bition at $3.2 \pm 0.6 \times 10^{-8}$ mol/l ($n = 20$) and $1.7 \pm 0.4 \times 10^{-6}$ mol/l ($n = 24$) respectively (mean values ± s.e. mean) The inhibitory effects of 5-HT and methysergide were potentiated by cyproheptadine (1.0×10^{-6} mol/l) but were unaffected by haloperidol (1.0×10^{-6} mol/l), propranolol (1.0×10^{-6} mol/l), atropine (1.0×10^{-6} mol/l), mepyramine (1.0×10^{-6} mol/l) or cimetidine (1.0×10^{-5} mol/l). 5-HT (1.0×10^{-7} mol/l) and methysergide (3.0×10^{-6} mol/l) inhibited the electrically stimulated release of tritium by 78 ± 4% ($n = 6$) and 47 ± 7% ($n = 6$) respectively and these inhibitory effects were not antagonised by phentolamine (1.0×10^{-6} mol/l) which itself increased tritium release by about four fold, 5-HT and methysergide also inhibited the electrically stimulated release of [^{3}H]-noradrenaline.

Our results show that methysergide inhibits release of noradrenaline from noradrenergic nerves in dog saphenous vein possibly by activating the presynaptic receptor for 5-HT. This suggests that the presynaptic 5-HT receptor is similar to the postsynaptic 5-HT receptor in this preparation and that both are different from the classical D-receptor (see Apperley, Humphrey & Levy, 1977).

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Evidence for an autoreceptor-mediated presynaptic control of serotonin release in central nerve endings

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The release of noradrenaline from peripheral and central nerve endings is modulated by presynaptic α-autoreceptors (Langer, 1977; Starke, 1977). We have investigated whether a similar mechanism existed in serotonergic terminals, by analyzing the effect of extra-cellular 5-hydroxytryptamine (5-HT) on the release of [^{3}H]-5-HT previously accumulated by hypothalamic synaptosomes.

Crude synaptosomes, prepared from adult male Wistar rats, were prelabelled with [^{3}H]-5-HT (0.1 μM, 10 min at 37°C) and distributed in parallel superfusion chambers (Raiteri, Angelini & Levi, 1974). The superfusion media contained chlorimipramine (Cl–IMI, 5 μM) to prevent 5-HT uptake. 5-HT was added after 10 min superfusion with Cl–IMI-containing Krebs-Ringer medium and, 8 min later, the synaptosomes were depolarized with KCl (15 mM). Serotonin antagonists were present from the beginning of superfusion. The superfusion rate was 0.5 ml/min. The [^{3}H]-5-HT in each 1-min fraction and in the synaptosomes at the end of superfusion was measured after isolation on Biorex columns.

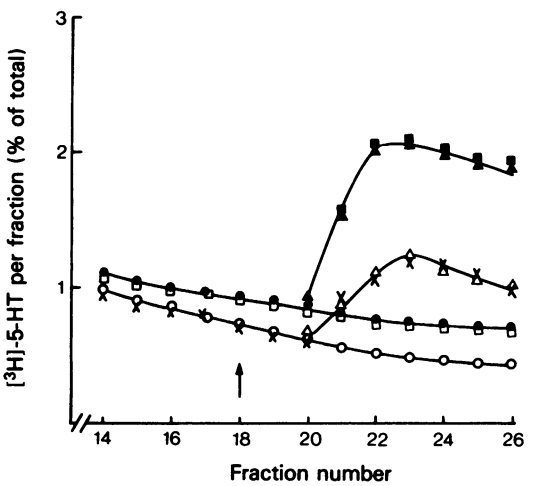

Figure 1 Spontaneous and high K^+-induced release of [^{3}H]-5HT from hypothalamic synaptosomes: inhibition by extracellular 5HT and antagonism between 5HT and methiothepin. (●) control (Cl-IMI present); (○) 0.5 μM 5HT; (□) 0.5 μM 5HT + 0.5 μM methiothepin; (▲) 15 mM KCl; (△) 15 mM KCl + 0.5 μM 5HT; (■) 15 mM KCl + 0.5 μM 5HT + 0.5 μM methiothepin; (×) 15 mM KCl + 0.5 μM 5HT + 1 μM cyproheptadine. Methysergide (1 μM) and mianserin (1 μM) behaved as cyproheptadine and are not shown in the Figure. The [^{3}H]-5HT present in each fraction is expressed as a percentage of the total [^{3}H]-5HT recovered (fractions + synaptosomes). The curves presented are averages of 3-5 quadruplicate experiments.

Extracellular 5-HT (0.5 μM) strongly inhibited the release of [^{3}H]-5-HT elicited by high K^+ (Figure 1). The inhibition was dose-related (not shown). The serotonin receptor blocker methiothepin (0.5 μM) (Monachon, Burkard, Jalfre & Haefely, 1972) counteracted the effect of 5-HT. Other 5-HT antagonists (cyproheptadine, methysergide and mianserin), tested at 1 μM, were ineffective. Also [^{3}H]-5-HT spontaneous release was inhibited by 5-HT and methiothepin antagonized the inhibition (Figure 1).

These results provide strong evidence for a modulation of 5-HT release through presynaptic autoreceptors. Only methiothepin appears to interact with these receptors; the other drugs tested may act preferentially as postsynaptic 5-HT receptor antagonists. Results from *in vivo* studies are in keeping with this view (Jacoby, Shabshelowitz, Fernstrom & Wurtman, 1975). 5-HT spontaneous release may occur in part through a mechanism similar to that of the depolarization-induced release (exocytosis?).

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Althesin as an anaesthetic in experimental animals susceptible to halothane-initiated malignant hyperthermia

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The malignant hyperthermia syndrome (MHS) occurs in man and the pig. In the former species it is associated with myopathy, in the latter with abnormal patterns of high energy phosphate (~P) and carbohydrate metabolism. The symptoms included muscular rigidity, hyperthermia, tachycardia, cardiac arrythmia and severe respiratory and metabolic acidosis. The trigger agent usually is halothane alone or in combination with the myorelaxant suxamethonium. The onset of halothane-initiated MHS may be delayed by premedication with neuroleptic drugs (McLoughlin, Somers, Ahern & Wilson, 1978) or induction of anaesthesia with a barbiturate (Ahern, Somers, Wilson & McLoughlin, unpublished). In the absence of such treatment these animals developed an acute and fatal form of MHS (McLoughlin & Mothersill, 1976). In the work described in this report MHS-susceptible pigs were anaesthetised with althesin and 1h later halothane was given (1–2% in O_2 at a rate of 2 litre/min). During althesin anaesthesia, the limbs remained relaxed, heart rate steady and rectal temperature fell. Following the administration of halothane, there was a progressive fall in the concentration of ATP and creatine phosphate (CP) and a rise in that of lactate and glucose -6-phosphate (G-6-P) in biopsy specimens of *m longissinus dorsi*. After 45 min under halothane the heart accelerated and rectal temperature began to rise and at about 45–60 min muscular rigidity set in. The results indicate that (1) althesin is a suitable anaesthetic for MHS-susceptible pigs, (2) induction with althesin delays the onset of rigidity for 45 to 60 min and (3) loss of ~P and stimulation of glycolysis in skeletal muscle precedes other changes.

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