The hypoglycaemic action of ICI 66082 (4-(2-hydroxy-3-isopropyl-aminopropoxy) phenyl acetamide) in the rat

B.L. FURMAN & F.M. TAYO*

Department of Physiology and Pharmacology, University of Strathclyde, George Street, Glasgow G1 1XW

We have shown propranolol to prevent or reduce the increases in plasma immunoreactive insulin (IRI) in response to glucose, sulphonylureas and isoprenaline (Furman & Tayo, 1973). Practolol and sotalol reduced only that hyperinsulinaemia produced by isoprenaline (Furman & Tayo, 1974). Results are now presented to show the effect of ICI 66082. (4-(2-hydroxy-3-isopropylamino-propoxy) phenyl acetamide), a new β-adreno-ceptor blocking agent, on plasma glucose and IRI concentrations in the rat. Methods used were those previously reported (Furman & Tayo, 1973).

ICI 66082 administered intraperitoneally to the conscious, fasted rat or intravenously to the anaesthetized rat produced a dose-dependent reduction in plasma glucose. Plasma immunoreac-tive insulin concentrations were significantly elevated but this response did not appear to be dose-dependent. In fed rats the drug produced hyperglycaemia. However, a hypoglycaemic response was demonstrated in fed adrenalecto-mized animals.

In order to assess the importance of the presence of functional β cell tissue for the production of this hypoglycaemic response, the effects of the drug were examined in rats made diabetic by the administration of alloxan (65 mg/kg i.v.). ICI 66082 produced a hypo-glycaemic response in rats which were severely diabetic (plasma glucose 600-900 mg/100 ml; plasma IRI 0-10 μU/ml) or moderately diabetic (plasma glucose 300-500 mg/100 ml; plasma IRI 20-40 μU/ml). Plasma IRI concentrations were elevated in both groups by the drug but this was statistically significant only in the group with moderate hyperglycaemia.

In anaesthetized rats an additive interaction was demonstrated between glibenclamide (2 mg/kg) and ICI 66082 (4 mg/kg) in producing hypo-glycaemia and increases in plasma IRI. The hypoglycaemic action of insulin was not poten-tiated by ICI 66082, the two substances producing an additive interaction in lowering the plasma glucose. ICI 66082 reduced the elevations in plasma IRI produced by isoprenaline (175 μg/kg by slow intravenous injection) as found with other β-adrenoceptor blocking agents. In a concentration of 1 or 10 μg/ml the drug increased glucose uptake into rat hemidiaphragm muscle or epididymal adipose tissue *in vitro*.

Unlike the other β-adrenoceptor blocking agents examined, ICI 66082 produces hypo-glycaemia in the fasted rat. The mechanism of the hypoglycaemic response may be related to increases in plasma IRI and direct effects of the drug in increasing peripheral glucose utilization.

References

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