On the basis of these results it might be suggested that the mode of action of therapeutic concentrations of bretylium in cardiac arrhythmias is different from that of the well known quinidine-like compounds.

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The action of procaine on transmission at the mammalian neuromuscular junction

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Procaine is able to produce neuromuscular paralysis both *in vivo* and *in vitro*, (Jaco & Wood, 1944 ; Straughan, 1961) but the mechanism of this paralysis is not fully understood. Evidence has been presented (Straughan, 1961) suggesting that in mammals the failure of normal neuromuscular transmission may have arisen from anaesthesia of the motor nerve terminals. Electrophysiological investigations in frog indicated that the paralysis arose from changes in the postjunctional membrane (Maeno, 1966 ; Furukawa, 1957). The present study was undertaken to obtain further information on the paralysis in rat phrenic nerve-diaphragm preparations.

Using intracellular recording electrodes, end-plate regions were identified in non-curarized tissue as the sites of spontaneous miniature end-plate potentials (m.e.p.p.s) of maximum amplitude (Liley, 1956). In curarized preparations end-plate regions were identified as those from which end-plate potentials (e.p.p.s) with a short rise time (<2 msec) were recorded after supra-maximal stimulation of the phrenic nerve.

Low concentrations of procaine hydrochloride (0.05 to 0.2 mM) rapidly reduced the mean size of the m.e.p.p.s without altering their frequency. Increasing concentrations resulted in an increased reduction in the mean size of the m.e.p.p.s. The rise times of the m.e.p.p.s were not altered by procaine but the decay of potential was greatly slowed. All effects were readily reversed by washing the preparations with drug-free Krebs solution.

End-plate potentials recorded from nerve-diaphragms in which transmission had been blocked by either (+)-tubocurarine hydrochloride (0.0015 mM) or magnesium chloride in high concentrations (12 to 14 mM) were reduced in amplitude by the addition of procaine (0.1 to 0.4 mM) to the perfusion fluid. In preparations paralysed by high Mg^{++} concentrations procaine did not change the mean quantal content of e.p.p.s per nerve impulse. In addition, the rate of decay of the end-plate potential was reduced, as had been shown for m.e.p.p.s with lower procaine concentrations.

Where paralysis was due to procaine alone (0.7 to 0.8 mM) e.p.p.s were readily recordable and these were qualitatively similar to those recorded from preparations paralysed by tubocurarine. A slower decay of potential was again observed.

On the basis of these findings it is suggested that in the rat diaphragm, the neuromuscular blocking action of procaine arises from a post-junctional action. Explanations of the slowed rate of decay of the end-plate potential will be discussed.

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Inhibition by cinnarizine and chlorpromazine of the contraction induced by calcium and adrenaline in vascular smooth muscle

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Recent studies have shown that cinnarizine (1-benzhydryl-4-cinnamylpiperazine dihydrochloride) and chlorpromazine reduce the contractile response induced by depolarization of isolated arteries with potassium (Godfraind, Kaba & Polster, 1968; Godfraind & Polster, 1969). The present experiments were designed to determine whether such inhibition is due to antagonism of the function of calcium in the contractile process of vascular smooth muscle.

Strips 4 cm long were prepared by spiral section of rabbit mesenteric arteries (outside diameter 0.4–0.8 mm). They were bathed either in a polarizing solution (NaCl 112, KCl 5, $NaHCO_3$ 25, KH_2PO_4 1, $MgSO_4$ 1.2, $CaCl_2$ 1.25, and glucose 11.5 mM) or a depolarizing solution (similar but containing 100 mM KCl instead of NaCl and with $CaCl_2$ added according to the concentration required).

Mesentery arterial strips contracted in a depolarizing solution in the presence of calcium. These contractions were proportional to the calcium concentration and were reversible. When muscles had been immersed in a calcium-free medium until no contraction was evoked by the depolarizing solution, they still responded to adrenaline (10^{-4}M) but developed only one-third of the contractile tension caused by adrenaline in polarizing solution. Cinnarizine and chlorpromazine (10^{-5}–10^{-4}M) inhibited the contractile response to calcium, and relaxed depolarized muscles previously contracted by calcium. A 50% reduction in the contraction effected by 20 mM $CaCl_2$ was obtained with cinnarizine (10^{-7}M) and chlorpromazine (4×10^{-7}M).

Chlorpromazine inhibited the response to adrenaline in both polarizing and calcium-free depolarizing solution, whereas cinnarizine inhibited the response in polarizing solution but not that in calcium-free depolarizing solution.