we could often antagonise GABA evoked inhibitions by the simultaneous application of ACTH (13 out of 21 tests). Conversely, CDP often potentiated GABA evoked inhibitions of the same neurone (5 out of 10 tests). Perhaps the most interesting observation is that we have been able to reproduce the neurochemical evidence of antagonism between CDP and ACTH. Thus we were able to reversibly block ACTH evoked inhibitions by the simultaneous application of CDP (4 out of 6 tests).

Using two different pharmacological techniques we have been able to corroborate the earlier behavioural data showing an antagonism between ACTH and benzodiazepines. Thus, if ACTH is an endogenous anxiogenic compound then a functional antagonism with benzodiazapines would provide one possible clue to the mode of action of anxiolytic agents.

Supported by an MRC programme grant to Professor D.W. Straughan. MLM and TAJ are in receipt of postgraduate studentships from the MRC and SRC respectively.

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Inactivation of released norepinephrine in rat tail artery by neuronal uptake

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Neuronal uptake of endogenously released norepinephrine plays an important role in transmitter disposition in vascular smooth muscle. Recent evidence (Verbeuren, Janssens & Vanhoutte, 1978) suggests that this neuronal pump operates mainly between nerve impulses and is inactivated during depolarization of the nerve endings. This allows for optimal diffusion of transmitter. If this reasoning is correct, an inhibitor of neuronal reuptake, such as cocaine, should differentially alter the contractile response to low and high frequency stimulation. This hypothesis was tested in the present study by comparing the contractile responses of rat tail artery strips to electrical stimulation in the presence and absence of cocaine. Adult male albino rats were killed by a blow to the head and tail arteries were obtained. The artery was cut helically into strips; the strips were mounted in organ baths between two platinum wire electrodes; and isometric contractions were recorded. Cumulative addition of cocaine to the bath produced contraction of the strips. This contractile response was blocked by phentolamine (10 μM) and was dependent upon the concentration of cocaine (10^{-8} to 10^{-4}M). Acute denervation of the strips with 6-hydroxydopamine (10 min, pH 4.0) reduced the contractile effect of cocaine. Contractions in response to low frequency field stimulation (0.1 to 1.0 Hz) were significantly potentiated by cocaine (10^{-6}M). Those in response to high frequency stimulation (2 to 16 Hz) were not significantly altered by the presence of cocaine. Cocaine produced a marked slowing of relaxation in tail artery strips contracted by field stimulation (1 and 16 Hz). This effect was concentration dependent (10^{-8} to 10^{-4}M); the relative magnitude of the interval of time required to reach half maximal relaxation was not different for low or high frequency stimulation. These results indicate: (1) contraction in response to cocaine alone probably results from the inhibition of uptake of spontaneously released norepinephrine; (2) the amine uptake mechanism in rat tail artery is differentially affected at low and high frequency electrical stimulation suggesting that neuronal uptake is not operative during the nerve impulse; and (3) the neuronal uptake of transmitter following electrical stimulation is an important disposition mechanism in rat tail artery.

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Could harmaline generate tremor by affecting 5HT release?

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Whole body tremor can be generated by rhythmical and synchronous activity in the inferior olivary nucleus and such activity can be induced by harmaline, presumably by modification of electrotonic

coupling of olivary neurones (see Headley, Lodge & Duggan, 1976, and references therein). These authors suggested that harmaline acts by inhibiting synaptic 5-hydroxytryptamine (5-HT) release, but other evidence (Wiklung, Sjölund (Björklund, 1978) is more compatible with an *increased* 5-HT release by harmaline.

We here describe experiments in which harmaline was examined for effects on the uptake and release of 5-HT and other neurotransmitters. The inferior olive is in practice too small (2 mg wet weight/rat) for making such measurements so we used rat cortex which also contains 5-HT terminals.

Freshly dissected chilled cortices were cut on a McIlwain chopper into 0.1 × 0.1 × 2.0 mm 'minislices' which were then suspended in 37°C Krebs-Ringer solution which, in experiments on monoamines, contained ascorbic acid and a monoamine oxidase inhibitor. Incubation with 0.1–1.0 μCi tritium-labelled compounds was as follows: 5-HT and noradrenaline 10^{-7}M; γ-aminobutyric acid (GABA) 4×10^{-7}M; glycine 1×10^{-9}M; L-glutamate and L-aspartate 4×10^{-9}M; D-glutamate and D-aspartate 2×10^{-6}M. In uptake experiments the tissue was then filtered, washed and assayed for radio-activity. In release experiments the tissue was filtered, washed and transferred to a perfusion chamber; 2.7 min superfusate collections were assayed. Harmaline (⩾3 concentrations) was tested for antagonism of uptake or of spontaneous or 20–40 mM potassium – stimulated release.

Harmaline inhibitory concentration 50% values were above 5×10^{-4}M for uptake of all the amino acids ($n \geqslant 3$); for noradrenaline, $4.38 \pm 0.55 \times 10^{-5}$M (mean ± s.e. mean) and for 5-HT $2.43 \pm 0.14 \times 10^{-5}$M. Harmaline 10^{-5}M had no effect on 5-HT release and at 10^{-4}M did not affect spontaneous release; potassium-stimulated release was however reduced on some occasions, but in double-label experiments [^{14}C]-GABA release was inhibited concurrently.

Tremor is generated in rats when harmaline concentrations in whole brain exceed 1.5×10^{-5}M (Zetler, Back & Iven, 1974). In our experiments harmaline at this concentration did not affect 5-HT release but did reduce the uptake of noradrenaline and 5-HT (see also Buckholtz & Boggan, 1977). If our results on cortical tissue *in vitro* are relevant to olivary tissue *in vivo* then it is unlikely that harmaline acts by modifying 5-HT release.

P.M.H. was a Queen Elizabeth II Fellow.

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Biochemical and morphological aspects of kainic acid injection into rat cerebellum

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Kainic acid is a potent neurotoxic agent when injected *in vivo* and it has been shown to destroy intrinsic neurones whilst sparing axons which pass through the injected area (Coyle & Schwarcz, 1977; McGeer & McGeer, 1977). The mechanism of this action is as yet unknown, but there is evidence to suggest that it may, at least partially, involve postsynaptic glutamate receptors (Campochiaro & Coyle, 1978). In support of this, Herndon & Coyle (1977) have shown that kainic acid when injected into the rat cerebellum, results in a loss of all neurones except the granule cells. These cells are thought to be glutamatergic and are known to synapse onto all other cell types in the cerebellum. We have investigated further this kainic acid-resistance of the granule cells.

Female Wistar rats (200–300 g) were anaesthetized with sodium pentobarbitone, placed in a stereotaxic frame and injected with doses of kainic acid (in 2 μl Tris citrate buffer, pH 7.1) at a depth of 3 mm below the vermis, through a burr hole in the calvarium. Animals were killed at various times following injection and the cerebella removed for histological examination or biochemical studies.

The preservation of granule cells following kainic acid injection was found to be both dose and time dependent. Twenty four h after an injection of 2 μg, there was extensive degeneration of neurones over most of the vermis and part of the cerebellar hemispheres but which was not apparent in the granule cell layer. At higher doses however, or with time intervals of greater than 24 h following injection, the granule cells were also affected and the whole layered structure of the cerebellar cortex was disrupted. Injection of dihydrokainic acid (2 μg) which is neuropharmacologically inactive, caused no apparent degeneration of any cellular components under iden-