of bradykinin into the blood supply of their peripheral receptive field. Electrical stimulation in the area of the central interior mucleus of raphé generally caused inhibition of nociceptive cells but about half the cells classified as non-nociceptive were also inhibited to a lesser degree and for a shorter duration. On many cells, even when inhibition was seen, brain stimulation evoked one or two action potentials at short latency, prior to the inhibition, and there was no correlation with nociceptive input.

The effect of 5-HT on spontaneous activity was excitatory on both nociceptive and non-nociceptive neurones but it selectively inhibited activity evoked by noxious stimuli on nociceptive cells, indicating a pre-synaptic site of action. In contrast, NA generally had little effect on non-nociceptive cells whilst causing long-lasting inhibition of nociceptive cells and there was a correlation between the amount of inhibition (measured as the percentage inhibition of control firing) caused by NA and the percentage inhibition from brain stem stimulation.

From these results it would appear that 5-HT is unlikely to be a candidate as the transmitter mediating inhibition from brain stem stimulation. However, descending excitatory tryptaminergic pathways may increase activity of interneurones which in turn inhibit other neurones transmitting nociceptive impulses.

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On the structural requirements for dopamine-like activity in homogenates of rat nucleus accumbens

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The dopamine-sensitive adenylate cyclase present in homgenates of rat striatum (Kebabian, Petzhold & Greengard, 1972) has proved to be a useful model system for the study of drugs affecting mammalian dopamine receptors (review by Iversen, 1975). Dopamine sensitive adenylate cyclases are also present in other brain regions including the nucleus accumbens (Horn, Cuello & Miller, 1974). We have now investigated the structural requirements for dopamine-like activity on the adenylate cyclase from rat nucleus accumbens.

The activity of adenylate cyclase in homogenates of rat nucleus accumbens was estimated using the method of Kebabian, Petzhold & Greengard (1972) and the resulting cyclic AMP was determined according to Gilman (1970). Potency of agonists was expressed as a percentage of the maximum response which was taken as that produced by 100 μM dopamine. A log concentration/response curve was constructed for each compound and EC_{50} values (concentration producing 50% of maximum response) were obtained.

In the absence of dopamine, the mean production of cyclic AMP by 50 μl nucleus accumbens homogenates was 49.9 ± 9.4 ($n = 12$) pmol/tube during the 3 min incubation. This was increased to 80.2 ± 9.4 ($n = 12$) pmol/tube by 100 μM dopamine. The potency of the compounds tested is shown in Table 1.

Table 1 Potency of drugs in increasing cyclic AMP production in homogenates of rat nucleus accumbens

Agonist	EC_{50} (μM)
ADTN*	0.7 ± 0.3
Epinine	1.8 ± 0.8
Dopamine	6.3 ± 1.2
(−)-Noradrenaline	25.1 ± 14.6
(−)-Adrenaline	50.1 ± 17.2
3,4-dihydroxy-5-methoxy phenylethylamine	141.3 ± 17.2
(±)-Isoprenaline	inactive
(−)-Phenylephrine	inactive
3,5-dihydroxy-4-methoxy phenylethylamine	inactive
3-hydroxy-4,5-dimethoxy phenylethylamine	inactive

* 2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydro-naphthalene.
EC_{50} values are the mean ± s.e. mean obtained from 4–8 observations.
All active compounds gave 100% stimulation.

The order of potency of the various agonists is similar to that previously determined in homogenates of rat striatum (Miller, Horn, Iversen & Pinder, 1974; Munday, Poat & Woodruff, 1976), suggesting a similarity between the dopamine receptors in the two regions of the brain. The high potency of ADTN is consistent with previous behavioural and electrophysiological studies with this compound.

K.J.W. is an MRC student.

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The effects of some indolalkylamines on the uptake and release of 5-hydroxytryptamine in rat striatum

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The mammalian CNS shows a differential anatomical distribution of 5-hydroxytryptamine (5-HT) (Bogdanski, Weissbach & Undenfriend, 1957) and *in vitro* exhibits an active transport system for the uptake of 5-HT which is distinguishable from that of noradrenaline and dopamine (Blackburn, French & Merrills, 1967; Shashkan & Snyder, 1970). In this study we have investigated the effects of various indolakylamines on the uptake and release of [^{3}H]-5-HT *in vitro* providing complementary data to the structure-activity study of Horn (1973) with these compounds on the uptake of 5-HT.

The method of Raiteri, Angeli & Levi (1974) was used; briefly rat striatum tissue was removed, weighed and chopped into cubes 0.1 x 0.1 x approximately 2.0 mm. The tissue was suspended in 10 ml cold incubation medium (containing 5.10^{-5} M pargyline) and pre-incubated for 15 min at 37° and subsequently incubated for 10 min [^{3}H]-5-HT at a final concentration of 1.10^{-8} M (5-[1,2-^{3}H(N)]; S.A. 22.5 Ci/mmol). In uptake experiments the drug was added simultaneously with the radioactive 5-HT and after the incubation the tissue was separated from its incubation medium either on Millipore filters or by centrifugation at 10,000 x g. The tissue, or tissue and filter, was solubilised with PCS (Amersham-Searle) and the amount of radioactivity accumulated determined by liquid scintillation counting. The results were corrected for non-specific uptake by subtraction of a zero time blank. In the release experiments the radiolabelled tissue resting on Millipore filters was superfused with incubation medium at 37°. This was drawn through the tissue bed at 0.5 ml/min and fractions were collected every minute. After 5 min the superfusing medium was replaced by a medium containing the indolakylamine studied and superfusion continued for a further 10 minutes. The percentage of total recovered radioactivity (filter + tissue + fractions) was calculated for each fraction and the combined values for the first 5 fractions subsequent to the initiation of release corrected for basal release, this value was expressed as a percentage of the maximal release of [^{3}H]-5-HT caused by cold 5-HT (1.10^{-4} M).

IC_{50} values were calculated from semi-log plots and in this preparation were found to be $2.6 \cdot 10^{-7}$ M for tryptamine, $2.7 \cdot 10^{-7}$ M for α-methyltryptamine, $5.5 \cdot 10^{-6}$ M for 5-methoxytryptamine and $1.9 \cdot 10^{-8}$ M for chlorimipramine. In the release experiments chlorimipramine (10^{-5} M) caused no release of 5-HT while tryptamine, α-methyltryptamine and 5-methoxytryptamine at the same concentration caused 69%, 71% and 41% release respectively calculated as described above. At a concentration of 10^{-7} M the values for tryptamine, α-methyltryptamine and 5-methoxytryptamine were 36%, 42% and 0% respectively.

In comparison with chlorimipramine, tryptamine and α-methyltryptamine were approximately an order of magnitude less potent as inhibitors of 5-HT uptake, while 5-methoxytryptamine was still less potent. However while chlorimipramine exhibited no ability to release 5-HT, the other indolakylamines investigated showed the same rank order of potency on release as against uptake inhibition.