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-

sant falls, the antagonism is reduced, but the concentration may still be sufficiently high to stimulate the more sensitive potentiating mechanism.

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Electrically induced contractions of guinea-pig isolated ileum resistant to tetrodotoxin

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Human isolated gastrointestinal muscle, and circular muscle from rabbit caecum, responds to electrical field stimulation at relatively low pulse widths with contractions which are only partly antagonized by tetrodotoxin (TTX) (Metcalfe & Bennett, 1971; Small, 1971). We (and Paton, personal communication) have found a similar effect in the longitudinal muscle of guinea-pig ileum. Segments of ileum 1–2 cm long were suspended in Krebs solution bubbled with 5% CO_2 in O_2 at 37° C under a load of 0·5 g. Each preparation was stimulated for 20 or 30 s by alternating square wave pulses between platinum wire electrodes at the top and bottom of the organ bath. Responses were recorded with an isotonic transducer and a pen recorder. The amplitude of the contractions varied with frequency (2–64 Hz), pulse width (0·1–100 ms) and voltage (7–17 V/cm). TTX (0·2–1 μg/ml) reduced but did not abolish the responses (Fig. 1). The subsequent experiments were to determine whether these unblocked contractions were due to stimulation of TTX-resistant nerves, to release of a mediator, or to direct electrical excitation of the muscle cells.

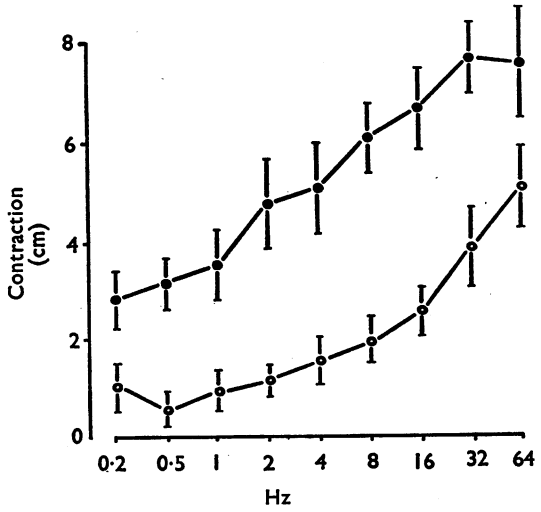

FIG. 1. Responses of longitudinal muscle from guinea-pig isolated ileum to 30 sec. trains of electrical field stimulation (17 V/cm; 1 msec pulses) before (●——●) and in the presence of TTX 5×10^{-7} g/ml. (○——○). Each point is the mean of 11 experiments ±S.E.M.