

Vascular reactivity to noradrenaline and 5-hydroxytryptamine in hypertensive rats

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Increased vascular responsiveness to pressor substances in human and experimental hypertension may be explained by changes in the neurogenic or humoral influences in the environment of arterial smooth muscle (Hinke, 1965), increases in muscle responsiveness (Gordon & Nogueira, 1962) and/or structural changes leading to altered vessel geometry (Folkow, Hallbäck, Lundgren & Weiss, 1970).

In the following experiments the changes in vascular reactivity were compared in hypertensive and normotensive male rats by determining dose-response relationships for 5-hydroxytryptamine (5-HT) and noradrenaline (NA). Measurements were made of their pressor effects in pithed rats and of their vasoconstrictor effects in hindquarters (McQueen, 1956) and mesenteric artery (McGregor, 1965) preparations perfused under conditions of constant flow. Hypertension of each of three types was studied: (a) hypertension following application of a renal artery clip, leaving the contralateral kidney intact (Wilson & Byrom, 1941), (b) hypertension induced by 50 mg/kg deoxycorticosterone acetate s.c. biweekly for 4 weeks in unilaterally nephrectomized rats (Stanton & White, 1965) and (c) genetic hypertension in rats of the New Zealand strain (G-line) (Phelan, 1968). In all experiments animals were paired with normotensive Wistar controls matched for age and weight.

In established hypertension of all three types the maximal responses produced by 5-HT and NA were increased in all preparations with approximately 1.5–3fold steepening in slope of the dose-response curves. In pithed rats and in perfused mesentery preparations but not in perfused hindquarters, the threshold dose of 5-HT also decreased. In contrast no change in the threshold for NA occurred. The change in 5-HT threshold became apparent in some pithed animals in approximately 2.5 weeks and was maximal by 4 weeks after applying the renal clip. Despite the increased sensitivity to 5-HT no lowering of blood pressure was observed following the daily oral administration of 2 or 10 mg/kg B.W. 501C67, a potent 5-HT antagonist (Mawson & Whittington, 1970) in either genetic or renal hypertensive rats. Vascular sensitivity to intravenous 5-HT but not NA was considerably reduced in pithed animals given the antagonist.

In rat fundus strips taken from genetic hypertensive rats sensitivity to 5-HT was similar to that in normotensive rats.

These findings agree with those of McGregor & Smirk (1970) who found greater enhancement of cardiovascular responses to 5-HT than to NA in genetic and renal hypertensive rats and extend their observations to show that a similar difference also occurs in DOCA hypertension. This supports the contention that geometric factors cannot alone account for increased vascular responsiveness during the disease. However, some vasculature showed no preferential sensitization to 5-HT and in these geometric factors could be solely responsible.

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A method for providing intermittent intravenous injections in unrestrained animals

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As part of an investigation into the pharmacological effects of nicotine in relation to tobacco smoking, a method has been devised for intermittent intravenous administration of drugs to unrestrained Squirrel monkeys. The injector system is self contained and can be carried permanently, or occasionally, by the animal. The injector, constructed largely of perspex, contains a 20 ml chamber for solution for injection; the solution is maintained at a constant positive pressure by liquefied gas ('Arcton' 114—I.C.I. Ltd.) contained inside a rubber balloon within the chamber. A battery powered circuit operates a relay at pre-selected intervals (usually 30 or 60 sec) which momentarily opens a valve allowing a small volume (between 0.005-0.010 ml) of solution to be ejected from the device. The solution is injected into the animal via a silicone rubber cannula permanently implanted into an external jugular vein. The injector is fitted to an aluminium backplate attached to leather harness which is worn permanently by the animal.

The device has been used to investigate the effects of small doses of nicotine on the performance of trained monkeys on several operant conditioning schedules, but could be adapted to provide intermittent intravenous injections to other species of experimental animal.

Two dimensional immunoelectrophoresis of human serum proteins for the investigation of protein binding of drugs

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Two dimensional immunoelectrophoresis has been used by Freeman & Pearson (1969) to study the binding of ¹²⁵I-thyroxine to human serum proteins. Using the method described by Clarke & Freeman (1968) the present study has extended this work to the investigation of the protein binding of a variety of drugs.

Pooled human serum (4-6 μ l) was separated on agarose strips by electrophoresis in barbitone buffer (pH 8.6, 0.03 M, ionic strength 0.035) with the addition of calcium lactate (1.8 mM). A second dimension electrophoresis, perpendicular to the first