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Anti-acetylcholine, and adrenaline-potentiating activity of oxotremorine on guinea-pig isolated vas deferens

Oxotremorine produces a sharp but transient fall in blood pressure, as does acetylcholine or carbachol, which is prevented both by atropine methylbromide and atropine sulphate. On the guinea-pig and rat isolated ileum and on the rat isolated urinary bladder, oxotremorine causes contractions similar to those elicited by acetylcholine or carbachol (Haslett, 1963; György, Pfeifer & Kenyeres, 1970). According to results reported by Cox & Hecker (1971), oxotremorine has the same activity on the guinea-pig isolated intestine as has acetylcholine.

We have examined some effects of oxotremorine on the guinea-pig isolated vas deferens.

Vasa deferentia, freshly removed from the guinea-pig and desheathed, were suspended at 31° in 15 ml of Locke solution with oxygen bubbled through it. Contractions were recorded kymographically on a smoked drum. The test compounds were added to the bath fluid either in a single concentration or cumulatively, always doubling the preceding concentration. The concentrations stated refer to the salts of the following compounds: oxotremorine oxalate, physostigmine salicylate, atropine sulphate, carbachol chloride, acetylcholine chloride.

At $5 \cdot 10^{-7}$ to $5 \cdot 10^{-5}$ g/ml oxotremorine produced contractions of the vas deferens in about 60% of the experiments. Oxotremorine (10^{-6} g/ml) added to the bath fluid at not less than 10 min intervals induced contractions of the same magnitude, but at 2 to 5-min intervals, or a higher concentration (10^{-5} g/ml), the contractions became smaller. Physostigmine enhanced, atropine methylbromide (10^{-8})—even at low concentrations—inhibited oxotremorine (10^{-6})-elicited contractions, and phentolamine (2 and 5×10^{-7}) had no effect. Oxotremorine was in all experiments less effective in eliciting contractions than was acetylcholine: in eight experiments the mean value for contractions elicited by acetylcholine at 10^{-7} g/ml concentration was $51 \cdot 6 \pm 3 \cdot 9$ mm as against $49 \cdot 6 \pm 3 \cdot 1$ mm for contractions induced by oxotremorine at 10^{-6} g/ml concentration in nine experiments. Accordingly, oxotremorine exhibited an about ten times lower activity on this preparation than did acetylcholine. The maximum contractions obtainable were all lower with oxotremorine than with acetylcholine or carbachol. Measured on the same piece of vas deferens, the mean value (23 experiments) for maximum contraction produced by oxotremorine was only $23 \cdot 6 \pm 6 \cdot 3$% of that obtained with either of the other two compounds, whose maxima were always identical. At $5 \cdot 10^{-7}$ to $5 \cdot 10^{-5}$ g/ml, oxotremorine reduced

Table 1. *Effects of oxotremorine (OT) on carbachol-induced contractions in guinea-pig isolated vas deferens.*

Oxotremorine concentrations g/ml	n	ED50 of carbachol μg/ml		ED50 after OT
		ED50, controls	ED50 after OT	ED50, controls
$5 \cdot 10^{-7}$	6	$3 \cdot 2 \pm 1 \cdot 4$	$6 \cdot 5 \pm 1 \cdot 5$	2·0
$5 \cdot 10^{-6}$	8	$4 \cdot 4 \pm 1 \cdot 1$	$51 \cdot 4 \pm 35 \cdot 9$	11·7
$5 \cdot 10^{-5}$	5	$2 \cdot 7 \pm 0 \cdot 4$	$178 \cdot 3 \pm 65 \cdot 5$	66·0

± = s.e.

Table 2. *Effects of oxotremorine on adrenaline-induced contractions in guinea-pig isolated vas deferens.*

Oxotremorine g/ml	n	ED50 of adrenaline μg/ml		ED50 after OT
		ED50, controls	ED50, after OT	ED50, controls
$5 \cdot 10^{-7}$	6	1·4 ± 0·4	0·4 ± 0·18	0·29
$5 \cdot 10^{-5}$	5	1·3 ± 0·3	0·1 ± 0·03	0·08

± = s.e.

contractions elicited by a single dose of acetylcholine or carbachol, as well as by cumulative carbachol administration (Table 1) and produced a parallel rightward shift of the dose-response curve.

Oxotremorine was found to be a more potent inhibitor of carbachol-induced than of acetylcholine-elicited contractions. To achieve the same degree of inhibition, larger doses of oxotremorine (3·9-, 6·7-, > 7·6-, > 5-times) were required with acetylcholine, presumably because the compound possesses a mild depressant effect on cholinesterase. This seems a reasonable assumption in the light of our observation that oxotremorine caused about 50% stronger inhibition of acetylcholine-induced contractions in the presence of 10^{-6} g/ml of physostigmine than in normal Locke solution.

On the guinea-pig vas deferens oxotremorine increased the magnitude of adrenaline-elicited contractions (Table 2). Atropine (10^{-8} g/ml) reduced this effect of oxotremorine by 65 to 75%. On no other organ could we observe the adrenaline-potentiating effect of oxotremorine.

The adrenaline-potentiating effect of oxotremorine may offer a clue to a plausible explanation for the observation made by Somogyi (personal communication) and, independently, by ourselves that on the guinea-pig vas deferens the compound increases the magnitude of the contractions elicited by transmural stimulation.

Pilocarpine and arecoline affected carbachol- and adrenaline-induced contractions similarly to oxotremorine.

It seems that on the guinea-pig isolated vas deferens the mechanism of action of oxotremorine differs in part from that of acetylcholine and carbachol.

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