PRELIMINARY REPORT :

EFFECT OF MERSALYL AT CHOLINOCEPTIVE SITES†

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Summary : The effects of an organic mercurial compound, mersalyl, were tested at the muscarinic and nicotinic sites (the smooth muscles, frog heart and frog rectus muscle) *in vitro*. Mersalyl had an antimuscarinic effect in the smooth muscle tissues and in the myocardium. On the frog rectus muscle, mersalyl had some potentiating effect on acetylcholine response.

Key words : mersalyl antimuscarinic smooth muscle sulfhydryl group sulfhydryl reagent

INTRODUCTION

Evidence for reactive sulfhydryl (SH) groups on the cholinergic receptors have been reported (5). Mercurials are one of the most potent inhibitors among the SH agents. Hence mercurials can be expected to exert effect at the cholinoceptive sites. However, excluding for the effect on renal functions, surprisingly few investigations of the effects of mercurials *per se* on tissue functions have been made, most of them being on the heart (9). A study with a mollusc muscle (8) suggested that mersalyl may either have an anticholinesterase activity or may act on the acetylcholine receptor. In view of the aforesaid we assessed the effect of mersalyl *in vitro* at various cholinoceptive sites. The preliminary results obtained are reported below.

MATERIALS AND METHODS

Effects of mersalyl was tested *in vitro* using preparations of smooth muscle of the gut, myocardium and skeletal muscle. Isolated perfused frog's heart (6), preparations of

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guineapig ileum, rat colon and rabbit jejunum (7) and frog rectus abdominis (7) were mounted using standard procedure.

Drugs used were : acetylcholine bromide (Sigma), histamine diphosphate (Sigma), barium chloride (BDH) and 5-hydroxytryptamine hydrochloride (Sigma). Drug solutions were freshly prepared on each day just before the experiment. Doses refer to the salts. Mersalyl (British Pharmaceutical Laboratories) solution of desired concentration was prepared in physiological salt solution and the bath fluid was replaced with this solution when exposure was needed.

Each observation was based on minimum of 6–10 separate experiments. Doses of agonists, which produced 40–60% of the maximum response were used; they were : 0.02 *μg/ml* for acetylcholine, 0.2 *μg/ml* for histamine, 2.0 *μg/ml* for 5-hydroxytryptamine and 0.2 *mg/ml* for barium chloride.

RESULTS

Smooth muscle preparations :

Mersalyl (7.5 to 48 *μg/ml*) neither produced a contraction nor a relaxation of the smooth muscle. Exposure to mersalyl (48 *μg/ml* for 10 min) had no effect on the contractions induced by barium chloride or 5-hydroxytryptamine but it produced total blockade of acetylchline response. The same dose inhibited response to histamine (mean inhibition, 62±4%). Smaller doses of mersalyl (7.5 and 10 *μg/ml*) were used in rat colon experiments. The inhibition of acetylcholine responses was dose dependent and developed maximally by 30 min.

Frog heart :

Mersalyl (0.24 *mg*) depressed the frog heart. It produced only a negative inotropic effect, the force of contraction being reduced by a mean value of 25±5%; the rate was affected the least. This dose had an atropine like effect and totally blocked the response to acetylcholine. In higher doses mersalyl produced irreversible depression and total stoppage of heart in diastole and hence such doses were not used further.

Frog rectus muscle :

Mersalyl (1 *mg/ml* and higher doses) produced contracture of the frog rectus abdominis. In much smaller doses (0.24 *mg/ml*, exposure time - 15 min) mersalyl showed physotigmine-like potentiation of acetylcholine responses (Fig. 1).

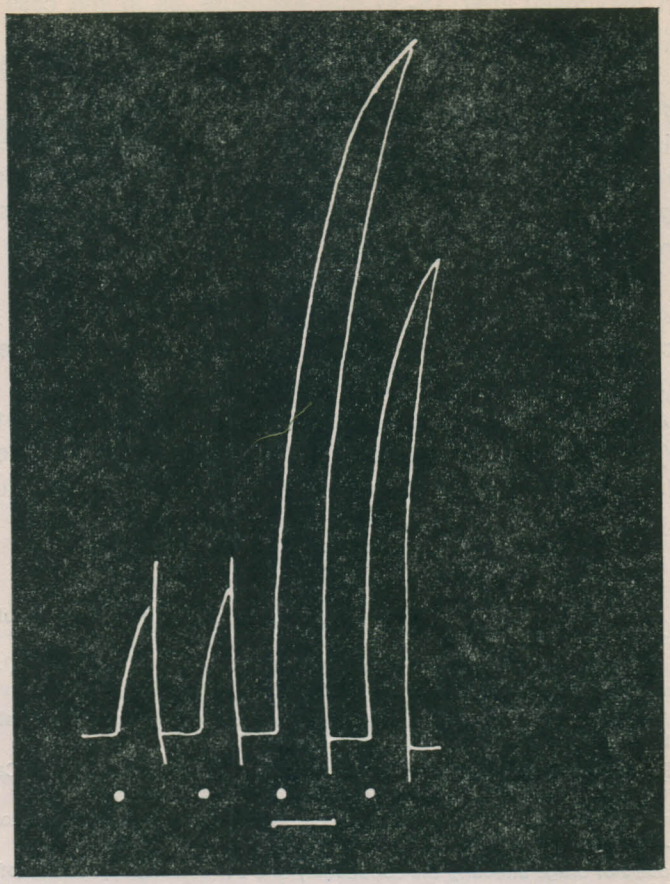

Fig. 1 Responses to acetylcholine (0.2 *μg/ml)* of frog's rectus abdominis. The response with a bar below is after mersalyl exposure (0.24 *mg/ml* for 15 min).

DISCUSSION

Cholinomimetic and/or anticholinergic effect has been reported earlier for some mercurials like merbaphen, p-mercurybenzoate, Hg^{++} *etc.*, on smooth muscle (3, 9) myocardium (9) and in the electroplax (5). However, mersalyl was reported to lack vagal blocking effect (9).

In contrast to its cholinomimetic effect reported in the mollusc (8), mersalyl has anticholinergic effect on various mammalian smooth muscle preparations of the gut and in the frog's heart. Experiments on rat colon have shown that the antiacetylcholine effect of

mersalyl developed maximally after 15-30 min exposure, as in the case of the anti-5-HT effect in *mytilus* (8).

The antihistaminic effect observed with higher dose could be the result of blockade of SH groups which bind the indole nitrogen. Since SH groups have been implicated in different drug receptor systems (2, 4) a detailed study of the antagonism by mersalyl against various agonists like oxytocin, vasopressin, noradrenaline, histamine and 5-HT *in vivo* and *in vitro* experiments is warranted.

Our results with the frog skeletal muscle are in agreement with the earlier reports for mersalyl and/or mercurials. The potentiation of acetylcholine response could be due to an inhibition of muscle cholinesterase (9). The contracture produced with higher doses could be due to activation of cholinergic receptors (1) and/or mediated atleast in part through ATPase (9). The present study has shown deviations in the pharmacological effects of mersalyl as compared to other mercurials reported in the literature.

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