Non-saturable co-operative binding of tolbutamide to isolated islets of Langerhans

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Functionally active islets of Langerhans isolated from rat pancreas with bacterial collagenase and gathered by means of calibrated sieves, bind tritiated tolbutamide (Alric, Manteghetti, Puech, Lignon & Loubatières, 1975). The bound drug was measured as the amount taken up at equilibrium at 37°C in excess of the [^{14}C]-sucrose space of the preparation. Both isotopes were measured separately by liquid scintillation following combustion of the samples.

The uptake exhibits some features characteristic of binding to cellular structures rather than diffusion to the intracellular space. In particular, tolbutamide uptake shows a non-saturable co-operative pattern in relation to concentrations. The concentration-binding relationships (binding isotherms) show a steadfast upward concavity up to about 5×10^{-5} M, then turn to a straight line.

Such a co-operative pattern indicates that the binding ability of islet cell structures is modified by the binding itself as long as few binding sites are occupied by the drug. This occurs precisely in the range of concentrations which exert a graded stimulating action on the secretion of insulin *in vitro*. At greater concentrations, the binding follows a linear relationship similar to simple physical adsorption on an inert support. Other investigations (Sehlin, 1973) have already shown that this binding finally goes to saturation, but at tolbutamide concentrations far beyond pharmacologically active ones, with a half-maximum at 2×10^{-3} M.

Binding of tolbutamide to exocrine pancreas shows much less co-operativity in the same conditions, indicating a great deal of organ specificity. As was expected, unlabelled tolbutamide 5×10^{-5} M cancels the co-operativity of binding when added just prior to the labelled drug. A similar effect is produced by chlorpropamide and carbutamide at equiactive concentrations (Alric & Portal, 1969) as well as diazoxide at an equi-antagonistic concentration (Loubatières, Mariani, Alric, Chapal & Portal, 1967). But 'second generation' hypoglycemic sulphonylureas glibenclamide and glipizide at equiactive concentrations, and even glisoxepide, in an equimolar amount, failed to do so. Variations of glucose (1 to 16×10^{-3} M) or calcium concentrations did not affect co-operativity of binding.

In spite of the lack of interference of glucose, calcium and second generation sulphonylureas, it remains tempting to consider that the co-operativity of tolbutamide binding to islets could be related to the cell perturbation involved in the stimulating action exerted by this drug on the secretion of insulin by beta cells.

References

ALRIC, R., MANTEGHETTI, M., PUECH, R., LIGNON, F. & LOUBATIÈRES, A. (1975). Liage coopératif du tolbutamide par les îlots de Langerhans isolés de rat. *C. R. Acad. Sci.*, Série D, **281**, 2029–2032.

ALRIC, R. & PORTAL, A. (1969). Activité pharmacologique des sulfonylurées insulino-sécrétrices étudiée en fonction de leur solubilité aqueuse. *C. R. Soc. Biol.*, **163**, 703–707.

LOUBATIÈRES, A., MARIANI, M.M., ALRIC, R., CHAPAL, J. & PORTAL, A. (1967). Antagonisme entre le diazoxide et le tolbutamide sur l'insulino-sécrétion. Etude 'in vitro' sur le pancréas isolé et perfusé du rat. *C. R. Soc. Biol.*, **161**, 1755–1759.

SEHLIN, J. (1973). Evidence for specific binding of tolbutamide to the plasma membrane of the pancreatic B-cells. *Acta Diabet. Lat.*, **10**, 1052–1060.

Interrelations between MAO activity and carbohydrate metabolism

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The possible interrelations between monoamine oxidase (MAO) activity and metabolism of carbohydrates in central and peripheral regions was studied. Ninety per cent inhibition of MAO activity by administration of deprinil (20 mg/kg) in normally fed male rats resulted in 60% decrease in hepatic glycogen whereas cerebral glycogen stores were completely exhausted but the cardiac glycogen rose by 30% Similar administration of deprinil to rats starved for 24 h produced a three-fold increase in hepatic glycogen but cardiac and cerebral glycogen reserves were slightly affected. Activity of enzyme catechol O-methyl transferase (COMT) in the adrenals of fed rats declined by 47% after selective inhibition of MAO by