The dual action of the antidepressants can be interpreted in terms of two independent mechanisms: a lower concentration of the antidepressant affects the more sensitive 'potentiating' mechanism only, whereas a higher concentration activates the 'antagonistic' mechanism as well. The size of any particular response to ACh is determined by the interaction between these two mechanisms (Bradshaw, Roberts & Szabadi, 1973).

Osborne & Sigg (1960) have reported that imipramine has a dual action on peripheral cholinergic mechanisms: smaller doses potentiate, higher doses antagonize the effects of ACh. These authors interpreted these findings on the basis of the anti-cholinesterase activity of imipramine. This, however, cannot be an explanation for our findings, since responses to carbachol are also potentiated, and it is known that carbachol is not hydrolysed by cholinesterase (Goodman & Gilman, 1970). It has been observed in invertebrate ganglia that excitatory and inhibitory receptors for ACh can exist on the same neurone (Kehoe, 1972). It is possible, therefore, that in our experiments the 'potentiating' mechanism is in fact the antagonism of inhibitory receptors. This proposal is supported by our observation that a small dose of atropine can potentiate the response to ACh. We suggest that a smaller concentration of the antidepressant may antagonize inhibitory receptors only, thus causing an apparent potentiation of the response; higher concentration, on the other hand, may antagonize both the inhibitory and excitatory receptors, causing a reduction in the size of the response.

As there is evidence that both excitatory and inhibitory monoamine receptors may occur on the same neurone in the mammalian brain (Szabadi & Bradshaw, 1973), the dual action of antidepressants on responses to noradrenaline and 5-hydroxytryptamine (Bradshaw *et al.*, 1973) can also be interpreted purely in terms of postsynaptic receptor blockade. Thus it is possible that the central effects of the antidepressants are due to their anticholinergic and monoamine-antagonistic properties.

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Rhythmical field potentials induced in the Inferior Olive Complex by iontophoretically applied harmaline and other unrelated alkaloids

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Harmaline is one of a group of carboline alkaloids which, when injected systemically, causes generalized and synchronized muscle tremor at a frequency of 8–12 Hz. The site of initiation of this tremor has not yet been elucidated, although reports have been published describing activity at this frequency in the inferior olive, cerebellum, lateral vestibular nucleus and Nucleus gigantocellularis, as well as in lumbar motoneurones and in ventral roots (Lamarre & Mercier, 1971; Bruggencate, Teichmann & Weller, 1972). We are studying the pharmacology of evoked activity in the olive and have tested the action of this and other drugs applied iontophoretically.

Experiments have been performed on 21 male albino rats, 320–450 g, either anaesthetized with pentobarbitone or decerebrated under halothane anaesthesia. Stimulating electrodes in the region of the fastigial nuclei were used to identify the olivary complex by antidromic invasion. Seven barrelled microelectrodes of tip diameter 4–10 μm were used to eject drugs and to record the field potentials in the olivary complex.

Harmaline injected intravenously (5 mg/kg)in barbiturate anaesthetized rats, induced intermittent bursts of olivary field potentials at a frequency of 5–10 Hz, each potential having a duration of 50–150 ms.

When ejected iontophoretically, harmaline, and also harmine, dihydro-β-erythroidine, (+)-tubocurarine, strychnine and bicuculline induced intermittent bursts of field potentials. These potentials were of similar frequency, amplitude and duration to those elicited by systemic harmaline. Gallamine triethiodide also induced potentials, but the bursts were more intermittent and of shorter duration, and the potentials were similarly shorter (20–100 ms). Atropine did not induce any potentials.

Preliminary experiments suggest that this rhythmical activity can be recorded at a distance of 400 μm or more from the site of drug ejection.

In a further series of 13 experiments harmaline and harmine have been ejected near Renshaw cells and other spinal interneurones. While testing their interaction with transmitter candidates, no induced rhythmical firing was seen.

The extent of the rhythmical activity which follows the electrophoretic ejection of these drugs in the inferior olive is being investigated further.

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Antagonism of the effects of iontophoretically applied (+)-amphetamine by chlorpromazine on single neurones

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Chlorpromazine (CPZ) blocks the EEG desynchrony and behavioural alerting produced by (±)-amphetamine (Bradley & Hance, 1957). Bradley, Wolstencroft, Hösli & Avanzino (1966) reported that iontophoretically applied CPZ antagonized the excitatory action of iontophoretically applied (−)-noradrenaline (NA) on single neurones in the cat brain stem. In a recent study it was found that iontophoretically applied (+)-amphetamine could mimic the excitatory action of NA on rat brain stem neurones and this effect was shown to be due to the release of endogenous NA (Boakes, Bradley & Candy, 1972).

In the present experiments the interactions of iontophoretically applied (+)-amphetamine and NA with CPZ have been examined on single neurones in the brain stem of rats anaesthetized with halothane (0·5–1·5%) or urethane (1·8 g/kg). 5 Hydroxytryptamine, acetylcholine or glutamate were used as control agonists. Some neurones were identified histologically by marking with Pontamine sky blue (Hellon, 1971). Excitatory responses to (+)-amphetamine were observed on 25 neurones and inhibitory responses on 3 neurones recorded in 15 rats. CPZ, ejected iontophoretically from a 0·5% or 2% solution for short periods (*ca.* 2 min) or with low currents (0–20 nA), specifically antagonized the excitatory responses to (+)-amphetamine in 24 neurones, but not the 3 inhibitory responses. The actions of NA were examined on 19 of these neurones; NA excited 12 neurones which were also excited by (+)-amphetamine and CPZ reduced 4 of these excitations. Thus NA excitation appeared to be less susceptible than (+)-amphetamine excitation to block by CPZ. One neurone showed a short-lasting inhibitory response to NA which was unaffected by CPZ; the remaining 6 neurones gave a long-lasting inhibitory response to NA and CPZ antagonized 3 of these.

CPZ antagonized the long-lasting inhibitory responses to NA in 7 out of 8 neurones, revealing an excitatory phase in 3 cases where none had been apparent previously, and did not antagonize the excitatory phase of 2 mixed responses (i.e. consisting of long-