The start-control value (mean ± s.e. mean) was 151.4 ± 20.1 s (n = 81). Variation in control times from animal to animal greatly exceeded that between L and R eyes of each rabbit, while variation between start-control and end-control times was not statistically significant. Several preservatives, in concentrations equivalent to those used in eyedrop preparations, produced statistically significant hastening of the drying time: 0.01% (w/v) benzalkonium chloride (22.9% of start-control time); 0.03% n-propyl p-hydroxybenzoate (54.1%); 0.3% 2-phenylethanol (53.1%); 0.01% chlorhexidine (38.2). All of these substances produced dose-related decreases in drying time at the lower concentrations tested, in some cases down to one-hundredth the concentration indicated. Two mercurial preservatives, 0.3% (w/v) thiomersal and 0.1% phenylmercuric nitrate, caused no change in the rate of corneal drying.

A time-course study indicated that the effect of applying 2 drops of 0.01% benzalkonium chloride could still be detected 45 min afterwards. The presence of 0.01% benzalkonium chloride also significantly hastened the drying time following application of 0.3% or 1.5% (w/v) hydroxypropylmethylcellulose drops.

An approximate relationship was shown to exist between the ability of these substances to lower surface tension and to hasten the formation of dryspots on the cornea. This indicates that the mechanism of this effect may involve adsorption to, or solubilization of, either the conjunctival mucus layer or the oily Meibomian secretion.

The effect of melatonin on pinealectomy-induced hypertension in the rat

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Surgical removal of the pineal gland has been shown to elevate blood pressure in anaesthetized rats (Zanoboni & Zanoboni-Muciaccia, 1967) and a modest hypertension (20 mmHg) has been described in unanaesthetized rats after electrocoagulation of the pineal gland (Karppanen, Vapaatalo, Lahovarra & Paasonen, 1970). These authors suggest that an increased adrenal steroid level after pinealectomy contributes to the observed hypertension. Karppanen, Airaksinen & Särkimäki (1973) have proposed that melatonin and/or related pineal hormones may act as natural anti-hypertensive agents, possibly by stimulating central inhibitory adrenergic pathways.

In the present study the effect of melatonin administration on hypertension produced by electrolytic lesion of the pineal gland in the rat was investigated.

Male Sprague-Dawley rats (180-220 g), anaesthetized with pentobarbitone sodium (60 mg/kg i.p.), had a 21 g hypodermic needle positioned 2.0 mm vertically below the surface of the skull at lambda. A d.c. current of 40 mA passed between the needle and a negative electrode on the ear for 20 s was found to produce destruction of the pineal gland with minimal damage to surrounding cortical tissue. Destruction of the pineal gland was verified macroscopically in all animals at the end of the experiment. Sham-operated rats had identical electrode placement but no current was applied. Systolic blood pressure was measured indirectly from unanaesthetized rats using the tail-cuff method.

A modest, but statistically significant, hypertension (15-20 mmHg) was seen in the pinealectomized animals (n = 16), compared to sham-operated or unoperated controls, from 1 week after operation until at least 7 weeks. Melatonin administered in the drinking water [1 mg/ml in 1.25% ethanol vehicle started immediately after operation] prevented the emergence of pinealectomy-induced hypertension and significantly depressed the blood pressure to below that of vehicle-treated control animals. Replacement of drug treatment with vehicle alone resulted in the development of hypertension in these pinealectomized animals. Administration of melatonin to animals in which hypertension had become established resulted in a significant fall of blood pressure to below sham-operated levels after 2 weeks of treatment. It was estimated that the average daily intake of melatonin for each rat was approximately 100 mg/kg.

These results suggest that the hypertension caused by pinealectomy is, at least in part, due to the lack of normal melatonin secretion by the gland.

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BRL 13776: a novel antihypertensive agent with interesting noradrenaline-depleting properties

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Whilst studying a series of 4-(4-pyridyl)-chroman-5-ols which were being evaluated for activity in the central nervous system, a compound BRL 13776 (7-n-pentyl-4-[1-(2-naphthylmethyl)-1, 2, 5, 6-tetrahydro-4-pyridyl]-2, 2-dimethylchroman-5-ol) was found to have antihypertensive activity yet be devoid of behavioural properties. The antihypertensive activity was assessed in deoxycorticosterone acetate/NaCl-treated hypertensive rats (Sprague-Dawley) and renal hypertensive cats (cellophane perinephritis model, see Poyser, Shorter & Whiting, 1974). In both models, BRL 13776 (suspended in 1% w/v methylcellulose) caused a significant lowering ($P < 0.05$) of blood pressure at doses of 30 mg/kg p.o. and above. The antihypertensive response was evident 4-6 h after dosing and blood pressure had almost returned to pre-dose values at 24 hours. No behavioural changes nor adverse symptoms were observed in either species.

Studies on the mechanism of action of BRL 13776 revealed that the compound depleted noradrenaline in various peripheral organs of both normotensive and hypertensive rats. Noradrenaline was measured by the method of Shellenberger & Gordon (1971), and animals receiving BRL 13776 were compared with vehicle-dosed controls. Six or more rats were used in each group and all animals were killed 6 h after dosing. In the normotensive rats, a single dose of BRL 13776 (100 mg/kg p.o.) reduced the noradrenaline content of heart, spleen and adrenals by 78%, 80% and 82% respectively ($P < 0.001$). A similar depletion occurred in hypertensive rats (e.g. 65% in the heart, $P < 0.001$).

In contrast to the depletion in peripheral tissues, BRL 13776 did not affect the noradrenaline content of whole brain. Nevertheless, more detailed studies revealed a significant reduction ($P < 0.01$) in the hind-brain region (pons/medulla) of both normotensive and hypertensive rats. This was in the order of 37-40% at 6 h following the 100 mg/kg single p.o. dose. No concomitant decrease in the noradrenaline concentration of the cerebral hemispheres, mid-brain or hypothalamus was observed. In this respect BRL 13776 differed from reserpine. Even on repeated dosage with BRL 13776 (100 mg/kg p.o. twice daily for 14 days) the cerebral hemispheres were not depleted of their noradrenaline whereas the reduction in the hind-brain was still apparent (18%, $P < 0.01$). However, in the repeated-dose study there was also some depletion of the hypothalamus (28%, $P < 0.01$). Throughout the 14 day study no gross toxicity, behavioural changes or side effects were observed.

In conclusion, BRL 13776 is a novel structure displaying antihypertensive and noradrenaline-depleting properties. Noradrenaline depletion in the brain of rats is restricted to certain areas, and this may be relevant to both the antihypertensive response and the lack of behavioural effects. Reductions of noradrenaline in the periphery could contribute to the antihypertensive response or on the other hand be totally responsible. Obviously BRL 13776 warrants further investigation and it is intended to proceed to clinical studies.

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