inhibitor theophylline (1·0–30 μg/ml, n=4) nor blocked by the phosphodiesterase activator imidazole (0·1–1·0 mg/ml, n=4).

Burnstock has reported the presence of a non-adrenergic inhibitory nervous pathway in gastro-intestinal muscle (Burnstock, 1972). They suggested that the neurotransmitter mediating the inhibitory response is probably ATP. In the present study the adenosine uptake blocking drug dipyridamole (1–3 μg/ml) potentiated the NAIR in 9 out of 11 experiments and unmasked the inhibitory response to ATP (10 μg/ml) and adenosine (10 μg/ml) added to the bathing medium.

It is concluded that electrical stimulation of the guinea-pig trachea, in addition to activating cholinergic and adrenergic nervous pathways, may activate a separate and distinct inhibitory nervous pathway. The results of initial experiments suggest some similarity to the non-adrenergic inhibitory nervous pathways in gastro-intestinal muscle described by Burnstock (1972).

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Further studies on the interaction between acetylcholine antagonists and anticholinesterases on cat soleus muscle

R. W. BRIMBLECOMBE and SANDRA N. WEBB*

Chemical Defence Establishment, Porton Down, Salisbury, Wilts. and Department of Physiology, University of Bristol

It was shown previously by Brimblecombe & Everett (1969a, 1970a) that certain acetylcholine antagonists, notably N-ethyl-2-pyrrolidylmethyl-cyclopentylphenylglycollate (PMCG), caused augmentation of the twitch, indirectly or directly elicited, in both slow-twitch (soleus) and fast-twitch (flexor digitorum longus) muscles of the cat hind limb. It was also shown (Brimblecombe & Everett, 1968b, 1970b) that the same compounds prevented or reversed sarin-induced twitch augmentation in these muscles. The experiments described here were designed to explore the latter effects in more detail.

The method used for recording contractions of the soleus was essentially that described by Buller & Lewis (1965a, b) and all drugs were injected intra-arterially via the sural artery. The acetylcholine antagonists used were the glycollates PMCG and N-methyl-4-piperidylphenylcyclohexyl glycollate (PPCG), the latter both as the racemate and as its R and S enantiomers, and the carboxylate 4′-N-methylpiperidyl-1-phenylcyclopentane carboxylate (G3063).

Sarin (5 μg) was administered to both legs. In one leg 2 mg of an acetylcholine antagonist was given 5 min previously. All the compounds at this dose level which produced little or no twitch augmentation protected the muscle from sarin-induced twitch augmentation. When the augmented maximal twitch on the unproected side had reached a steady state, doses of the acetylcholine antagonist, beginning at 0·1 mg and increasing by a factor of 2, were given. A dose-dependent reduction in maximal twitch tension occurred and dosing was continued until the control tension was reached.

Experiments were also carried out with neostigmine. The acetylcholine antagonists protected the muscle from the effects of 10 μg neostigmine in a dose-dependent manner. Complete protection was given by 2 mg while 1 and 0·5 mg gave only partial protection. The maximal twitch augmentation produced by neostigmine could also be reversed by the acetylcholine antagonists.

The two enantiomers of PPCG, which differ by a factor of not less than 20 in their potency as acetylcholine antagonists, are approximately equiactive in causing augmentation of maximal twitch and in preventing or reversing anticholinesterase-induced twitch augmentation showing that these effects are unrelated to the acetylcholine antagonist activities of the compounds.

Experiments have also been carried out with caffeine which causes augmentation of the twitch but does not antagonise the anticholinesterase effects and also with the local anaesthetic lignocaine which reverses and prevents the anticholinesterase effects but produces only slight twitch augmentation . It is suggested, therefore, that the acetylcholine antagonists being studied possess both caffeine-like and local anaesthetic activity.

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Antagonism by burimamide of inhibitions induced by histamine in plexus-containing longitudinal muscle preparations from guinea-pig ileum

N. AMBACHE, S. W. KILLICK* and M. ABOO ZAR

Medical Research Council, Department of Physiology, Royal College of Surgeons of England, Lincoln's Inn Fields, London, WC2A 3PN

In plexus-containing longitudinal muscle preparations, in which histamine-contraction has been largely eliminated by H_1-receptor blockade with mepyramine, histamine produces a second effect, namely a dose-related inhibition of the neurogenic atropine-resistant tetanic spasms elicited by field stimulation (Ambache & Zar, 1970). Since Black, Duncan, Durant, Ganellin & Parson (1972) introduced 4-methyl histamine and burimamide [N-methyl-N'-(4-(4(5)-imidazolyl)-butyl)thiourea] as selective agonist and antagonist, respectively, for H_2-receptors, these compounds have now been tested.

Atropine, 10^{-7} g/ml, and mepyramine, $1–10\times10^{-7}$ g/ml, were present throughout. Tetanic spasms were elicited every 1 min by trains of ten 0·2 ms pulses (50 Hz).

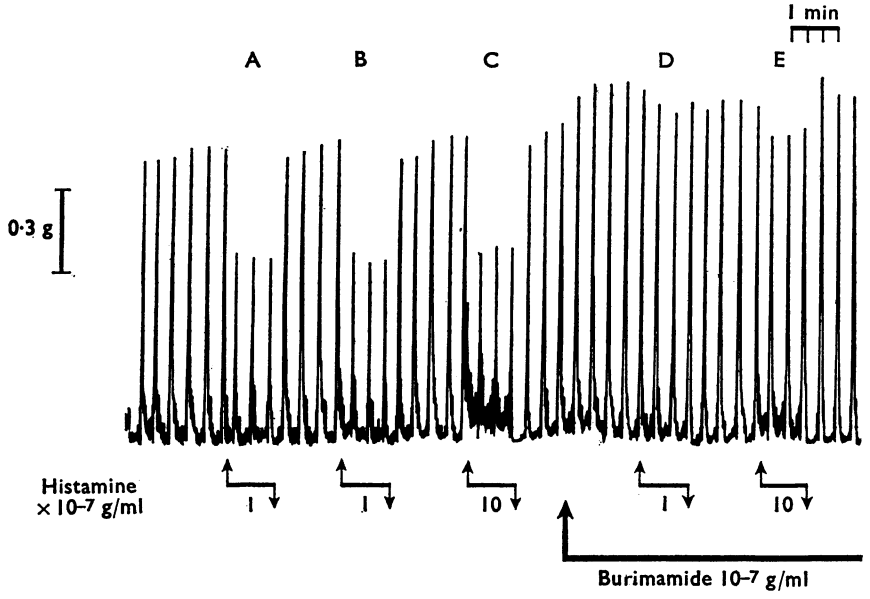

FIG. 1. Antagonism of histamine induced inhibitions by burimamide.