STUDIES ON THE HYPOGLYCAEMIC ACTION OF GLICLAZIDE, A SULPHONYL-UREA DRUG

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Sulphonylurea drugs are effective in lowering blood glucose in maturity onset diabetic patients. Gliclazide is a relatively new sulphonylurea compound which, unlike previous drugs, appears to have a protective effect on the microcirculation in diabetes (Duhault & others,1972). Although insulin secretion has been shown universally to be stimulated by sulphonylurea drugs, evidence has been presented to implicate extra-pancreatic mechanisms in the hypoglycaemic action of these compounds (Feldman & others,1971). The aim of the work presented in this report was to investigate the role of insulin in the hypoglycaemic action of gliclazide and to examine the possibility that part of the action of the drug may involve augmentation of the effects of insulin. Some comparisons are made with glibenclamide. Male Wistar rats were used throughout. In some experiments the drug or control solutions were injected i.p. and blood removed at the desired time from the femoral vein using light ether anaesthesia. In most experiments animals were prepared 48h before use by placing fine polythene cannulae in the abdominal aorta (for blood sampling) and the right external jugular vein (for i.v. injection). The cannulae were exteriorized on the dorsal surface of the neck. In these animals solutions could be injected and serial blood samples obtained without anaesthesia and with the minimum of handling of the rats. Plasma was analysed for glucose, free fatty acids (FFA)and immunoreactive insulin (IRI).

In fasted rats gliclazide (1-20 mg/kg) or glibenclamide (0.05-1 mg/kg) produced dose-dependent decreases in plasma glucose and plasma FFA concentrations. The hypoglycaemic action was apparent at 5 minutes after injection and the duration of the effect was dose related. Both drugs produced dose dependent increases in the plasma IRI concentration. Sub-maximal hypoglycaemic doses of glibenclamide produced greater increases in plasma IRI concentrations than those produced by gliclazide despite similar glycaemic responses. Plasma IRI concentrations were transiently increased by gliclazide, showing elevation above the contral level at 5 minutes but not at 30 minutes after injection. Injected insulin was found to disappear rapidly from rat plasma in vivo.

Neither gliclazide (1-10 mg/kg) nor glibenclamide (0.05 mg/kg) produced any augmentation of the effects of insulin (0.1-1 U/kg) in lowering plasma glucose or FFA concentrations.

In alloxan diabetic rats (alloxan 65 mg/kg i.v.65hours before the experiment) neither gliclazide nor glibenclamide produced any reduction in glucose or FFA concentrations and failed to elevate the plasma IRI concentrations. Moreover the plasma glucose and FFA-lowering actions of insulin (0.5-1U/kg) were not augmented by gliclazide in these animals.

The results suggest that the acute hypoglycaemic action of gliclazide is mediated by the observed increases in plasma IRI concentrations and that the two drugs examined do not have any important action in augmenting the effects of insulin. It is difficult to demonstrate the importance of extrapancreatic effects in the intact rat, in which insulin secretion is invariably increased by sulphonylureas. The acutely diabetic rat shows a degree of insulin insensitivity and thus may not be the best model in which to study extrapancreatic actions. Moreover extrapancreatic actions may appear only during prolonged treatment with these drugs.

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