stimulate insulin release from the $\beta$ cells of the Islets of Langerhans. However, many findings have come to light which cannot be explained by a pancreatic locus of action (Madsen, 1967 and Feldman *et al.*, 1969). In the case of glibenclamide, skeletal muscle and liver have already been proposed as potential extrapancreatic sites and indeed the present authors have shown that glibenclamide will enhance glucose uptake into the rat hemidiaphragm preparation in the absence of insulin (Foy & Standing, 1970).

The current investigation explored the possibility that the sulphonylureas may, in some way, reduce glucose release from the liver. Decreased liberation of glucose from the liver may be attributed to the blocking of key enzymes concerned either in the glycogen-glucose conversion, or in the conversion of non-carbohydrate precursors to glucose (gluconeogenesis). The effect of glibenclamide on two such enzymes, glucose-6-phosphatase (G-6-P) and phospho(enol)pyruvate carboxykinase (PEPCK, responsible for oxaloacetate→PEP), was investigated in rats both *in vivo* and *in vitro*.

*In vitro*, using the enzyme assay procedures of Wimhurst & Manchester (1970) statistically significant inhibitions were only shown at 0·39 mM for G-6-P and at 0·39 and 0·97 mM in the case of PEPCK.

*In vivo* alloxan diabetic animals were selected for the experimental group on the basis of a high blood sugar, care being taken to ensure that the hypoglycaemic phase was well past. No inhibition of enzyme activities was observed in animals which showed no evidence of functional pancreatic tissue.

If, as has been proposed, glibenclamide does in fact inhibit hepatic glucose output, it is unlikely that inhibition of these two enzymes plays a significant role.

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## The effect of cyproheptadine on water and food intake and on body weight in the fasted adult and weanling rats

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Appetite stimulation and body weight increases following the use of cyproheptadine have been reported in man (Lavenstein, Dacaney, Lasagna & Van Mere, 1962; Bergen, 1964; Shah, 1968; Noble, 1969; Sanzgiri, Mohamad & Raja, 1970) and in cats (Chakrabarty, Pillai, Anand & Singh, 1967), and an increased food consumption in fasted rats (Baxter, Miller & Soroko, 1970) while no effect was observed in mature dogs or in mature or weanling rats or guinea-pigs (Lavanstein *et al.*, 1962; Bergen, 1964). However, we have observed some increase in body weight and in the water intake in fasted adult, but not in weanling rats.

Male adult rats (mean body weight range 133–176 g) and weanling rats (mean body weight range 33–37 g) were individually caged and fasted overnight but water allowed *ad libitum*. Body weight and 4 h water and food intake were recorded daily throughout the experimental period. After 1 week of control observation, 5 rats were given saline and 5 rats were given cyproheptadine 30 min before receiving food and water daily during the subsequent week.

Cyproheptadine (5 and 10 mg/kg) significantly increased the body weight in a graded manner (Table 1). The effect of 15 mg/kg s.c., however, was almost the same as 10 mg/kg oral, but it failed to produce any increase in the body weight in weanling rats. There was increase in water but not food intake following the highest dose in the adult rats.

TABLE 1. *Effect of cyproheptadine on 4 h water and food intake and on body weight of fasted rats*

| Treatment | Water intake 4 h† (ml./100 g) | Food intake 4 h† (g/100 g) | Body weight†† (% gain or loss) |
|---|---|---|---|
| Adult male rats | | | |
| Control (saline oral) | +1·6 | +2·3 | +0·7 |
| Cyproheptadine (5 mg/kg oral) | +1·3 | −0·5 | +3·3** |
| Control (saline oral) | +1.3 | +0.5 | 0 |
| Cyproheptadine (10 mg/kg oral) | +0.7 | −0·8 | +6·4** |
| Control (saline s.c.) | 0 | +0.8 | +0·6 |
| Cyproheptadine (15 mg/kg s.c.) | +2·7* | −0·5 | +6·8** |
| Weanling male rats | | | |
| Control (saline s.c.) | +3·8 | +1·2 | +21·4 |
| Cyproheptadine (15 mg/kg s.c.) | +8·5 | +1·4 | +18·0 |

† Values indicate difference in the weekly average of pretreatment and treatment periods for 5 rats. †† Values indicate percentage gain or loss following 1 week treatment. * Significance of difference $P < 0{\cdot}01$. ** Significance of difference $P < 0{\cdot}001$.


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## Pyridostigmine pharmacokinetics: evidence for an apparent capacity limited urinary elimination of the metabolites of pyridostigmine


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Deviations from apparent first order drug excretion kinetics may be detected by changes in the fractional composition of the excretion products with dose (Levy, 1968). The excretion of pyridostigmine and its metabolites were studied in the rat after portal administration of different doses, since no previous work has examined dose effects on pyridostigmine excretion.

$^{14}$C-pyridostigmine (dose: 1·25, 3 or 6 μmoles/kg) was administered by rapid intravenous injection via the portal vein to male Wistar rats (body weight 300–350 g) under urethane anaesthesia and mannitol diuresis (6% mannitol in 0·9% NaCl; infusion rate: 0·075 ml/min). Urine was collected from both ureters and assayed for total $^{14}$C by liquid scintillation spectrometry, for pyridostigmine and its metabolites by electrophoresis (Somani, Roberts & Wilson, 1972).

When the rate of excretion of pyridostigmine was plotted semi-logarithmically with time at the midpoint of each urine collection period, the maximum rate was observed at about 30 min. It is considered that this indicates that the hepato-portal system behaves as a separate compartment in the distribution process.