POTENTIATION BY METOCLOPRAMIDE OF RESPONSES TO CHOLINERGIC NERVE STIMULATION IN THE ISOLATED GASTRIC FUNDUS PREPARATION OF THE RAT

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Metoclopramide is used clinically both as an anti-emetic and also to increase the rate of gastric emptying (Pinder & others, 1976). The anti-emetic effect of metoclopramide is probably related to its action in blocking dopamine receptors (Peringer & others, 1975; Day & Blower, 1975). However, the mechanism of its action on the gastrointestinal tract is not clear and a number of possibilities have been suggested (for review see Pinder & others, 1976). In the present investigation the action of metoclopramide has been examined on the smooth muscle of the rat gastric fundus preparation (Vane, 1957) in which the intrinsic neural elements have been activated by electrical field stimulation. Field stimulations were applied for trains of 100 pulses of supramaximal strength (140 volt) and 2 m.sec pulse width at frequencies over the range 0.5 to 20 Herz. The responses to field stimulation in control preparations were frequency-related contractions which were potentiated by neostigmine (10-100 ng/ml) or eserine (10-100 ng/ml) and were abolished by either tetrodotoxin (1 µg/ml) or atropine (20 to 100 ng/ml). It was concluded that the contractile responses were mediated via activation of cholinergic nerve elements in the muscle. Metoclopramide (1 to 10 µg/ml) increased the responses to cholinergic nerve stimulation at all frequencies of stimulation although the effect was most marked over the frequency range 0.5 to 2 Herz; responses to added acetylcholine (1 to 50 ng/ml) were not significantly changed by metoclopramide.

The possibility was investigated that metoclopramide was increasing responses to cholinergic nerve stimulation by blocking either inhibitory noradrenergic or "purinergic" (Burnstock, 1972) nervous elements also activated by field stimulation. The sympathetic component of the field stimulation responses were abolished by either phentolamine (1 to 3 µg/ml) or bethanidine (1 to 20 µg/ml) which resulted in a small increase in the contractile responses but did not prevent the usual enhancement of the responses in the presence of metoclopramide. Non-adrenergic inhibitory responses to field stimulation were revealed in the presence of barium chloride (100 µg/ml) which raised the tone of the preparation, bethanidine (10 µg/ml) and atropine (1 µg/ml) which inhibited noradrenergic and cholinergic components respectively. Metoclopramide in concentrations which increased the responses to cholinergic nerve stimulation in control preparations produced only a very slight impairment of the "purinergic" inhibitory responses. It is concluded that the site of action of metoclopramide in enhancing responses to cholinergic nerve stimulation in this preparation is presynaptic on cholinergic nerves since it did not change the sensitivity of post-synaptic receptors to added acetylcholine. It is further suggested that impairment of responses to either noradrenergic or purinergic inhibitory nerves is unlikely to be implicated in the action of metoclopramide in this preparation.

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