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-

lasting inhibitory and excitatory phases). Thus, where an excitatory response to NA was associated with, or even masked by inhibition this response is probably related to (+)-amphetamine excitation.

These results demonstrate that CPZ can antagonize the excitatory action of (+)-amphetamine on brain stem neurones. The fact that NA excitation appeared to be less susceptible to block by CPZ indicates a probable presynaptic mechanism for the CPZ/(+)-amphetamine antagonism. Such a mechanism could provide a basis for antagonism of the alerting effects of (+)-amphetamine by CPZ.

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The effects of clonidine on single cortical and medullary neurones

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Clonidine (Catapres, St. 155) has been shown to produce an initial hypertension, followed by a more prolonged hypotension after its systemic injection. The pressor effect appears to be due to stimulation of peripheral α-adrenoceptors. The hypotension appears to be due to an action on the central nervous system, and most of the available evidence suggests an interaction with noradrenaline (NA) systems in the brain. The present experiments were intended to clarify the action of clonidine in the brain by applying it directly to neurones by microiontophoresis and comparing its effects with those of NA.

Male rats anaesthetized with urethane were used in these experiments. Clonidine was ejected with a current of 80 nA from a 200 mM solution of clonidine hydrochloride (pH 5·5). Experiments were performed on 185 randomly encountered spontaneously active cells in the somatosensory cerebral cortex and 62 in the medullary reticular formation at the level of exit of the IX and X cranial nerves.

The most frequently observed effect of clonidine was a depression of neuronal firing. This effect was seen on cells which were also depressed by NA. In general, cells which would not respond to NA were unaffected by clonidine. On seven cells a potentiation of NA depression occurred after the ejection of clonidine, and on three cells there was evidence of an antagonism of NA.

On approximately 18% of all neurones tested, however, clonidine caused an increase of firing rate. This response usually had a latency of about 30 s after a 1 min application of clonidine. The response occurred even on cells which were depressed by NA.

In accordance with previous experience (Stone, 1973 ; Lake, Jordan & Phillis, 1973) few cells were encountered which were excited by NA. In these cases clonidine either did not affect the firing rate of the neurones or produced a slight excitation.

The results support the idea that clonidine can act on NA receptors in the brain, usually mimicking the depressant responses of the catecholamine. Preliminary experiments indicate that depressant responses to both substances can be specifically antagonized by bulbocapnine applied by microiontophoresis. The mechanism of clonidine's excitatory action is unclear. These responses could be secondary to an action on blood vessels as has been suggested for the excitatory effects of NA (Stone, 1971). An alternative possibility is that clonidine reduces the release of NA from nerve endings. Such a reduction of NA release has been demonstrated in the rabbit heart (Starke, Wagner & Schumann, 1972). If this effect occurs after the systemic injection of clonidine, it may explain the need for an intact NA neurone system in the production of clonidine's hypotensive effect (Dollery & Reid, 1973).

We thank Boehringer Ingelheim Ltd. for the gift of clonidine.