EFFECT OF INDAPAMIDE ON INSULIN SECRETION BY THE ISOLATED PERFUSED PANCREAS OF THE RAT

B.L. Furman and Tariq Bin Abdul Razak, Department of Physiology and Pharmacology, University of Strathclyde, George Street, Glasgow G1 1XW, Scotland.

Benzothiadiazine and other diuretics may impair glucose tolerance in certain patients, although the mechanism is uncertain (Furman, 1977). Indapamide* is a sulphamoyl-4-chlorobenzamide indoline drug with potent antihypertensive and diuretic properties. It has been shown to have direct relaxant effects on vascular smooth muscle (Moore & others, 1977) which may be mediated by an inhibition of inward calcium currents (Gargouil & Mironneau, 1977). If such an effect on calcium handling occurs in the pancreatic islets an inhibition of glucose-induced insulin secretion may be expected (Malaisse, 1973). Although in vivo experiments (Furman, 1977) have not revealed any effect of indapamide on insulin secretion or glucose tolerance, the above observations prompted an examination of its effects on insulin secretion in vitro.

Male Sprague Dawley rats (300-400g) fasted overnight were used. The pancreas was isolated and perfused according to Loubatieres & others (1971) with a Krebs bicarbonate buffer (pH 7.3;37°C;95%O_2/5%CO_2) containing bovine albumin. Preparations were perfused at a rate of 3.5ml/minute initially with buffer containing a low concentration of glucose (0.6mg/ml) this being followed by perfusion with a high glucose medium (3.0mg/ml). During perfusion with the basal glucose medium insulin secretion averaged 42μU/min. Exposure to a high concentration of glucose produced a peak of insulin release at two minutes (625±96μU/min) declining to around 400μU/min, this level being maintained for the remainder of the perfusion. Indapamide in a concentration of 0.1 or 1.0μg/ml did not modify basal or glucose induced insulin release. Higher concentrations (10 or 100μg/ml) produced a reduction in the early peak of insulin release although this was not statistically significant. However in a concentration of 500μg/ml indapamide produced a marked and significant reduction in the early peak. The three higher concentrations of indapamide produced a dose-dependent and statistically significant reduction in the total insulin secretory response to the high concentration of glucose during a twenty minute perfusion period. The concentrations of indapamide producing inhibition of insulin release are much greater than those found (20-50ng/ml) after administration of therapeutic doses (Campbell & others, 1977). Diazoxide, a non-diuretic, antihypertensive benzothiadiazine drug, known to inhibit insulin secretion in vivo produced a complete inhibition of glucose-induced insulin release in a concentration (50μg/ml) compatible with that found in human plasma during therapy. However, the concentrations of indapamide inhibiting insulin release in the present work are similar to those producing direct effects on vascular smooth muscle. There is no evidence that indapamide impairs glucose tolerance or diminishes insulin secretion in patients although it produces a useful reduction in blood pressure. If the demonstrated direct actions of indapamide on vascular smooth muscle are related to its antihypertensive effect there must be a marked separation in vivo of the sensitivities of vascular tissue and the insulin secreting cells to the actions of the drug.

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*Servier Laboratories