Inhibition of the stimulant effect of 5-hydroxytryptamine on cardiac sympathetic nerves by 5-hydroxytryptamine and related compounds

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5-Hydroxytryptamine (5-HT) stimulates noradrenaline release from isolated rabbit hearts by activating tryptamine receptors on the terminal sympathetic nerves (Fozard & Mobarok Ali, 1976; Fozard & Mwaluko, 1976). A characteristic feature of the response is the tendency to rapid and reversible tachyphylaxis (Fozard & Mwaluko, 1976), which, in the absence of selective antagonists (Fozard & Mwaluko, 1975), is an important criterion for mediation through tryptamine receptors (Fozard & Mobarok Ali, 1976). This report explores this phenomenon further and details the potencies and selectivity of 5-HT and four structurally related compounds as antagonists of the stimulant effects of 5-HT on the cardiac sympathetic nerves.

Hearts were removed from rabbits given heparin (500 u/kg) 5 min before killing and perfused at constant pressure by the Langendorff technique with Tyrode solution containing atropine (0.5 μg/ml) at 37°C. Right atrial and ventricular tensions and cardiac rate were recorded as previously described (Fozard & Muscholl, 1971). Drugs were given by bolus injection or incorporated into the perfusion fluid.

Cardiac stimulant responses to bolus injections of 5-HT (0.5–128 μg) were inhibited, concentration dependently, by perfusion of hearts with 5-HT (78 and 312 ng/ml), concentrations which did not themselves cause cardiac stimulation. The inhibition was selective in that responses to noradrenaline (0.04–40 μg) and dimethylphenylpiperazinium (5–320 μg) were unaffected.

Perfusion of hearts with tryptamine, 5,6-dihydroxytryptamine, *N*-methyl-5-HT, and *N,N*-dimethyl-5-HT which have been shown to activate neuronal tryptamine receptors (Fozard & Mobarok Ali, 1976) also inhibited responses to 5-HT. In each case, inhibition was selective in that responses to the ED_{50} of noradrenaline and dimethylphenylpiperazinium were unaffected. Similarly, inhibition was produced without evidence for preliminary receptor stimulation. Using 5-HT as the agonist, the pA_2 values for the antagonist activities of 5-HT and its analogues were estimated by the method of Arunlakshana & Schild (1959) and are presented in Table 1. Also in Table 1 are the activities relative to 5-HT as excitants and inhibitors of the cardiac sympathetic neuronal tryptamine receptors.

The data suggest that 5-HT and several of its analogues with the property of stimulating neuronal tryptamine receptors can desensitize these receptors at concentrations lower than those required for excitation. If these experiments have physiological relevance, then it seems likely that neuronal inhibition would be the normally expected response since excitation occurs only at high concentrations or after bolus injection of the drugs.

Table 1

Compound	pA_2†	*Molar concentration ratio (inhibition)* Antilog (mean pA_2 5-HT-mean pA_2 drug)	*Molar dose ratio‡ (excitation)* ED_{50} drug/ED_{50} 5-HT
5-HT	6.75 ± 0.11 (6)	1	1
N-methyl-5-HT	6.48 ± 0.10 (3)	1.7	2.2 (1.7–2.8) (4)
N,N-dimethyl-5-HT	7.06 ± 0.10 (5)	0.5	2.3 (1.8–3.0) (5)
5,6-dihydroxytryptamine	6.66 ± 0.15 (4)	1.3	4.7 (3.2–6.9) (3)
tryptamine	4.98 ± 0.09 (4)	53	302* (135–676) (4)

* Molar dose ratio ED_{25} drug/ED_{25} 5-HT.

† Mean values with standard errors.

‡ Mean values with 95% confidence limits (from Fozard & Mobarok Ali, 1976).

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Effects of carbonic anhydrase inhibitors upon cerebral cortex oxygen availability and resistance to hypoxia

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Acetazolamide has been used in the treatment of respiratory insufficiency and appears to aid accommodation to altitude in man. This drug is able to increase cerebral blood flow without influencing the cerebral metabolic rate of oxygen. This effect seems to be due to raised pCO_2 of brain tissue (Gotoh, Meyer & Tomita, 1966).

The influence of carbonic anhydrase inhibitors (acetazolamide, methazolamide, dichlorphenamide) upon cerebral tissue pO_2 has been studied in unanaesthetized rabbits with chronically implanted oxygen electrodes. Intravenous administration of these drugs (5–25 mg/kg) rapidly induced a significant and long-lasting rise of cerebral pO_2. Meanwhile, the pO_2 response to CO_2 inhalation was not reduced.

Resistance to atmospheric decompression in mice was increased by carbonic anhydrase inhibitors, but these drugs displayed no protection against asphyxial hypoxia in rats.

These results are in accordance with the reported clinical data.

Reference

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Long-lasting effects of the opening of the blood brain barrier on the modifications induced by intracarotid injection of noradrenaline

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There are three problems concerning the haemodynamic effects of noradrenaline: (1) Does noradrenaline cross the blood brain barrier, when injected into the carotid artery? (2) What are the effects of such an injection on cerebral blood flow, whether the blood brain barrier is opened or not? (3) Which haemodynamic effects might be considered to be of central origin?

The following observations were made on dogs: (1) Vertebral blood flow was decreased after the intracarotid injection of noradrenaline. Thus, the vertebral artery is responsive to noradrenaline. After the blood–brain barrier had been opened (urea 36%, 10 ml), the decrease of the vertebral blood flow was more marked and so was related to the effects of noradrenaline itself on the vertebral artery and/or its underlying system. (2) Cardiac output increased immediately after the injection of noradrenaline subsequent to the first injection of urea. Thus, there must be central cardiostimulating structures responsive to noradrenaline. (3) Mean arterial blood pressure, total peripheral resistance and heart rate decreased, and femoral blood flow increased only after the injection of noradrenaline given after a second injection of urea.

Hence, the bradycardia and the increase of cardiac output, which are both centrally mediated, are therefore related to two different mechanisms, since noradrenaline increased cardiac output immediately after the first injection of urea, but induced bradycardia only after the second injection of urea. Thus, the effects of noradrenaline can be modulated by modifications of the permeability of the blood brain barrier.