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The influence of glucagon on regional blood flow in the rhesus monkey

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It has recently been demonstrated that the total liver blood flow is rate limiting for the clearance of drugs which are extensively metabolized by the liver and have a high hepatic extraction ratio. Glucagon, which has been reported to increase splanchnic flow in experimental animals and man might therefore be expected to increase drug clearance. This has been investigated using (+)-propranolol as a marker drug in the rhesus monkey preparation which is known to have similar cardiovascular responses to man (Forsythe, Nies, Wyler, Neutze & Melmon, 1968).

Regional blood flow was measured by the injection of radioactive labelled microspheres into the left ventricle. At the same time systemic haemodynamic parameters, including cardiac output by a dye dilution method were measured. At the conclusion of the experiment, the animal was killed and the radioactivity present in various organs was counted in a Nuclear Chicago gamma 4 scintillation counter. The influence of 30 min infusions of glucagon 1 (μg/kg)/min and 10 (μg/kg)/min) on systemic haemodynamics and regional blood flow was measured, and the high dose infusion was then continued for a further 60 min. Control measurements were made before the first infusion and two hours after the last infusion.

Glucagon induced a dose dependent increase in cardiac output and pulse rate, with an increase in the proportion of the cardiac output going to the splanchnic vascular bed, and a decrease to the skeletal vascular bed. Total liver blood flow increased by $37\% \pm 10\%$ at 1 (μg/kg)/min and $165\% \pm 23\%$ at 10 (μg/kg)/min after 30 min of glucagon infusion and falling to $61\% \pm 11\%$ at 90 min. Smaller increases occurred in the coronary and renal blood flows.

The effect of the same doses of glucagon on the clearance of a steady state infusion of (+)-propranolol was measured in the same monkeys under similar conditions. At the high dose, the clearance increased by $14{\cdot}4\% \pm 3{\cdot}7\%$ while hepatic extraction fell from $32{\cdot}6\% \pm 6{\cdot}2\%$ to $17{\cdot}1\% \pm 1{\cdot}8\%$. The data is quantitatively consistent with a perfusion limited kinetic model which predicts that, for drugs with a high hepatic extraction ratio, increases in liver blood flow of the type induced by glucagon, will significantly increase drug clearance. Drugs with a low hepatic extraction ratio will be relatively unaffected by alterations in liver blood flow.

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Biliary excretion of methylmercury in male rats

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Reabsorption of methylmercury excreted into the gut with the bile is one of the factors responsible for the long biological half life of this compound (Norseth & Clarkson, 1971).

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The possibility of breaking the enterohepatic circulation of methylmercury by the oral administration of a non-absorbable mercury binding resin (Clarkson, Small & Norseth, 1971) focused our attention on the mechanisms by which methylmercury is excreted in the bile.

After the I.V. administration of 1 mg/kg Hg as methylmercury chloride, labelled with ^{203}Hg, to male rats of 190–220 g body weight, bile was collected at 1 h intervals from the cannulated bile duct of conscious animals. It has been found that in the first 4–5 h more than 95% of biliary mercury retained the metal to carbon bond. Radioactive distribution of Sephadex G-10 showed that methylmercury was mainly bound to a low molecular weight compound with a molecular weight lying between cysteine and glutathione. *In vitro* incubation of control bile with methylmercury chloride resulted in the same elution pattern as that of bile of rats injected with methylmercury chloride. This indicates that methylmercury is probably complexed by a normal bile constituent. Treatment of rats with cysteine after the injection of methylmercury caused a temporary increase in the biliary excretion of methylmercury without alteration in the elution pattern. This finding seems to indicate that methylmercury was not excreted with cysteine, but treatment increased the availability of the usual mercury acceptor for the removal of mercury with the bile. The elution pattern was also the same in phenobarbitone pre-treated rats, though methylmercury excretion was significantly higher.

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Drinking in the cat induced by centrally administered angiotensin

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It has been proposed that drinking following reduction of the extracellular fluid volume is due to an action of angiotensin on the central nervous system (Fitzsimons, 1972). This view is supported by reports that intracerebral administration of angiotensin II causes drinking in the rat, rabbit, goat, monkey and dove (Fitzsimons, 1972).

The domestic cat does not readily drink water (Carver & Waterhouse, 1962) and there are no reports of drinking behaviour induced by central chemical stimulation in this species. Therefore we have investigated the central dipsogenic activity of angiotensin in the cat.

Cats which had a modified Collison cannula implanted into a lateral cerebral ventricle (Feldberg & Sherwood, 1953) were housed in separate cages and allowed free access to water. The spontaneous water intake was measured daily and the mean value was found to be 6 ± 1 g.

Angiottnsin II amide (Hypertensin CIBA) 0·1–4 μg was infused intracerebroventricularly in a volume of 100 μl 0·9% NaCl over four min. Drinking began 1 to 10 min after the start of the infusion and continued for 10 to 20 min. The range of water consumption initially was 60 to 180 g and there was no dose-response relationship over the range investigated. The response could be evoked at hourly intervals but the quantity of water consumed declined progressively. After an animal had been used on several occasions the magnitude of the response to angiotensin declined and stabilized at a new value (range 30–50 g).

The possibility that angiotensin may act peripherally to initiate drinking was excluded because intravenous administration of a centrally effective dose did not elicit the response.

We have investigated the central mechanisms involved in angiotensin-induced drinking using various blocking agents administered intracerebroventricularly one hour before angiotensin.

Atropine 200 μg caused an increase in motor activity but did not reduce drinking. This