Action of methysergide on fenfluramine-induced contractions of the saphenous vein

A number of recent papers have discussed the relation between the actions of fenfluramine and 5-hydroxytryptamine (5-HT). Jespersen & Krüger-Schiel (1970) showed that the toxic hypothermic action of fenfluramine in dogs could be blocked by the 5-HT inhibitor methysergide. Funderburk, Hazelwood & others (1971) showed that the anorectic action of fenfluramine in rats could not be prevented by pretreatment with *p*-chlorophenylalanine but was inhibited by AHR-3009, a potent 5-HT antagonist. They suggested that fenfluramine could act directly by stimulating the tryptaminergic neuron.

It has been previously shown that fenfluramine causes a contraction of human isolated saphenous vein spirals (Coupar, Hedges & others, 1969). This effect has been further studied by investigating the action of methysergide on these responses. Four separate specimens of human saphenous vein spirals were set up in an isolated organ bath in Krebs-bicarbonate solution oxygenated with 5% carbon dioxide in oxygen. One end of the spiral was attached to a frontal writing lever and the responses were recorded on a kymograph. Two constant cumulative dose response curves to fenfluramine were obtained and then a further curve was obtained in the presence of the antagonist. After washing out, a further two constant fenfluramine curves were obtained before the procedure was repeated with a second dose of methysergide.

The results from one such estimation are shown in Fig. 1. Similar results were obtained in all four experiments, although the sensitivity of the tissues to fenfluramine and methysergide varied. Minimum effective doses of fenfluramine ranged from 0·5 to 10 μg/ml and of methysergide from 0·25 to 10 μg/ml.

The shift to the right and the lowered maxima of the fenfluramine dose response curves allow the conclusion that the antagonism by methysergide is non-competitive. The pA_2 value of methysergide against 5-HT on human vein is about 8·2 (Metcalfe & Turner, 1969) concentrations of 0·5 and 1 ng/ml being sufficient to produce marked inhibition of 5-HT responses. The higher concentrations necessary to inhibit fenfluramine responses may indicate a non-specific action of methysergide, and suggest that while the central nervous effects of fenfluramine may be related to 5-HT, this is not so clearly demonstrated in its peripheral actions on smooth muscle.

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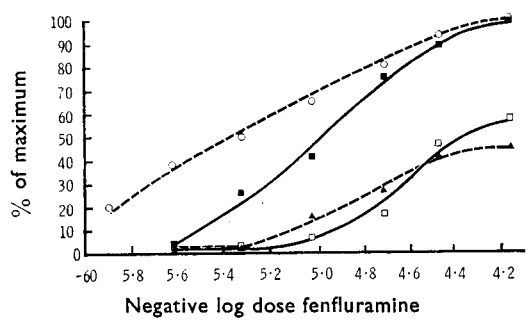

FIG. 1. The height of contraction produced by fenfluramine is expressed as a percentage of the maximum of the control curves (A ○– –○ and B ■–■) obtained before the adminstration of either 250 (□–□) or 500 (▲– –▲) ng/ml of methysergide to the bath fluid, and is plotted against the $\log_{10}$ of molar concentration of fenfluramine.

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Potentiation of the responses of the vas deferens of the guinea-pig to transmural stimulation and to noradrenaline, by triethylcholine and tetraethylammonium

The actions of triethylcholine (TEC) and tetraethylammonium (TEA) at cholinergic sites is well documented and an additional action at an adrenergic site was reported for TEA by Thoenen, Haefely & Staehelin (1967), who observed a potentiation by TEA of the contractile response of the cat spleen to stimulation of the splenic nerve. I now report a potentiation by TEC and TEA of the response of the vas deferens of the guinea-pig to adrenergic stimulation.

Adult male guinea-pigs, 500 g, were killed by stunning and bleeding and the vasa deferentia removed, stripped of their mesentery (Bentley & Sabine, 1963), and suspended in Krebs solution at 37°, bubbled with 5% carbon dioxide in oxygen. In some experiments the vasa were stimulated transmurally (Birmingham & Wilson, 1963) for 15 s every 4 min at a frequency of 20 impulses/s. Each impulse was of 500 μs duration and 100 V. In other experiments noradrenaline was added to the bath to stimulate the adrenergic receptors. Contractions were recorded by frontal writing levers on smoked paper. Concentrations of drugs are given in the weight of the base.

Each vas deferens was stimulated regularly until consecutive contractions were uniform. The tissue was then exposed to Krebs solution containing TEC (5×10^{-4} g/ml) or TEA (10^{-4} g/ml). In each experiment these concentrations of the drugs produced a potentiation of the response of the vas to transmural stimulation, although the extent of the potentiation varied from vas to vas it averaged $1\frac{1}{2}$ times. The potentiation was maintained while the drug remained in contact with the tissue, but was readily reversed. Control vasa, not exposed to the drug, showed no change in the size of the contractile response. The onset of the potentiation was rapid, maximum potentiation being reached within 30 s of administration of the drug.

Prior administration of cocaine (5×10^{-6} g/ml) or desipramine (10^{-6} g/ml) did not alter the potentiation.

A similar potentiating effect was described for choline by Bell (1967), but which differed from the present experiments in being blocked by hyoscine; the action of TEC and TEA did not appear to be at muscarinic or nicotinic ganglionic sites since neither atropine (5×10^{-6} g/ml) nor hexamethonium (5×10^{-6} g/ml) altered the potentiation.

In other experiments the effects of TEC and TEA on the response of vasa to a submaximal concentration of noradrenaline were tested. The response to $1{\cdot}6 \times 10^{-6}$ g/ml of noradrenaline (corresponding to about 30% of a maximal contraction) was, in the presence of TEC (5×10^{-4} g/ml) or TEA (10^{-4} g/ml), reproduced by a concen-