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Reflex and other vascular changes in anaesthetized dogs after β-adrenoceptor antagonism with alprenolol, bunolol and propranolol

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The purpose of this investigation was to compare reflex and other vascular changes produced by alprenolol with those of other β-adrenoceptor blocking agents which are devoid of stimulant activity on β-adrenoceptors. Intravenous doses of propranolol (0·5 mg/kg), alprenolol (0·5 mg/kg) (Åblad, Brogård & Ek, 1967) and bunolol (0·2 mg/kg) (Robson, Simon & Thompson, 1970; Kaplan & LaSala, 1970) were selected to cause equal β-adrenoceptor antagonism, as shown by the inhibition of the increase in heart rate produced by isoprenaline.

Dogs of either sex were anaesthetized with a mixture of barbitone sodium (300 mg/kg intravenously) and pentobarbitone sodium (approximately 20 mg/kg intravenously). Dogs used in femoral perfusion studies were anaesthetized with chloralose (100 mg/kg intravenously). A Sigmamotor pump was used to autoperfuse a hind limb through the femoral artery. The spleen was enclosed in a Perspex container and pressure changes in the enclosed system recorded as indicative of changes in spleen volume. Aortic flow was detected by a probe placed round the ascending aorta and measured with an electromagnetic flowmeter. Heart rate was recorded by a cardiotachometer triggered by the electrocardiogram. Systemic arterial blood and other pressures were measured with appropriate transducers and recorded on a Beckman Type R dynograph.

The selected doses of the blocking agents administered to groups of three or four dogs caused bradycardia and significant ($P<0·01$) reductions in spleen volume. Blood pressure was most depressed by alprenolol. Subsequent doses of bunolol or propranolol were ineffective, but the splenic and depressor effects persisted with later doses of alprenolol. The splenic contractions were prevented or abolished by splenic nerve section or ganglion blockade in normal or adrenalectomized dogs, and the response, therefore, appeared to be reflexly mediated. After these procedures, alprenolol still caused hypotension and frequently caused splenic relaxation. The relatively weak β-sympathomimetic *dextro*-isomer (Åblad *et al.*, 1967) had less depressor activity and induced smaller splenic changes than *racemic* alprenolol in each of three dogs. Thus, the β-sympathomimesis of alprenolol may be responsible for the above differences, their persistence after bunolol or propranolol indicating that the selected doses were insufficient to prevent the sympathomimesis of alprenolol (0·5 mg/kg).

In chloralose-anaesthetized animals, propranolol (six dogs) and bunolol (five dogs) increased femoral perfusion pressure ($P<0·01$), but alprenolol (seven dogs) had little effect. Only alprenolol caused a significant fall ($P<0·01$) in diastolic blood pressure.

Propranolol lowers and alprenolol has no significant effect on cardiac output (Åblad *et al.*, 1967); bunolol had an effect similar to that of propranolol.

Propranolol may increase femoral perfusion pressure by reflex activation of the sympatho-adrenal system (Nakano & Kusakari, 1965; Kalaalp & Kiran, 1966), the initiating stimulus being a reduced pulse pressure or rate of change of pressure (Heymans & Neil, 1958). The β-sympathomimetic activity of alprenolol, possibly by supporting cardiac function above the depressed level usually following β-adrenoceptor antagonism and by causing diastolic hypotension, may maintain pulse pressure and thereby attenuate one stimulus for initiating cardiovascular reflexes.

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The kinin-forming system in rabbit hind limb lymph after thermal injury

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It was shown that after injury to dog hind limbs, the kinin-forming potential of the lymph draining the limb increased (Edery & Lewis, 1963). Pseudoglobulin was used to provide excess substrate. Later Jacobsen & Waaler (1966) suggested that the increase was due to an enzyme impurity in the pseudoglobulin acting on an increased amount of kininogen entering the lymph from the plasma. In the present experiments in rabbits, it was found that excess kininogen was always present in plasma and lymph. It was therefore unnecessary to use pseudoglobulin.

However, it was necessary to activate the kinin-forming enzyme. This was done in two ways—first, by 5 min contact with glass ballotini (100 mg/0·6 ml) in the presence of the kininase inhibitor *o*-phenanthroline HCl (0·1 ml of 1% solution) and second by acidification to pH 2·0 with N HCl and 0·2 N HCl/KCl. Kinin formation was measured by assay on the rat uterus in the presence of bromolysergic acid diethylamide (0·6 mg/l.). After glass activation the kinin was assayed immediately, but after acidification the sample was neutralized with 0·33 N NaOH and phosphate buffer to pH 6·4, *o*-phenanthroline (0·1 ml. of 1% solution) was added; the sample was then assayed after 20 min.

After thermal injury there was an increase of up to 70 times in the activity produced by acid activation, but no increase in that following glass contact. The increase generally occurred in two peaks—within 2 h and 4–6 h after injury. These two peaks of activity appeared to correspond to changes in vascular permeability as indicated by increases in lymph protein. However, it is not clear whether the changes in permeability were the cause or the effect of changes in the kinin system.