Rabbit hearts were perfused at constant pressure with Tyrode solution containing atropine (0.5 μg/ml) at 37°C. Right atrial and ventricular tensions and cardiac rate were recorded as previously described (Fozard & Muscholl, 1971). Drugs were given by bolus injection or incorporated into the perfusion fluid. Segments of guinea-pig ileum were set up in Tyrode solution containing methysergide (1 μg/ml).

On the heart, (−)-cocaine antagonized chronotropic responses to bolus injections of 5-HT (0.5–32 μg) over the range 0.5–8 μg/ml. At 0.5 and 2 μg/ml, the curves were shifted to the right in a parallel fashion and there was no depression of the maximum response. At 8 μg/ml the maximum response to 5-HT was markedly depressed. (−)-Cocaine (0.5 μg/ml) had no effect on responses to 1,1-dimethyl-4′-phenylpiperazinium iodide (DMPP; 5–160 μg/ml) although 8 μg/ml caused marked inhibition with depression of the maximum response. (−)-Cocaine (0.5 μg/ml) significantly enhanced responses to noradrenaline (0.01–2.56 μg). pA_2 values for the antagonism of 5-HT and DMPP by (−)-cocaine were 6.24 ± 0.08, $n=4$ and 4.95 ± 0.09, $n=3$ respectively. (+)-Cocaine, which does not block noradrenaline uptake, was a more potent antagonist of 5-HT than (−)-cocaine. The pA_2 values for the antagonism of 5-HT and DMPP by (+)-cocaine were 6.90 ± 0.07, $n=3$ and 5.02 ± 0.003, $n=3$ respectively. Lignocaine proved to be only a weak antagonist of 5-HT ($pA_2 = 3.87 \pm 0.09$, $n=3$) and showed no selectivity (pA_2 lignocaine against DMPP $= 4.16 \pm 0.09$, $n=3$). On the ileum treated with methysergide (−)-cocaine antagonized responses to 5-HT over the concentration range 0.5–8 μg/ml. The pA_2 value for the antagonism of 5-HT by (−)-cocaine was 6.00 ± 0.14, $n=5$.

Local anaesthetic properties seem unlikely to explain the 5-HT blocking actions of the cocaine isomers since lignocaine lacked potency and specificity as an antagonist of 5-HT. Similarly, the effects cannot be referred to events at the noradrenaline uptake pathway of the terminal fibres since both the (+)- and the (−)-isomers were effective and there was antagonism of 5-HT at cholinergic nerve endings. The data can be interpreted in terms of an interaction of the cocaine isomers with 5-HT at pre-synaptic tryptamine receptors. Should this be correct then the data provide support for the suggestion that neuronal receptors of the heart and ileum for 5-HT are similar (Fozard & Mobarok Ali, 1976).

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A benzotriazinium salt as a potential antiarrhythmic agent

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Four series of substituted benzotriazinium iodides have recently been synthesized (Stevens & Stevens, 1970). These compounds have many pharmacological properties similar to those of quinidine, notably the effects on cardiac tissue. We have investigated 2-n-propyl-4-p-tolylamino-1,2,3-benzotriazinium iodide (TnPBI) in view of its potential antiarrhythmic properties.

Guinea-pig isolated atrial pairs were mounted on a Sylgard 182 resin base in a channel cut from a perspex block and perfused at 32°C with oxygenated Locke solution of the following composition (mM) NaCl 154, KCl 5.6, $CaCl_2$ 2.16, glucose 5.5, $NaHCO_3$ 2.4. Cells were impaled with glass microelectrodes filled with 3M KCl, and the action potentials were amplified by a Grass P16 DC preamplifier and displayed on an Advance OS 4000 digital storage oscilloscope. Stored action potentials were then drawn out on a pen recorder via an Advance OS 4001 analogue output unit. The atria were stimulated at a frequency of approximately 10% above their spontaneous frequency by means of bipolar platinum electrodes in contact with the surface of the left atrium.

TnPBI increased the duration of the action potential (APD), decreased the maximum rate of depolarization (MRD) and decreased conduction velocity. These effects were dose related between 1×10^{-6} M and 1×10^{-5} M. TnPBI did not significantly alter the resting membrane potential but the size of the overshoot and consequently of the action potential were reduced. With one exception, these effects are similar to those produced by quinidine: the exception is the prolongation of the APD. The work of Vaughan Williams (1958) on

rabbit atria is widely quoted, indicating that quinidine does not prolong the APD, although we have found in preliminary experiments that quinidine does, in fact, prolong the APD in guinea-pig atria.

In strips of electrically stimulated guinea-pig ventricles, TnPBI had much less marked effects on the APD, but significantly reduced the MRD and conduction velocity. As in the atria, the resting membrane potential was unchanged, but there was a significant reduction in the magnitude of both the overshoot and the action potential especially at the concentrations of 5×10^{-6} M and 1×10^{-5} M.

At the concentrations used for the intracellular studies, TnPBI reduced the spontaneous rate of beating of guinea pig isolated atrial pairs, but had only slight inhibitory effects on the force of contraction.

It thus appears that TnPBI produces essentially similar effects on guinea-pig cardiac muscle as quinidine, and may deserve further investigation as an antiarrhythmic agent.

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