To investigate this possibility, aspirin, sodium salicylate or combinations of the two drugs were given orally in a range of concentrations in 1 ml of water to male Wistar rats previously starved for 24 hours. The animals were killed two hours later, their stomachs removed, cut open and everted for examination.

The results show that whether given as aspirin or sodium salicylate or as a mixture of the two, a dose of 175 mg salicylate/kg produced significantly more lesions than a dose of 87.5 mg salicylate/kg and a dose of 350 mg salicylate/kg produced significantly fewer lesions than a dose of 175 mg salicylate/kg. Thus the ulcerogenic effects of aspirin and sodium salicylate are clearly additive. The sodium salicylate induced inhibition of ulcerogenecity previously reported appears, from these results, to be due only to the use of a high total dose of drugs exceeding the optimal lesion-inducing dose.

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Effects of diltiazem and verapamil on the mechanical performance of the rabbit myocardium perfused with an oxygenated and an hypoxic medium

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Heart muscles from several animal species undergo an increase in resting tension accompanied by a decrease in developed contractile force when perfused with an hypoxic medium (Winbury, 1956; Bing, Brooks & Messer, 1973; Nayler, Yepez & Poole-Wilson, 1978). These effects which are accompanied by marked biochemical and structural modifications of myocardial tissue (Nayler, Grau & Slade, 1976), have been shown to be influenced by several experimental conditions such as, glucose concentration (Winbury, 1956) and pH (Bing, *et al.*, 1973) of the perfusing fluid or addition of various drugs to the perfusate (Nayler, *et al.*, 1978; Durrett & Adams, 1979).

The present communication describes the effects of diltiazem and verapamil, two compounds presently classified as calcium antagonists, on the diastolic and systolic tension of rabbit hearts perfused with an oxygenated and an hypoxic medium. In this preparation verapamil has been reported to exert a protective action against both the mechanical and biochemical deterioration produced by hypoxia (Nayler, *et al.*, 1976).

Rabbits (Fauve de Bourgogne, 2–3 kg body weight) were sacrificed by cervical dislocation and their hearts perfused using the Langerdoff technique at constant flow (20 ml/min) with glucose-free (replaced with mannitol) Krebs–Henseleit buffer (pH 7.4) solution gassed with 95% O_2 + 5% CO_2. Following an initial 30 min stabilisation period, the oxygenated solution was replaced for certain preparations with an hypoxic perfusate (gassed with 95% N_2 + 5% CO_2) for 30 minutes. Thereafter, perfusion was continued for further 30 min with an oxygenated medium. Isometric myocardial force of contraction was measured with a transducer (Grass FT03C) attached via a thread to the ventricular apex. The heart (deprived of both atria) was always paced (6–8 V, 1 ms, 137 beats/min) with the exception of a group of preparations in which the electrical driving was suspended during the period of hypoxia. Experiments were carried out in hearts perfused over 30 min with either oxygenated or hypoxic solutions containing no drug, diltiazem (1.0–10.0 μM) or verapamil (0.03–3.0 μM).

Both resting and peak systolic tension in the paced rabbit heart perfused with oxygenated Krebs–Henseleit solution remained constant over the 90 min control period. In this preparation diltiazem (1.0–10.0 μM) and verapamil (0.03–3.0 μM) produced concentration-related decreases in developed tension and their EC_{50}'s (concentration decreasing tension by 50%) were 3.36 ± 0.25 and 0.12 ± 0.01 μM, respectively. Thus, verapamil was about 28 times more cardiodepressant than diltiazem. The systolic contractile force was decreased by approximately 90% at the end of 30 min perfusion with an hypoxic medium. In contrast, the myocardial resting tension (control value: 2.9 ± 0.3 g, n = 10) increased by 13.8 ± 1.0 g for the same time period. Addition of diltiazem (10.0 μM) or verapamil (3.0 μM) to the hypoxic perfusate acceler-

ated the fall in developed tension produced by hypoxia and significantly reduced the rise in resting tension. At the end of the 30 min reoxygenation period the developed tension in diltiazem-perfused hearts was 65% of the control value, whereas it was only 24% for the verapamil-treated group. The best protection against the rise in resting tension produced by hypoxia was observed in hearts in which pacing was suspended at the moment of the exchange from the oxygenated to the hypoxic perfusate. Under these experimental conditions the recuperation of the developed contractile at the end of the successive 30 min reoxynation period was about 80% of the pre-hypoxic value.

In conclusion, these results confirm that the degree of increase in resting tension produced by hypoxia is dependent upon the myocardial mechanical work. This has been reported, for instance, by Nayler, *et al.* (1978) for the guinea-pig heart paced at different rates. The attenuation of this deleterious effect by verapamil and diltiazem can be accounted for, at least to a substantial extent, by the reduction in contractile force produced by both compounds. Other mechanisms, such as an action on intracellular calcium availability, may contribute to this beneficial action.

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The pharmacological activity of some choline analogues and their acetylated derivatives

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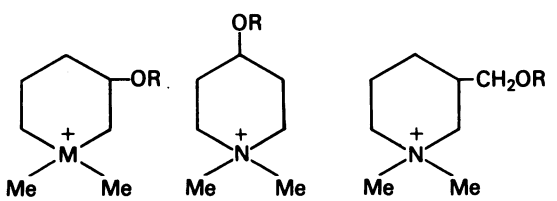
A study was made of some piperidine derivatives containing a choline like moiety to investigate their pharmacological properties on cholinergic transmission and to determine their potential as false neurotransmitters. The structural formulae of the compounds studied are shown below. The alcohols I (650 μg/ml), II (700 μg/ml) and III (300 μg/ml) were shown to produce a pre-junctional blocking action on the rat phrenic nerve hemidiaphragm preparation which was, in each case, reversed by choline. On the frog rectus abdominis muscle compounds I (450 μg/ml) and II (500 μg/ml) potentiated the responses to acetylcholine. On the same preparation compound III (200 μg/ml) had a direct depolarising action; its equipotent molar ratio to acetylcholine being 1,000:1.



The compounds were acetylated *in vitro* by choline acetyltransferase at a rate of I, 53%; II, 1%; and III, 2% compared to the acetylation of choline, 100%, at a concentration of 5×10^{-3} M.

Although the muscarinic activity of the acetylated compounds IV, V and VI has previously been studied, (Lewis, Barker, Fox & Mertes, 1973), the action of these compounds at the neuromuscular junction and their degradation by cholinesterase enzymes has not been fully investigated. The equipotent molar ratios of the acetylated compounds relative to acetylcholine in producing a contracture of the frog rectus muscle were shown to be IV, 57%; V, 60; VI, 105 and acetylcholine, 1. The degradation of the acetylated compounds by bovine erythrocyte acetylcholinesterase was investigated using a pH stat method. The relative rates of breakdown of the analogues at a concentration of 1.2 mM was found to be, acetylcholine, 1.0; IV, 0.75; V, 0.45 and VI, 0.6.

The results show that of the three piperidinols examined, compound I is acetylated *in vitro* by choline acetyltransferase; the acetylated product, compound IV is readily broken down by cholinesterase, however it is much less effective than acetylcholine