sant falls, the antagonism is reduced, but the concentration may still be sufficiently high to stimulate the more sensitive potentiating mechanism.

REFERENCES

BRADSHAW, C. M., ROBERTS, M. H. T. & SZABADI, E. (1971). Effect of tricyclic antidepressants on monoamine responses of single cortical neurones. *Br. J. Pharmac.*, **41**, 394P–395P.

CARLSSON, A., CORRODI, H., FUXE, K. & HÖKFELT, T. (1969). Effect of some antidepressant drugs on the depletion of intraneuronal brain catecholamine stores caused by 4,α-dimethyl-meta-tyramine. *Eur. J. Pharmac.*, **5**, 367–373.

KIEHOLZ, P. (1968). Die Behandlung endogener Depressionen mit Psychopharmaka. *Dt. med. Wschr.*, **93**, 701–704.

ROSS, S. B. & RENYI, A. L. (1969). Inhibition of the uptake of tritiated 5-hydroxytryptamine in brain tissue. *Eur. J. Pharmac.*, **7**, 270–277.

SIGG, E. B., SOFFER, L. & GYERMEK, L. (1963). Influence of imipramine and related psychoactive agents on the effects of 5-hydroxytryptamine and catecholamines on the cat nictitating membrane. *J. Pharm. Exp. Ther.*, **142**, 13–20.

Electrically induced contractions of guinea-pig isolated ileum resistant to tetrodotoxin

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Human isolated gastrointestinal muscle, and circular muscle from rabbit caecum, responds to electrical field stimulation at relatively low pulse widths with contractions which are only partly antagonized by tetrodotoxin (TTX) (Metcalfe & Bennett, 1971; Small, 1971). We (and Paton, personal communication) have found a similar effect in the longitudinal muscle of guinea-pig ileum. Segments of ileum 1–2 cm long were suspended in Krebs solution bubbled with 5% CO_2 in O_2 at 37° C under a load of 0·5 g. Each preparation was stimulated for 20 or 30 s by alternating square wave pulses between platinum wire electrodes at the top and bottom of the organ bath. Responses were recorded with an isotonic transducer and a pen recorder. The amplitude of the contractions varied with frequency (2–64 Hz), pulse width (0·1–100 ms) and voltage (7–17 V/cm). TTX (0·2–1 μg/ml) reduced but did not abolish the responses (Fig. 1). The subsequent experiments were to determine whether these unblocked contractions were due to stimulation of TTX-resistant nerves, to release of a mediator, or to direct electrical excitation of the muscle cells.

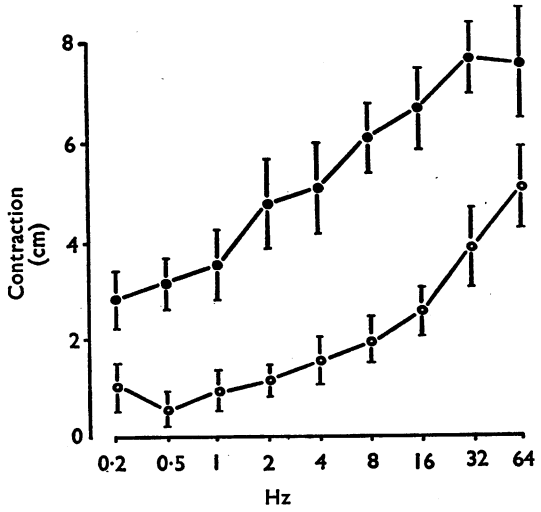

FIG. 1. Responses of longitudinal muscle from guinea-pig isolated ileum to 30 sec. trains of electrical field stimulation (17 V/cm; 1 msec pulses) before (●——●) and in the presence of TTX 5×10^{-7} g/ml. (○——○). Each point is the mean of 11 experiments ±S.E.M.

Lignocaine (1–100 μg/ml), cocaine (10–100 μg/ml) anoxia (5% CO_2 in N_2) or cooling (22–32° C) either had no effect on the TTX-resistant contractions or simultaneously depressed responses to acetylcholine or KCl. Hyoscine (2–10 μg/ml) or morphine (10–100 μg/ml) did not affect the contractions selectively, and methysergide (1–20 μg/ml), mepyramine (1 μg/ml) and polyphloretin phosphate (10–1,000 μg/ml) in doses which antagonized responses to 5-hydroxytryptamine, histamine and prostaglandin E_2 respectively were mainly without effect.

We conclude that the TTX-resistant contractions were probably due to direct electrical excitation of the smooth muscle cells. Paton (1955) found that atropine completely blocked contractions of guinea-pig ileum to single pulses of short duration and concluded that the response was mediated entirely by cholinergic nerves. The situation is clearly not so with repetitive stimulation. Furthermore, TTX seems likely to be more suitable than atropine for analysing nerve mediated responses since TTX would be expected to block all nerves whereas the response after atropine would include a component from inhibitory nerves (Ambache, 1955).

REFERENCES

AMBACHE, N. (1955). The use and limitations of atropine for pharmacological studies on autonomic effectors. *Pharmacol. Rev.*, **7**, 467–494.

METCALFE, H. L. & BENNETT, A. (1971). The intrinsic innervation of the human stomach. *Rendic. R. Gastroenterol.*, **3**, 132–133.

PATON, W. D. M. (1955). The response of the guinea-pig ileum to electrical stimulation by coaxial electrodes. *J. Physiol., Lond.*, **127**, 40–41P.

SMALL, R. C. (1971). Transmission from cholinergic neurones to circular smooth muscle obtained from the rabbit caecum. *Br. J. Pharmac.*, **42**, 656–657P.

Evidence for a non-adrenergic inhibitory nervous pathway in guinea-pig trachea

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Electrical stimulation of the isolated intact guinea-pig trachea causes a biphasic response, initially excitatory and then inhibitory. The excitatory response was abolished by atropine (10 ng/ml) (Farmer & Coleman, 1970).

In the present study, the nature of the inhibitory response has been examined. Propranolol (10–100 ng/ml, n=4) and guanethidine (100–300 ng/ml, n=4) reduced but never completely abolished the inhibitory response. The optimum stimulation period for the inhibitory response increased in the presence of these drugs from 7 s to 12 s. A small inhibitory response was also obtained in tracheas in which sympathetic nerve function was abolished by pretreatment with syrosingopine (5 mg/kg I.P. 16–20 h before the experiment, n=54) or with 6-hydroxydopamine (2×25 mg/kg I.V. on day 1, 2×50 mg/kg I.V. on day 7, experiments performed on days 8–10, n=2). In these preparations the inhibitory response was not modified by propranolol (1 μg/ml) or guanethidine (5 μg/ml).

These results show that the inhibitory response to electrical stimulation consists of two distinct responses, an adrenergic inhibitory response and a non-adrenergic inhibitory response (NAIR). Further investigation of the NAIR carried out in tracheas from syrosingopine pretreated guinea-pigs and in the presence of atropine (100 ng/ml) to eliminate adrenergic and cholinergic effects respectively. The NAIR was abolished by lignocaine (100–300 μg/ml, n=5) and by tetrodotoxin (10–100 ng/ml, n=5), suggesting that it is of nervous origin.

An attempt was made to characterize the transmitter mediating the NAIR. It was concluded that the transmitter was unlikely to be (1) histamine—NAIR not blocked by mepyramine (0·1–1·0 μg/ml, n=5) or burimamide (1–10 μg/ml, n=5), (2) 5-hydroxytryptamine—NAIR not blocked by methysergide (10 μg/ml, n=4), (3) a prostaglandin—NAIR not blocked by the prostaglandin synthesis inhibitor indomethacin (1–3 μg/ml, n=5) or (4) cyclic 3′5′-AMP—NAIR was neither potentiated by the phosphodiesterase