Tetrodotoxin (0.2 μg/ml) had no significant effect ($P > 0.2$, $n = 3$) on the formation of [^{14}C]-acetylcholine in stimulated preparations, though it abolished the twitch responses to stimulation. However, in non-stimulated preparations the formation of [^{14}C]-acetylcholine during the 150 and 225 min periods of incubation was significantly decreased ($P < 0.001$, $n = 6$) by tetrodotoxin.

Hyoscine (0.02 μg/ml) abolished responses to stimulation but had no effect on the incorporation of [^{14}C]-choline into acetylcholine in stimulated preparations.

Noradrenaline (1 μg/ml) caused an increase in formation of [^{14}C]-acetylcholine which was significant ($P < 0.05$, $n = 3$) in non-stimulated but not in stimulated preparations with a 75 min incubation period. Contractile responses to stimulation were only transiently depressed.

The presence of hemicholinium (50 μg/ml) during the period of incubation with [^{14}C]-choline decreased the incorporation of label into acetylcholine to about 12% of control in both stimulated and non-stimulated preparations during the incubation periods studied. This finding is compatible with the view that hemicholinium blocks choline uptake. However, contractile responses to stimulation were not affected by hemicholinium, so it appears that preformed stores of acetylcholine were not exhausted with the regimen of stimulation used.

When strips were washed repeatedly after incubation, the level of radioactivity in the bath fluid fell to a fairly constant level after 20 min. Then, stimulation at 0.1 Hz for 3 min did not lead to an increase in radioactivity in the fluid unless hemicholinium (10 μg/ml) was present.

The findings suggest that [^{14}C]-choline was incorporated into acetylcholine, at least part of which was intraneuronal, but the release of the radio-labelled transmitter could only be detected if reuptake of choline (or acetylcholine) was blocked.

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Definition of the antagonistic action of burimamide and metiamide on the positive inotropic effect of histamine in isolated heart preparations

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Burimamide and metiamide have been defined as histamine H_2-receptors antagonists since they were found capable of blocking some mepyramine-insensitive histamine responses, such as the positive chronotropic effect on guinea-pig atria, and the stimulation of gastric acid secretion in the rat (Black, Duncan, Durant, Ganellin & Parsons, 1972; Black, Duncan, Emmet, Ganellin, Hesselbo, Parsons & Wyllie, 1973).

Since it is known that histamine increases both frequency and force of contraction (Mannaioni, 1972) experiments have been carried out to study whether burimamide and metiamide antagonizes the positive inotropic actions of histamine. Moreover the inotropic action of histamine was compared with that of noradrenaline.

Isometric contraction curves and their

derivatives obtained from isolated electrically driven ventricle strips of guinea pigs were analysed with regard to the force of contraction, time to peak tension and of relaxation, velocity of tension development and of relaxation.

Histamine stimulates cardiac contraction more effectively than noradrenaline, leaving unchanged the relaxation time which was strongly diminished by noradrenaline. The histamine effects were antagonized by burimamide and metiamide, which produced a dose-related displacement of the cumulative dose-response curves to histamine, without significantly affecting their slope or maximum. The dissociation constants were 2.1 and 4.2 respectively.

Both drugs in concentrations up to 10^{-4}M, failed to displace the dose-response curves to noradrenaline significantly.

Other antihistamines, such as triprolidine, shifted the cumulative dose-response curves to histamine in a non-competitive way.

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The pharmacological effects of imidazole and some of its derivatives on neuromuscular transmission

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The pharmacological activity of imidazole, 2-methyl-imidazole, *N*-methyl-imidazole and *N*-butyl-imidazole, has been studied using striated neuromuscular preparations *in vivo* and *in vitro*.

The results obtained suggest that imidazole and 2-methyl-imidazole increase *per se* neuromuscular contraction, while *N*-methyl-imidazole and *N*-butyl-imidazole are devoid of any pharmacological activity. *In vivo* experiments show that the effect of 2-methyl-imidazole is more potent and longer lasting than that of imidazole itself in potentiating the contractions of the *tibialis anterior* muscle of the cat, evoked by electrical stimulation of the sciatic nerve.

The pharmacological analysis performed in order to clarify the mechanism of actions of different imidazoles, show that these compounds exert a pronounced and long-lasting antagonism against paralysis induced by *d*-tubocurarine.

These imidazoles, on the other hand, do not show any activity against succinylcholine induced blockade of neuromuscular transmission.

The adrenergic receptors involved in striated neuromuscular transmission (Bowman & Raper, 1967; Bowman & Nott, 1969), do not seem to be relevant to the imidazole activity.

Since exogenous cyclic AMP has been demonstrated to increase the frequency but not the amplitude of the spontaneous m.e.p.p. and the number of the transmitter packets in response to nerve stimulation (Goldberg & Singer, 1969), imidazole, which has been shown to activate phosphodiesterase activity in rabbit skeletal muscle (Huang & Kemp, 1971), does not seem to exert its pharmacological action through the cyclic AMP system. A possible mechanism of action of these compounds was discussed.

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