Effects of $\alpha_1$, $\alpha_2$- and $\beta$-adrenoceptor blockers on insulin secretion in the rat

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Abstract. The effects of $\alpha$- and $\beta$-adrenoceptor blockers on plasma concentrations of insulin and glucose were studied in the anaesthetized rat. Infusion of the $\alpha_1$-adrenoceptor blocker prazosin (80 µg/min), the $\alpha_2$-adrenoceptor blocker yohimbine (15 µg/min) or the non-selective $\beta$-adrenoceptor blocker phentolamine (15 µg/min) during 50 min increased plasma insulin levels by about 1.5–2.5 ng/ml. The effects of phentolamine and prazosin on circulating insulin persisted throughout the infusion whereas the effect of yohimbine seemed to be more transient. Plasma glucose levels increased slightly during infusion of prazosin, but tended to decrease in response to phentolamine and yohimbine. The $\beta$-adrenoceptor blocker propranolol (15 µg/min) lowered basal plasma insulin and glucose levels. It also depressed plasma insulin during infusion of all three $\alpha$-adrenoceptor blockers without any appreciable influence on plasma glucose. It is suggested that both $\alpha_1$- and $\alpha_2$-adrenoceptors as well as $\beta$-adrenoceptors are involved in the regulation of basal insulin secretion in the rat.

Materials and Methods

Animals

The experiments were carried out on adult male Wistar rats (240–390 g body weight) purchased from Møllegaard Avslaboratorium, Skensved, Denmark. The rats were kept on standard pellets (Astra-Ewos, Södertälje, Sweden) and tap water ad libitum.

Drugs

Prazosin hydrochloride (Pfizer Ltd., Brussels, Belgium) was dissolved in distilled water. Yohimbine hydrochloride (Serva, Heidelberg, West Germany), phentolamine methanesulphonate (CIBA-Geigy AG, Basel, Switzerland), propranolol hydrochloride (ICI Ltd., Macclesfield, England), and nembutalsodium (sodium pentobarbital; ACO AB, Solna, Sweden) were dissolved in saline.

Experiments

The rats were anaesthetized ip with pentobarbitone (60 mg/kg). Polyethylene catheters were inserted into the right femoral vessels. The venous catheter was connected to a pump and used for infusions of drugs and the arterial catheter was used for collection of blood samples. All drugs were infused at a rate of 0.1 ml/min. This volume rate was chosen to compensate for the blood samples (0.3–0.5 ml) which were withdrawn every 5 min during the course of each experiment.

After two control blood samples, a 50 min infusion of prazosin (80 µg/min), yohimbine (15 µg/min), phentolamine (15 µg/min), or saline was started. The doses of the three different $\alpha$-adrenoceptor blockers were selected so as to cause similar effects on plasma insulin concentrations. Twenty-five min after the start of the first infusion, propranolol (15 µg/min) or saline was given as a continuous iv infusion for 25 min.
Determination of insulin and glucose

Plasma immunoreactive insulin concentrations (IRI) were measured with radioimmunoassay (Heding 1966). With this method the rat insulin standard curve was superimposable on the standard curve for human insulin within the range of 0–3 ng/ml. Plasma glucose concentrations were determined with a glucose oxidase method (Bruss & Black 1978).

Calculations

The insulin values are expressed as incremental changes from the mean value of two control blood samples, whereas plasma glucose concentrations are given as absolute values. Statistical evaluation of the data was assessed with Student's t-test. Mean values ± SEM are given.

Results

Non-selective α-adrenoceptor blockade with phentolamine

Fig. 1 shows that infusion of the non-selective α-adrenoceptor blocker phentolamine at a dose of 15 µg/min enhanced insulin secretion by about 1.5–2.5 ng/ml. The phentolamine-induced insulin response tended to decrease slightly during the end of the infusion period. This secretory pattern was changed by the β-adrenoceptor blocker propranolol which caused an abrupt fall in plasma insulin concentration.

Plasma glucose levels decreased modestly in response to phentolamine and were not appreciably changed by the propranolol infusion.
**α₁-adrenoceptor blockade with prazosin**

Fig. 2 shows that infusion of prazosin at a dose of 80 µg/min caused a gradual increase in plasma insulin concentrations to about 2 ng/ml above the control value (P < 0.001). Propranolol induced an immediate and maintained reduction in plasma insulin levels, the maximal decrement being 1.2 ± 0.3 ng/ml (P < 0.001).

Plasma glucose levels gradually increased in response to prazosin. However, the maximal elevation was only about 1.3 mM (P < 0.01). Propranolol did not change plasma glucose, despite its marked reduction of plasma insulin concentration.

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**α₂-adrenoceptor blockade with yohimbine**

Fig. 3 shows that yohimbine (15 µg/min) induced a moderate and transient increase in plasma insulin (P < 0.01). Propranolol caused an immediate but transient drop in plasma insulin concentrations (P < 0.05) during infusion of yohimbine.

Plasma glucose levels declined gradually throughout the yohimbine infusion. The difference between the pre-infusion value and that obtained 50 min after the start of the yohimbine infusion was significant (P < 0.001). Propranolol did not influence plasma glucose concentration.

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**Non-selective β-adrenoceptor blockade with propranolol**

Fig. 4 illustrates the influence of propranolol (15 µg/min) on plasma insulin and glucose levels in untreated rats. Propranolol induced a significant fall in both plasma insulin and glucose concentrations in these animals (P < 0.01).
Discussion

The α-adrenoceptors have recently been classified into α1- and α2-subtypes with quite different localizations and pharmacological properties (Langer 1974; Hoffman & Lefkowitz 1980). Hence, it is not surprising that the three different α-adrenoceptor blockers used in this study varied in their effects on the circulating levels of glucose and insulin. In agreement with previous observations (Nakadate et al. 1980; Ahrén et al. 1982) the selective α1-blocker prazosin slightly increased plasma glucose concentration whereas the selective α2-blocker yohimbine had negligible effects thereon. This effect of prazosin is difficult to explain. It cannot possibly be secondary to changes in plasma insulin concentrations since these were elevated by prazosin, nor seems it due to an influence on hepatic glycogenolysis since this is inhibited by α1-blockers (Aggerbeck et al. 1980). Theoretically, the effect might be secondary to a diminished peripheral uptake of glucose, although non-selective α-adrenoceptor blockade has been reported to enhance peripheral glucose utilization (Lundquist 1972).

All three α-adrenoceptor blockers elevated plasma insulin concentrations. This finding is in accordance with earlier reports (Järhult et al. 1979; Ahrén et al. 1982) and the insulinotrophic effect has been explained by abolition of the α-adrenoceptor tone which normally inhibits insulin secretion (Gerich & Lorenzi 1978; Ahrén et al. 1981a). In addition, the stimulative effect of prazosin on insulin secretion might be potentiated by the rise in plasma glucose, although the slight hyperglycaemia did not clearly precede the increment in plasma insulin concentration.

The α2-blocker yohimbine transiently elevated plasma insulin concentration, whereas blocking of the α1-adrenoceptors with prazosin lead to a sustained elevation of plasma insulin levels. Thus, both subtypes of α-adrenoceptors seem to be involved in the regulation of insulin secretion. The difference in time course of insulin release induced by the two drugs might also suggest that the two subtypes are linked to different steps in the complex process of insulin secretion. It should be emphasized, however, that our present experiments were performed in vivo and thus do not exclude certain differences in the extrapancreatic effects of the various α-adrenoceptor blocking drugs. The complexity and difficulties in assessing a clearcut α-adrenoceptor classification which holds true both in vitro and in vivo has recently been reviewed (McGrath 1982).

Non-selective β-adrenoceptor blockade inhibited insulin secretion both during normal conditions (cf. Gagliardino et al. 1970; Gerich & Lorenzi 1978) and during α-adrenoceptor blockade. A similar inhibitory effect on insulin release by β-adrenoceptor blockade has previously been demonstrated in splanchicotomy-adrenalectomized rats which have elevated basal plasma insulin concentrations (Ahrén et al. 1981b), probably due to circulating amines with β-adrenoceptor-stimulatory properties. These results suggest an important interactive balance between the α- and β-adrenoceptors of the insulin cell.

It is concluded that the activity of α1-, α2- and β-adrenoceptors are all involved in the normal regulation of basal plasma insulin and glucose concentrations in the rat.

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