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The Effect of Adrenaline on Insulin Releasing Polypeptide (IRP) Mediated Insulin Release *in vivo* in the Rat*

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Summary. Intestinal insulin releasing polypeptide (IRP) has been shown to potentiate the release of insulin in response to glucose both *in vitro* and *in vivo* in the rat. Adrenaline reduced the insulin secretory response to the intravenous infusion (I.V.) of glucose and to the infusion of glucose with IRP given either as a rapid injection or as constant infusion.

Key words: Adrenaline, IRP, intestinal hormones, insulin release, glucose infusion, secretin, glucose tolerance.

The nature of the mediator of intestinal augmentation of insulin secretion has aroused much speculation since the phenomenon was first described by McIntyre *et al* in 1964 [1]. Most of the well-known and characterised intestinal hormones have been proposed at some time or other but none satisfactorily fulfils the role of the intestinal mediator [2, 3]. An intestinal insulin releasing polypeptide [IRP] which contains none of these hormones has recently been isolated and partially purified [4, 5]. It has been shown to potentiate the release of insulin in response to glucose, both *in vitro* and *in vivo*, but to have no, or little effect in the absence of induced hyperglycaemia [5, 6].

* The present study incorporates work accepted for the award of M.Sc. in Clinical Biochemistry to Ahmad A. Shabaan at the University of Surrey.

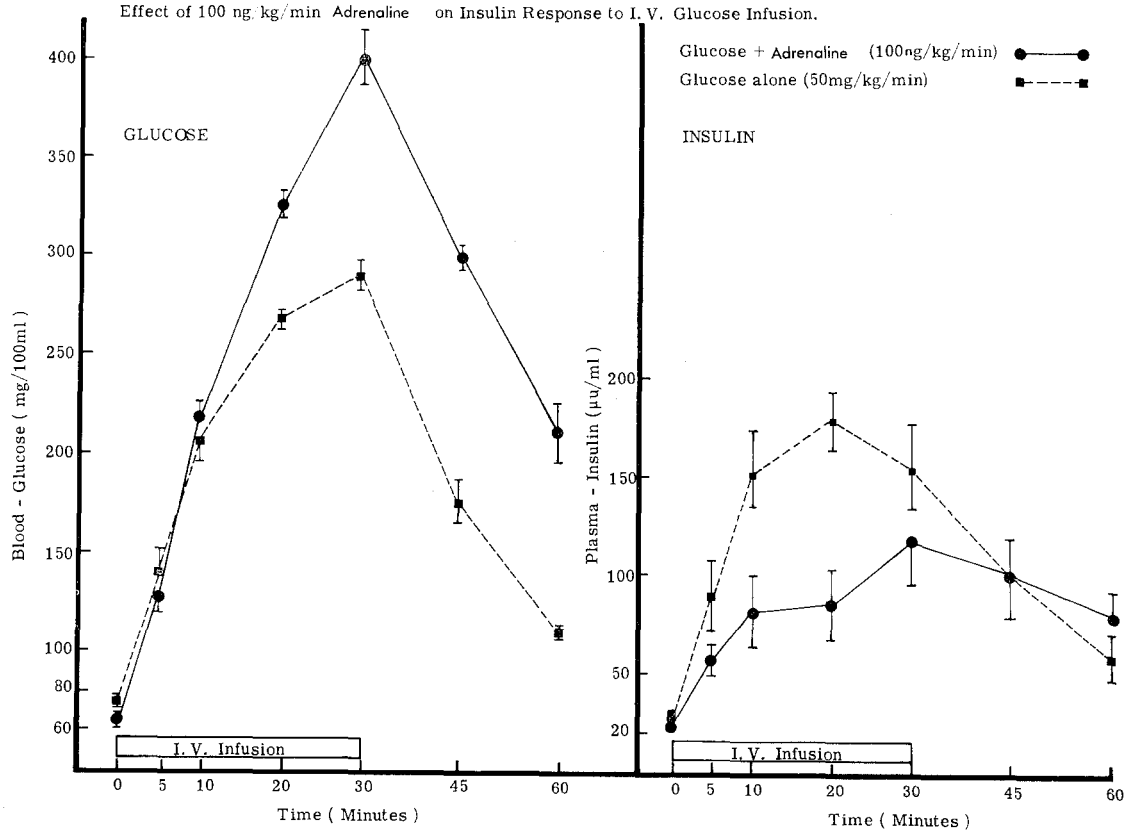

Fig. 1. Mean blood glucose and plasma insulin levels (± S.E.M.) in two groups of six rats given either an I.V. infusion of glucose (50 mg/kg/min) or glucose plus adrenaline (100 ng/kg/min)

The inhibitory effect of adrenaline and nor-adrenaline upon pancreatic insulin release provoked by intravenous glucose is well recognised [7, 8]. Much less information is available about their effect upon oral glucose mediated insulin secretion. In a brief note Langs and Friedberg [9] reported that, in man, the I.V. infusion of adrenaline at a rate sufficient completely to suppress glucose stimulated insulin secretion, did not suppress the effect of oral glucose on insulin release. This was not confirmed [10]. Nelson *et al* [11] reported that adrenaline did not suppress secretin induced insulin release and on this basis suggested that in man secretin might be a suitable candidate for the hypothetical alimentary mediator.

In the present paper the results of studies in the rat concerning the effect of adrenaline on the insulin response to the intravenous infusion of glucose and of glucose plus IRP are reported and their possible relevance to the nature of the intestinal mediator discussed.

Materials and Methods

Overnight fasted Wistar rats aged 12 weeks, weighing 300—325 g, were anaesthetised with Nembutal®

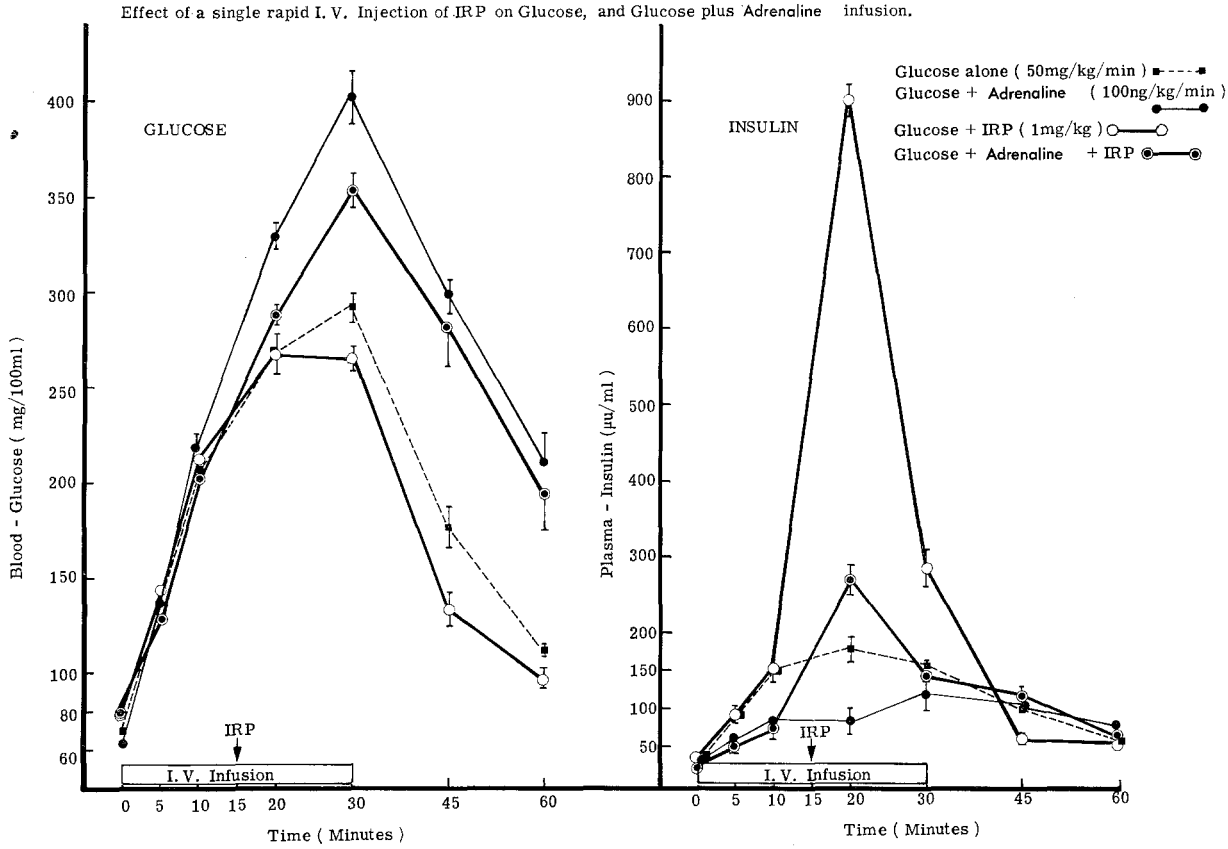

Fig. 2. Mean blood glucose and plasma insulin levels (± S.E.M.) in four groups of Wistar rats given an intravenous glucose infusion (50 mg/kg/min) over 30 min

Group No.	No. of Rats	Glucose (50 mg/kg/min)	IRP (in saline) (1 mg/kg)	Adrenaline (100 ng/kg/min)
1	6	+	—	—
2	6	+	—	+
3	4	+	+	—
4	4	+	+	+

(40 mg/kg body weight, I.P.). IRP, prepared as previously described [5] was dissolved in saline or, together with adrenaline (B.P. MacCarthys), either in 7% or 14% w/v glucose solution, containing ascorbic acid (2 mg/ml) as adrenaline preservative. The constant infusion of approximately 0.1 ml/min for 30 min of the glucose or glucose plus adrenaline solutions was given into a femoral vein using a syringe pump. The exact

protocol followed in each experiment is given in the results section.

Blood for glucose and plasma insulin measurements was obtained at regular intervals from the tail vein. Blood glucose was measured on the Autoanalyzer (Technicon Ltd) using an automated glucose oxidase method (Boehringer). Plasma insulin was determined by a double antibody radioimmunoassay procedure [12] using human insulin as standard.

The effect of adrenaline on insulin release after a rapid injection of IRP dissolved in saline was studied 15 min after the start of an infusion of either glucose or glucose plus adrenaline. The results, shown in Fig. 2, indicate that insulin release following rapid intravenous injection of IRP was markedly, but not completely, inhibited by adrenaline ($p<0.001$). The effect of adrenaline on insulin release provoked by a continous infusion of IRP is shown in Fig. 3. In this experi-

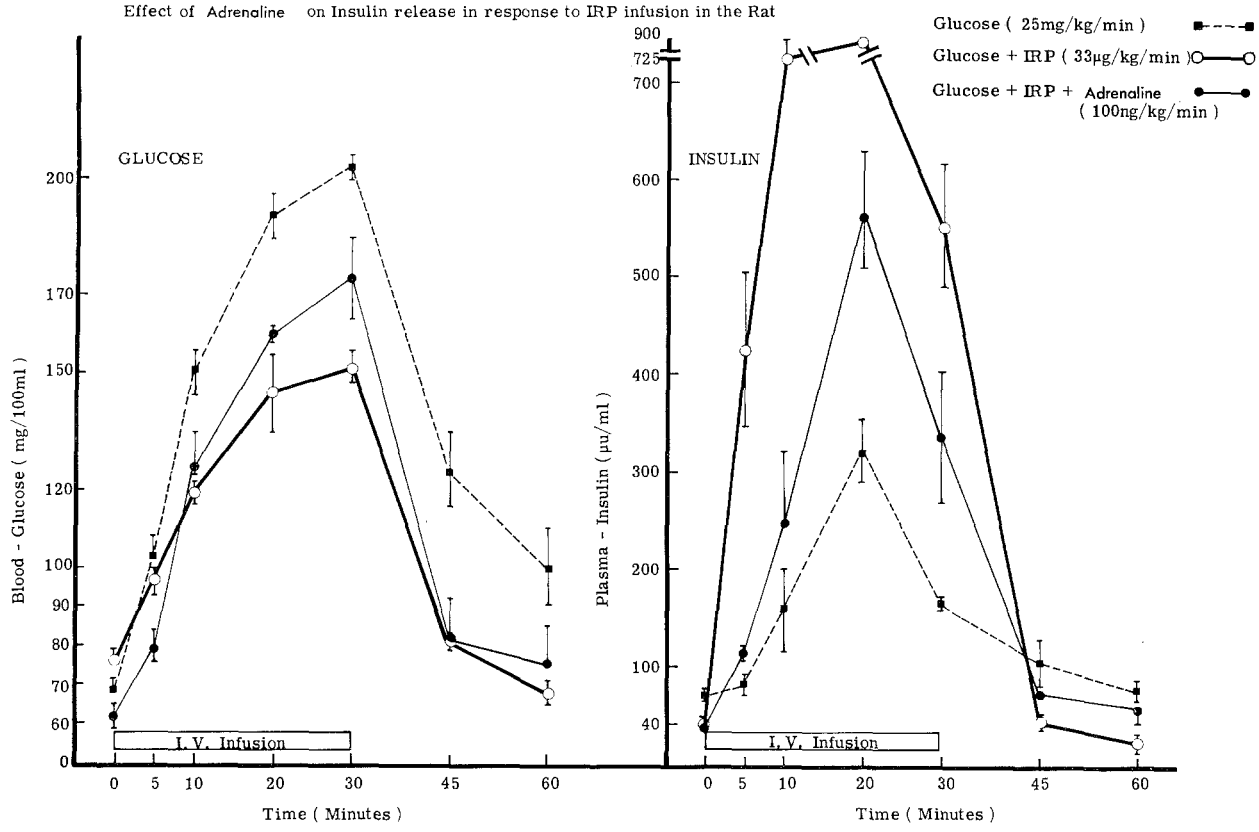

Fig. 3. Mean blood glucose and plasma insulin levels (± S.E.M.) in three groups of four rats. The first (control) group was given an I.V. glucose infusion (25 mg/kg/min) for 30 min and the second was given glucose plus adrenaline (100 ng/kg/min). The third group received IRP (33 µg/kg/min) in addition to glucose and adrenaline

Results

Preliminary experiments were carried out to find the smallest dose of adrenaline to suppress insulin secretion in response to I.V. glucose infusions in the rat. These experiments showed that adrenaline in doses within the range 10—60 ng/kg/min, which had previously been reported as effective in man, [8] did not cause significant inhibition of insulin release in the rat. Adrenaline at a dose level of 100 ng/kg/min inhibited insulin release at all time intervals (Fig. 1), despite blood glucose levels much higher than in animals receiving glucose alone. This dose of adrenaline was used in all subsequent experiments.

ment glucose was infused at a lower rate than in previous experiments, which accounts for the lower blood glucose levels throughout. The marked and sustained elevation of plasma insulin produced by IRP plus glucose, compared with that produced by glucose alone, was significantly attenuated, but not abolished, by adrenaline at all time intervals during the infusions ($p<0.001$ at 20 min).

Discussion

The dose of adrenaline found in the present study to be effective as an inhibitor of insulin secretion in re-

sponse to intravenous (I.V.) glucose infusions in rats was larger than that reported by Cerasi *et al.* [8] to be effective in humans, but similar to that actually used in man by most previous investigators [7, 9, 10, 12, 13].

It is clear from the experiments described that adrenaline markedly inhibits the potentiating effect of IRP upon glucose-stimulated insulin secretion in the rat. Whether this is evidence for or against its merits as a candidate for the role of alimentary mediator of insulin release is uncertain. In contrast to the plethora of studies demonstrating inhibition by catecholamines of glucose mediated insulin release *in vivo* and *in vitro*, both in animals and in man, the only studies of their effect upon alimentary mediated insulin release known to us are those of Langs and Friedberg [9] and Fallucca *et al.* [10]. The latter showed, in three post-gastrectomy patients, a substantial and highly significant, though incomplete, inhibition by adrenaline of the exaggerated insulinaemic response to oral versus intravenous glucose.

IRP would seem, therefore, to qualify for further consideration as an intestinal mediator of glucose stimulated hyperinsulinaemia.

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