Phentolamine is a competitive antagonist with no apparent selectivity for pre- or postsynaptic sites.

Rand, McCulloch & Storey (1975) have suggested that the ineffectiveness of α-adrenoceptor antagonists such as phentolamine as antihypertensive agents could be related to blockade of presynaptic receptors. This would result in a loss of the inhibitory feedback loop and enhanced release of noradrenaline from sympathetic nerves. The increased noradrenaline concentration could overcome competitive antagonism at α-adrenoceptors on vascular smooth muscle. It is possible that indoramin, an antagonist with specificity for the postsynaptic α-adrenoceptor, might prove more effective in lowering blood pressure in man.

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Effects of 4-aminopyridine on the isolated parasympathetically-innervated oesophagus of the domestic fowl chick

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4-Aminopyridine facilitates neuromuscular transmission in skeletal muscle by an action on the motor nerve endings through which acetylcholine release is increased (Molgo, Lemeignan & Lechat, 1975; Foldes, Agoston & others, 1976; Bowman, Harvey & Marshall, 1977; Lundh & Thesleff, 1977); it has been used as an anti-curare agent in anaesthetic practice (Stoyanov, Vulchev & others, 1976). The compound also facilitates adrenergic transmission in the rabbit isolated vas deferens (Johns, Golko & others, 1976), the rat isolated portal vein (Leander, Arner & Johansson, 1977), and the cat spleen (Kirpekar, Kirpekar & Prat, 1978).

In the experiments described here, the effects of 4-aminopyridine were studied on the isolated parasympathetically-innervated upper oesophagus preparation of domestic fowl chicks (White Leghorn, aged 3–8 days). The muscle in this preparation is entirely smooth muscle. The preparation, with its right parasympathetic nerve attached, was suspended in Krebs solution at 32°, exactly as described by Bowman & Everett (1964). The nerve was stimulated with rectangular pulses of 0·5 ms duration and of twice the strength required to produce a maximal contraction when stimulated at a frequency of 1 Hz. Contractions were recorded with an isometric (Grass model FTO3) or an isotonic (Washington, type T11) transducer, the latter loaded with 1 g, on a Servoscribe (model RE520.20) or a Washington (model 400 MD/2) pen recorder. Generally, the preparations responded more consistently when contracting isotonically, but similar results were obtained with both methods.

4-Aminopyridine in concentrations of 10^{-5} to 10^{-4} M increased the contractions produced by stimulation of the nerve when the applied frequency was below that which produced maximal responses, but maximal responses to nerve stimulation or those produced by acetylcholine, carbachol, or methacholine (2×10^{-7} to 10^{-6} M) were usually not affected. These results indicate that neuroeffector transmission was facilitated by these concentrations of 4-aminopyridine but that contractility of the smooth muscle was unaffected. Fig. 1 illustrates an experiment in which trains of 50 stimuli were applied to the nerve at different frequencies, and responses to methacholine were produced, before and in the presence of two concentrations (5×10^{-5} and 10^{-4} M) of 4-aminopyridine. With the higher concentration, a previously ineffective control frequency of stimulation now produced a substantial response, and the previous threshold frequency produced about the maximal response. With lower concentrations of 4-aminopyridine (10^{-5} M), the facilitatory action on transmission took about 20 min to reach its maximum. The effect developed more quickly with higher concentrations. In a concentration of 10^{-4} M, 4-aminopyridine restored contractions to nerve stimulation (1 Hz for 10 s) that had been blocked by atropine (5×10^{-7} M).

High concentrations of 4-aminopyridine (5×10^{-4} to 10^{-3} M) produced oscillating contractions of the muscle and a slowly developing increase in tone in the absence of nerve stimulation. The increase in tone was aug-

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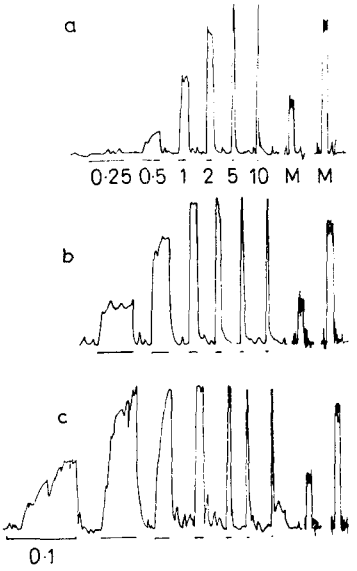

FIG. 1. Responses labelled M are to methacholine (5×10^{-7} and 10^{-6} M). All other responses are to 50 stimuli applied to the right parasympathetic nerve at different frequencies. The frequencies applied (in Hz) are indicated by the numbers, and the durations of the trains by the horizontal lines. (a) control responses; (b) responses in the presence of 5×10^{-5} M 4-aminopyridine; (c) responses in the presence of 10^{-4} M 4-aminopyridine.

mented by previous treatment with choline (5×10^{-4} M) or physostigmine (2×10^{-6} M), but was diminished after previous prolonged nerve stimulation. Atropine (10^{-6} M) or tetrodotoxin (5×10^{-7} M) in concentrations that abolished responses to nerve stimulation, also abolished the increase in tone produced by high concentrations of 4-aminopyridine. Physostigmine potentiated and atropine blocked responses to acetylcholine but tetrodotoxin was without effect.

The fact that, in the absence of nerve stimulation, the increase in tone produced by 4-aminopyridine was inhibited by tetrodotoxin or by previous prolonged nerve stimulation suggests that the acetylcholine to which the increase in tone is attributable was of nervous origin. Since tetrodotoxin acts by blocking nerve action potentials, its ability to block the increase in tone produced by 4-aminopyridine suggests either that 4-aminopyridine can excite the cholinergic nerves to the oesophagus, or that there is a continuous spontaneous local activity of intramural cholinergic nerves causing the release of small amounts of acetylcholine, and that this release is enhanced by 4-aminopyridine.

The oscillating contractions (as distinct from the increase in tone) to which large concentrations of 4-aminopyridine gave rise, were not blocked by atropine or tetrodotoxin, suggesting that they probably arose from a direct action of the compound on the smooth muscle cells.

Lack of calcium ions in the bath fluid abolished responses both to nerve stimulation and to 4-aminopyridine, while responses to acetylcholine were reduced but not abolished. The return of calcium restored the responses to normal. The action of 4-aminopyridine was thus dependent on the presence of calcium ions. 4-Aminopyridine could not substitute for calcium ions. In the absence of calcium ions, responses to nerve stimulation remained blocked when 4-aminopyridine in a molar concentration equivalent to the normal or twice the normal concentration of calcium ions was added.

The results confirm that 4-aminopyridine, though an effective anticurare agent, is not selective for somatic motor nerve endings, since it also affects autonomic adrenergic and cholinergic terminals in similar ways. Its convulsant action (Fastier & McDowall, 1958) may likewise be a consequence of enhanced release of central transmitters.

The important question, therefore, in relation to its use as an anticurare agent in anaesthetic practice is the degree to which its actions at the neuromuscular junction can be produced by doses with minimal effects at other sites.

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