Some liver microsomal effects of sparsomycin

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Sparsomycin, a sulphur-containing antibiotic (Wiley & MacKellar, 1970) with anti-tumour potential (Owen, Dietz & Camiener, 1963; Bhuyan, Scheidt & Fraser, 1972) is a potent inhibitor of ribosomal polypeptide assembly from aminoacyl tRNA (Monro, Celma & Vazquez, 1969). It has not been studied extensively in experimental animals hitherto.

We have now examined some liver microsomal drug metabolizing and protein synthesizing effects brought about by this antibiotic in pretreated female Wistar rats (160 gm). Inhibition of drug metabolizing activity *in vitro* (50% or greater) is seen when liver microsomal fractions prepared from rats (Jondorf, Johnson & Donahue, 1969) 24 h after injection with sparsomycin (1 mg/kg I.P.) are incubated with substrates for N-demethylation (aminopyrine) and aromatic ring hydroxylation (aniline) under standard conditions (Jondorf *et al.*, 1969; Mazel, 1971). Furthermore, when sparsomycin is administered to rats also receiving sodium phenobarbitone (100 mg/kg, I.P.), a known inducer of the drug metabolizing enzymes (Kato, Jondorf, Loeb, Ben & Gelboin, 1966), the inhibitory effects of sparsomycin prevent the expected 24 h induction. Inhibition appears to be related to the lower cytochrome P-450 content (Mazel, 1971) of the sparsomycin-treated microsomal preparations.

By following the time-course of the inhibitory effect of sparsomycin-pretreatment on drug metabolism, we find that this begins to develop at 12 h after injection, becomes maximal at 24 h and then diminishes until control activities are restored at 72 h. The absence of a short-term inhibitory effect is confirmed by measuring drug metabolism *in vivo* as indicated by the duration of sodium hexobarbitone-induced sleeping time (Jondorf *et al.*, 1969) in sparsomycin-treated rats. In contrast with the prolongation (100%) of the sleeping time seen 24 h after sparsomycin pretreatment, rats injected with sodium hexobarbitone 1 h after sparsomycin pretreatment show the same duration of anaesthesia as sham-injected controls.

However, by comparing the inhibitory effects on hepatic protein synthesis *in vivo* (Jondorf *et al.*, 1969) at 1 h and 24 h after sparsomycin treatment (1 mg/kg, I.P.), we find that the uptake of [^{14}C]-(−)-leucine into microsomal protein is inhibited by 95–98% and 50–58% respectively, indicating that the short-term effects on protein synthesis *in vivo* are the more pronounced. Sparsomycin pretreatment also inhibits liver microsomal [^{14}C]-(−)-phenylalanine incorporating activity *in vitro*. There is, however, a greater uptake into trichloroacetic acid-insoluble protein, in the pre-incubated, poly U-dependent system (Kato *et al.*, 1966) by sparsomycin-treated (1 mg/kg i.p. 1 h or 2 h) than by control preparations. In contrast, as expected by analogy with the rabbit reticulocyte system (Colombo, Felicetti & Baglioni, 1966), sparsomycin added directly to the liver microsomal system *in vitro* inhibits both endogenous mRNA- and poly U-directed phenylalanine incorporation in a concentration-dependent manner.

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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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