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Glucose absorption from the rat jejunum during acute exposure to metformin and phenformin

The mode of action of the blood glucose lowering biguanides is complex and not clearly understood. Relatively high concentrations of biguanides inhibit several metabolic enzymes *in vitro* but it is uncertain whether these actions contribute significantly to their action *in vivo* (Segre, 1969). Therapeutic concentrations of metformin, in the presence of insulin, increase glucose uptake by isolated diaphragms from alloxan diabetic rats. This effect may be due to an action on glycogen metabolism (Frayn & Adnitt, 1972). *In vitro* studies of rat small intestine indicate that high concentrations of biguanides inhibit glucose absorption (Love, 1969). These findings were confirmed in man *in vivo* (McColl, 1971) and *in vitro* (Wingate & Hadley, 1973). We have measured glucose absorption from the rat jejunum *in vivo* in the presence of intraluminal metformin and phenformin.

Male albino Wistar rats (350 g) were anaesthetized with pentobarbitone sodium (75 mg kg^{-1} subcutaneously) and the lumen of 50 cm of proximal small intestine was gently washed through with saline at 37 °. In the control group the loops were perfused with 20 ml of normal saline (0·9% w/v) containing 10mM D-(+)-glucose for 20 min. Treatment perfusions were similar but also included the drug in the saline-glucose solution. The solutions were initially pH 5·6 and were maintained at 37 ° while continuously recirculated through the lumen by gas lift using 5% carbon dioxide in oxygen (Nissim, 1965). At the end of the experiments the rats were killed by bleeding, and the perfusion fluid volume was measured and its glucose concentration estimated by the glucose oxidase-peroxidase method (Boehringer Corporation Ltd.) on an Auto Analyser. The loops were weighed and results are expressed as the amount of glucose absorbed per unit weight of wet tissue during the 20 min perfusion (μ mol g^{-1}, in 20 min). As there was a negative correlation between glucose absorption and loop weight (regression coefficient — 1·55) the treatment means were corrected for weight and were also tested for significant differences by analysis of co-variance. The significance of individual differences in treatment means compared to the control group was estimated by the product of the Student Range, "Q", and the effective residual standard error (Snedecor & Cochran, 1967).

The results are summarized in Table 1. Phlorizin is a potent inhibitor of glucose absorption (Jervis, Johnson & others, 1956) and caused significant inhibition at 5×10^{-5} and 2×10^{-4}M ($P<0{\cdot}005$). However, metformin (10^{-4}M) and high concentrations of phenformin (up to 10^{-2}M) did not alter glucose absorption significantly ($P> 0{\cdot}05$).

The relatively high concentrations of biguanides necessary to inhibit sugar absorption *in vivo* (Czyzyk, 1969) and *in vitro* (Love, 1969) may indicate that they have a slow onset of action. Biguanides have been shown to accumulate in the intestinal wall after oral and parenteral administration at higher concentrations than in other

Table 1. *Glucose absorption from the lumen of the rat jejunum* in vivo. The values of glucose absorption (μ mol g^{-1} in 20 min) are corrected means from the regression of glucose absorption on loop weight $\pm$ the residual standard error of the mean. The treatments significantly altered the corrected means ($F = 19{\cdot}95$, $P<0{\cdot}005$) but only phlorizin 5×10^{-5} and 2×10^{-4}M were significantly different from the control mean ($^{*}P< 0{\cdot}05$) as both differences were greater than the product of "Q" and the effective residual standard error.

Treatment	Initial luminal M concentration	Number of animals	Glucose absorbed (μ mol g^{-1} in 20 min)
Control	—	11	50·6 ± 1·7
Phlorizin	$\times 10^{-5}$	4	42·4 ± 2·6
	5×10^{-5}	4	28·7 ± 2·6*
	2×10^{-4}	4	23·5 ± 2·6*
Metformin	10^{-4}	4	50·3 ± 2·6
Phenformin	10^{-4}	4	49·9 ± 2·6
	10^{-3}	4	53·1 ± 2·6
	10^{-2}	4	45·9 ± 2·6

tissues (Wick, Stewart & Serif, 1960). In the rat, phenformin inhibits glucose absorption from everted sacs if given by stomach tube 2 h before death (Kruger, Altschuld & others, 1970). Our results support the view that acute exposure of the small intestine to phenformin does not significantly affect glucose absorption. However, it remains to be shown if the inhibition of glucose absorption caused by chronic administration of phenformin (Czyzyk, Tawecki & others, 1968; Czyzyk, 1969) and metformin (Berchtold, Bolli & others, 1969) is of clinical significance since therapeutic doses of biguanides do not cause diarrhoea associated with sugar malabsorption (Wingate & Hadley, 1973).

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