Analysis of the uptake of glutamate and aspartate indicated that the uptake could be resolved into two components. The apparent Km values calculated from the least squares fit for the high affinity uptake of aspartate and of glutamate were about 20–25 μM, while the low affinity Km values were about 0·7 and 0·6 mM respectively. Preliminary experiments indicated that glutamate and aspartate may competitively inhibit the uptake of each other, suggesting that these amino acids may be accumulated in the retina by the same transport system.

An attempt was made to distinguish between the high and low affinity uptake processes for glutamate by studying the characteristics of the uptake process at 10^{-3}M (low affinity) and 10^{-8}M (high affinity). It was found that both systems were inhibited by *p*-hydroxymercuribenzoate (10^{-5}M), and both were virtually abolished at 0° C and by the absence of sodium in the incubation medium. The specificity of both the high and low affinity systems was very similar: thus both uptake systems were inhibited by L-cysteate and L-aspartate, and were unaffected by glycine, L-serine and L-glutamine.

Similar high affinity and multiple uptake systems for amino acids have been described in other areas of the central nervous system but also in non-neural tissues such as kidney (Mohyuddin & Scriver, 1970), bacteria (Gross & Ring, 1971), and yeast (Koytk & Rihova, 1972). Thus, while high affinity uptake processes may be utilized in the central nervous system to inactivate transmitter substances, the mere presence of a high affinity uptake process for a substance cannot be taken as evidence that the substance is a neurotransmitter.

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The dual action of tricyclic antidepressant drugs on responses of single cortical neurones to acetylcholine

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The peripheral atropine-like action of tricyclic antidepressant drugs is well documented (Atkinson & Ladinsky, 1972), but it is not known how these drugs influence the effects of acetylcholine (ACh) at the level of the single brain cell. We used the microelectrophoretic technique in order to investigate this problem.

Spontaneously active neurones were studied in the somatosensory cortex of the halothane-anaesthetized cat. All the drugs were applied by microelectrophoresis. Repeated responses to ACh were compared following a brief application of imipramine or desipramine.

We have found that the antidepressants can both potentiate and antagonize responses to ACh. As increasingly high electrophoretic currents were used to apply the antidepressant, the following effects upon subsequent responses to ACh were observed: (1) potentiation of immediate onset; (2) delayed potentiation; (3) antagonism of immediate onset, followed by potentiation. Responses to carbachol were affected in the same way.

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.