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Responses of midbrain neurones to iontophoretically applied 5-hydroxytryptamine

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In a recent study (Aghajanian, Haigler & Bloom, 1972), it was reported that cells in the raphé system of the rat were always depressed by small amounts of 5-hydroxytryptamine (5-HT) applied iontophoretically, whereas other midbrain cells were unaffected. These findings were not in agreement with earlier findings from the same laboratory, in which it was reported that raphé neurones in cats were insensitive to iontophoretically applied 5-HT, but were generally excited by noradrenaline (Crayton & Bloom, 1969), or that a large proportion of raphé cells in rats were excited by 5-HT (Couch, 1970). In view of these conflicting reports it was decided to re-investigate the sensitivity of raphé and non-raphé cells to iontophoretically applied 5-HT.

Male albino rats were anaesthetized with chloral hydrate (350 mg/kg), and, using standard recording and microiontophoretic techniques, the responses of eighty midline midbrain cells to iontophoretically applied 5-HT (25–100 nA) were studied. The results are summarized in Table 1. The response to noradrenaline was studied and is also summarized in Table 1.

Five raphé neurones out of seven tested were depressed by lysergic acid diethylamide, in currents which did not affect twenty non-raphé neurones tested. On these latter neurones, however, excitatory responses to noradrenaline and glutamate as well as to 5-HT, were antagonized by lysergic acid diethylamide.

TABLE 1

		Responses				
		−	+	−+	0	
Raphé t recov. = 69 ± 12 s	Spont.	10	0	0	0	5-Hydroxytryptamine 25–100 nA
	Glutamate excited	3	1	0	1	
Non raphé t recov. = 18 ± 4 s	Spont.	8	7	2	6	
	Glutamate excited	25	9	0	8	
Raphé		3	0	0	1	Noradrenaline 50–100 nA
Non raphé		10	6	3	3	

t recov. (±S.E. of mean) represents the time in seconds recovery for depressions produced by 50 nA currents of 5-hydroxytryptamine.
Raphé neurones were identified by their position and characteristically slow firing rates.
Spont. = spontaneously active.
Glutamate excited with 0–40 nA currents.

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Raphé neurones were not unique among midline midbrain neurones in being depressed by 5-HT. However their sensitivity, as measured in terms of the average recovery time, appeared greater than other midbrain units. Although only a very small number of cells were tested, raphé neurones did not respond to noradrenaline with excitation as had previously been reported in cats. However, the finding that raphé neurones are selectively depressed by lysergic acid diethylamide, is in agreement with the findings of Aghajanian *et al.* (1972).

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Comparison of the effects of imipramine and desipramine on single cortical neurones

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According to clinical observations (Kielholz, 1968), the tricyclic antidepressant desipramine (DMI) is effective in alleviating psychomotor retardation, whereas imipramine is more potent in elevating the mood of depressed patients. It has been suggested (Carlsson, Corrodi, Fuxe & Hökfelt, 1969) that these observations may be related to a greater potency of DMI on noradrenaline (NA) mechanisms and a greater potency of imipramine on 5-hydroxytryptamine (5-HT) mechanisms (Ross & Renyi, 1969; Sigg, Soffer & Gyermek, 1963). There is no direct evidence, however, that such a difference in potency between the two antidepressants exists at the level of the single brain cell.

Spontaneously active neocortical neurones were studied in the halothane-anaesthetized cat. All the drugs were applied microelectrophoretically; the time-course of action of the antidepressant was studied by comparing repeated responses to the monoamine following a brief application of the antidepressant.

In a previous communication (Bradshaw, Roberts & Szabadi, 1971) we reported that smaller doses of imipramine potentiate, and higher doses antagonize the responses of single cortical neurones to microelectrophoretically applied 5-HT. Similar findings were obtained with DMI and NA.

In the present study we have found that imipramine can potentiate and antagonize responses to NA, and that DMI can potentiate and antagonize responses to 5-HT. As increasingly high electrophoretic currents were used to apply the antidepressant, the following effects upon subsequent responses to the monoamines were observed: (1) potentiation of immediate onset; (2) delayed potentiation; (3) antagonism of immediate onset, followed by potentiation; (4) antagonism, followed by recovery of the control response. The 'dose'-dependent nature of these interactions has been used to compare the relative potencies of the two antidepressants. We have found that a smaller dose of imipramine has the same effect as a larger dose of DMI on responses to 5-HT, whereas a smaller dose of DMI proved to be as effective as a larger dose of imipramine on responses to NA.

The greater potency of imipramine upon 5-HT responses and the greater potency of DMI upon NA responses is in agreement with observations of the peripheral actions and of the uptake blocking potency of the two antidepressants.

Our observation that both potentiation and antagonism of responses to the monoamines can occur on the same neurone, and that antagonism always precedes potentiation, may be explicable in terms of two independent mechanisms which are differently sensitive to the antidepressants. During the electrophoretic application, the local concentration of the antidepressant may rise rapidly to a level which may evoke antagonism of the response to the monoamine. Subsequently, as the concentration of the antidepres-