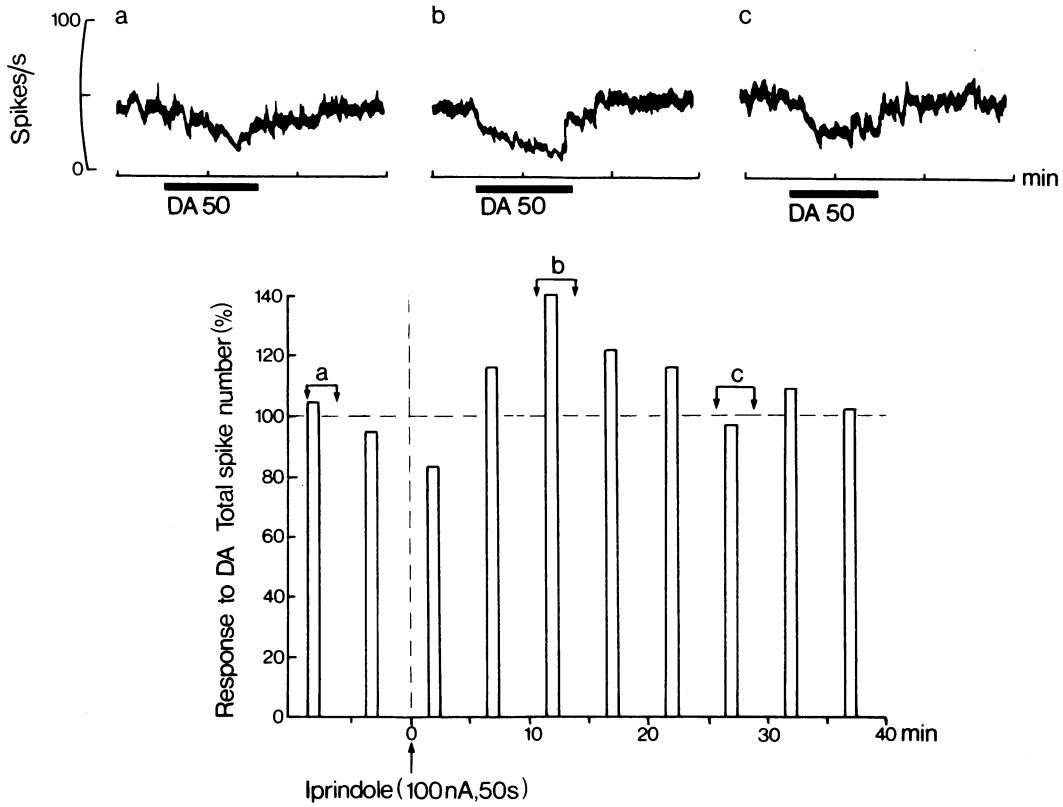

Figure 5 Potentiation of depressant responses of a single caudate neurone to dopamine (DA) by iprindole. Top of the figure shows excerpts from the ratemeter recording of the firing rate of the neurone (as in Figure 1). (a) Control response to DA. (b) Potentiated response to DA 12 min after a brief application of iprindole (100 nA; 50 seconds). (c) Recovery of the control response 27 min after the application of iprindole. Graph below shows the time course of the entire study (as is Figure 1).

et al., 1975a). Imipramine, desipramine and atropine have a similar dual effect on responses to ACh (Bevan *et al.*, 1975a). As in the case of imipramine, desipramine and atropine, the antagonism can be interpreted as a blockade of muscarinic receptors. It has been reported that iprindole blocks the effects of ACh in peripheral test systems, although it is less potent than atropine or imipramine (Gluckman & Baum, 1969). We have proposed earlier that potentiation of neuronal responses to ACh by imipramine, desipramine and atropine may be due to the selective blockade of masked inhibitory receptors (Bevan *et al.*, 1975a). This model could account for the potentiating effect of iprindole on responses to ACh.

Although inprindole differs from imipramine and desipramine in that it does not block the uptake of monoamines into brain tissue (Ross *et al.*, 1971), it shares the ability with imipramine and desipramine of potentiating and antagonizing neuronal responses to monoamines and ACh (Table 1). In contrast to the antidepressants, the monoamine antagonists methysergide and sotalol potentiate and antagonize responses to monoamines without affecting responses to ACh, whereas the cholinergic antagonist atropine potentiates and antagonizes responses to ACh without affecting responses to monoamines (see Table 2 in Bevan *et al.*, 1975a). As both antagonism and potentiation may be interpreted in terms of post-synaptic receptor blockade (see above), a common feature of the antidepressants may be the ability to block both monoamine and

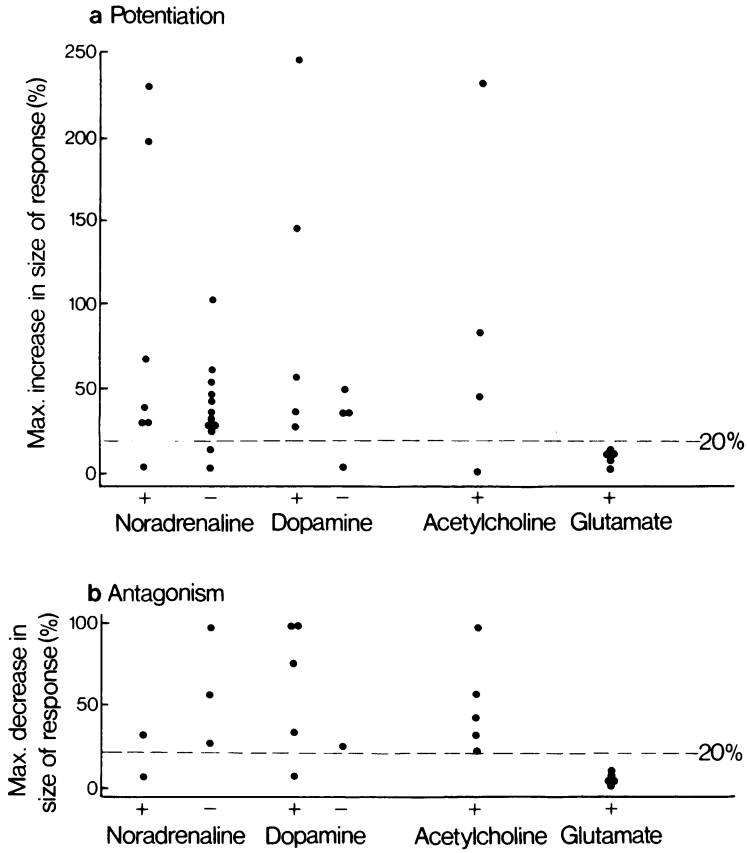

Figure 6 Summary of the effects of iprindole on responses of single cortical neurones to dopamine, noradrenaline, acetylcholine and glutamate. (a) Potentiation: each point shows the maximum potentiation observed in one individual cell (e.g. response (b) in Figure 1). + = excitatory responses; − = depressant 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 in one individual cell (e.g. response (b) in Figure 3). A response was regarded as antagonized if there was more than 20% decrease over the size of the control response (see text).

Table 1 Interaction between tricyclic antidepressants and potential neurotransmitters on single neurones in the mammalian brain

	Noradrenaline	*Dopamine*	*5-Hydroxytryptamine*	*Acetylcholine*	*Glutamate*
Cat—cerebral cortex					
Imipramine	P, A (1)	—	P, A (1)	P, A (2)	—
Desipramine	P, A (1)	—	P, A (1)	P, A (2)	0 (1)
Rat—cerebral cortex					
Iprindole	P, A	P, A	—	P, A	0
Rat—caudate nucleus					
Desipramine	P, A (3)	P, A (3)	P, A (3)	P, A (3)	0 (3)
Iprindole	P, A	P, A	P, A	—	0

P = potentiation; A = antagonism; 0 = not affected; — = not studied.
(1) Bradshaw, Roberts & Szabadi (1974); (2) Bevan, Bradshaw & Szabadi (1975a); (3) Bevan, Bradshaw & Szabadi (1975c).

ACh receptors in the brain. However, it remains to be determined whether other tricyclic compounds with a similar structure but with no marked antidepressant efficacy (e.g. phenothiazines) share this ability.

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