

Transient insulin resistance following infusion of adrenaline in Type 1 (insulin-dependent) diabetes mellitus

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Summary. Insulin resistance was assessed after an intravenous infusion of adrenaline ($50 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or saline (control study) given between 08.00 and 08.30 hours in nine patients with Type 1 (insulin-dependent) diabetes mellitus. The blood glucose level during a somatostatin ($100 \mu\text{g}/\text{h}$)-insulin ($0.4 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)-glucose ($4.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)-infusion-test performed between 10.30 and 14.30 hours served as an indicator of the total body insulin resistance. Blood glucose was maintained around $7 \text{ mmol}/\text{l}$ between 08.00 and 10.30 hours by a constant infusion of regular insulin ($0.57 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and a variable infusion of a 20% glucose solution. The infusion of adrenaline raised plasma adrenaline to $2.7 \pm 0.3 \text{ nmol}/\text{l}$ (mean \pm SEM) at the end of the infusion; thereafter it returned to its basal level within 30 min. The plasma levels of free insulin, glucagon, cortisol

and growth hormone were similar in the adrenaline and the control studies from 08.00 to 14.30 hours. In comparison with the control study the infusion of adrenaline decreased the need for intravenous glucose significantly over the initial 2 h. Furthermore, during the somatostatin-insulin-glucose infusion test the blood glucose rose significantly ($p < 0.05$) over the initial 2 h; thereafter no significant differences between the two studies were seen. It is concluded that a short term infusion of adrenaline, resembling the adrenergic hormone response to hypoglycaemia, induces a diabetogenic effect which subsides within 6 h after omission of the adrenaline infusion.

Key words: Adrenaline, insulin resistance, diabetes mellitus, counterregulatory hormones, the Somogyi phenomenon.

In response to insulin-induced hypoglycaemia the secretion of adrenaline, glucagon, cortisol and growth hormone (GH) is stimulated. Adrenaline and glucagon are essential for acute blood glucose recovery while cortisol and GH have no immediate effects [1]. In a previous study in Type 1 (insulin-dependent) patients we have demonstrated that hypoglycaemia is followed by insulin resistance for up to 12 h [2]. The role of each of the counterregulatory hormones in causing this phenomenon has not been established. We have previously demonstrated that GH exhibits a sustained diabetogenic action following a temporary increase in plasma GH and that cortisol acts in synergism with GH in this respect [3]. Whether adrenaline alone may induce such a longstanding state of insulin resistance is unclear. The aim of the present study was therefore to assess the total body insulin resistance by a somatostatin-insulin-glucose infusion test (SIGIT) for 6 h

following a short-term infusion of adrenaline in patients with Type 1 diabetes.

Subjects and methods

Subjects

Nine male diabetic patients, aged 20–44 years, without residual B-cell function (C-peptide $< 0.15 \text{ nmol}/\text{l}$ after a mixed meal) were studied. The duration of their diabetes was 12.3 ± 1.9 years, their body mass index (4) 22.9 ± 0.7 and their glycosylated haemoglobin concentration (HbA_{1c}) was $7.5 \pm 0.4\%$ (normal range $< 5.6\%$). The daily insulin dose was $46.7 \pm 3.3 \text{ U}$ divided into two, three or four injections. The plasma levels of antibody-bound insulin ranged from zero to 11% in all but two patients who had 19 and 26% respectively. None had hypertension, albuminuria or signs of peripheral neuropathy and their autonomic nervous function assessed by the Valsalva ratio [5] and respiratory sinus arrhythmia [6] was normal. None was taking medication other than insulin. The subjects were recruit-

ed from our out-patient clinic and were not selected on the basis of previous manifestations of metabolic brittleness. Informed consent was obtained from all subjects and the local Ethics Committee approved the study.

Study protocol

The last subcutaneous insulin injection was given 34–36 h prior to the study. The patients were admitted to a metabolic ward 24 h before the study and thereafter blood glucose was controlled by an i.v. insulin infusion (Actrapid, Novo Industri A/S, Copenhagen, Denmark), adjusted every 1–3 h according to the capillary blood glucose concentration, aiming at a level of 10 mmol/l. The patients had their regular meals and snacks during this period (day 1) but no food was ingested after 22.00 hours. The insulin infusion allowed the patients to walk inside the hospital but not to perform heavy exercise. On the following morning (day 2) between 06.00 and 08.00 hours blood glucose was adjusted to a level of approximately 7 mmol/l. The patients were placed in a comfortable semirecumbent position and a short teflon catheter was inserted into a forearm vein on each side, one being used for blood sampling and the other for hormone infusions. Between 08.00 and 10.30 hours the blood glucose level was clamped at 7 mmol/l by means of a variable 20% glucose i.v. infusion and a constant rate i.v. infusion of insulin ($0.57 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). In separate studies adrenaline ($50 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or saline was given as an i.v. infusion between 08.00 and 08.30 hours. In both studies at 10.30 hours the ongoing infusion of insulin and glucose was replaced by an i.v. somatostatin ($100 \mu\text{g}/\text{h}$, Ferring AB, Malmö, Sweden)-insulin ($0.4 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)-glucose ($4.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)-infusion test (SIGIT) terminated at 14.30 hours. Each patient participated in two studies, i.e. with and without infusion of adrenaline, performed in random order separated by at least one week.

Analytical procedures

Venous blood samples were obtained every 5–60 min between 08.00 and 14.30 hours for measurements of the concentration of blood glucose (Glucose analyzer 23 AM, Yellow Spring Instruments, Yellow Springs, Ohio, USA), free insulin [7], GH [8], cortisol [9], glucagon [10] and adrenaline [11]. The glycosylated haemoglobin con-

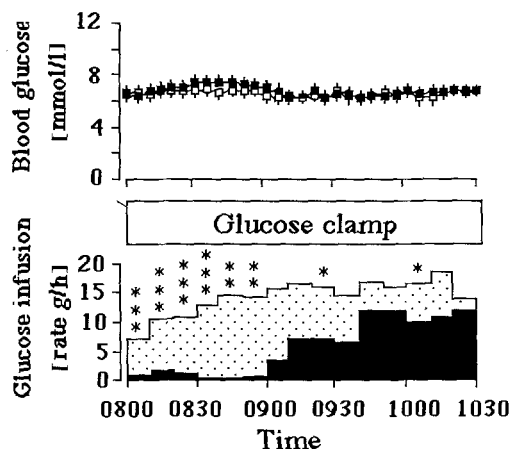


Fig. 1. The effect of the adrenalin infusion (08.00–08.30 hours) on blood glucose level and glucose infusion rate during the glucose clamp (08.00–10.30 hours). Upper panel: The blood glucose level with (■—■) and without (□—□) adrenaline infusion. Lower panel: The glucose infusion rate denoted for each 10 min period with (■) and without (□) adrenaline infusion. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

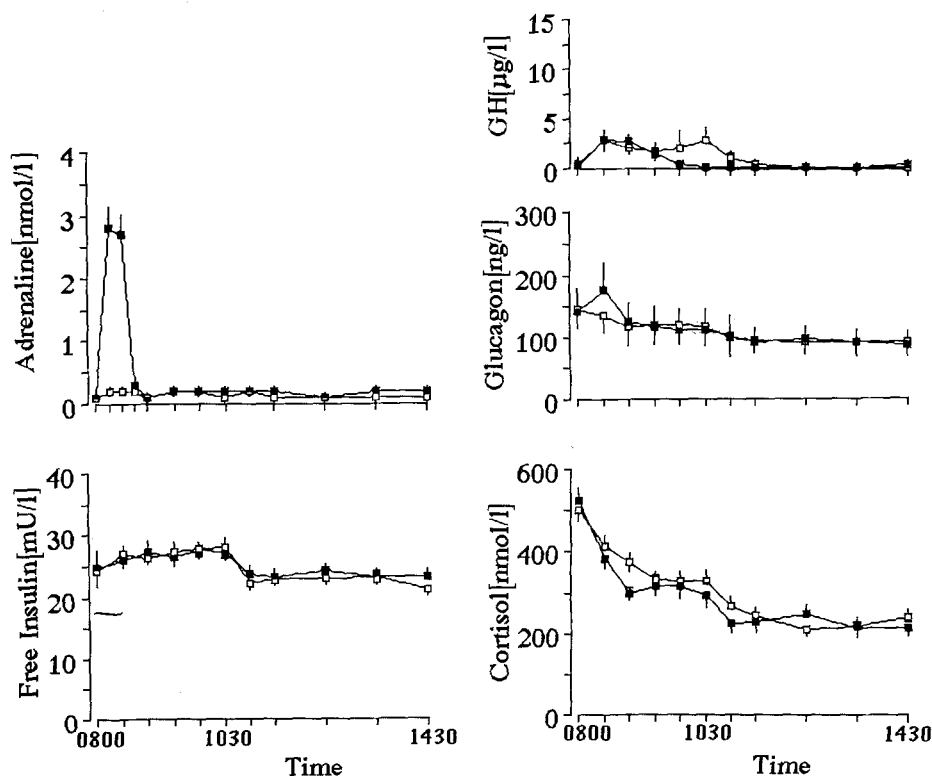


Fig. 2. Plasma adrenaline, free insulin, growth hormone, glucagon and cortisol levels during the glucose clamp (08.00–10.30 hours) and the somatostatin-insulin-glucose infusion test (10.30–14.30 hours) in the study with (■—■) and without (□—□) adrenaline infusion

centration [12], the plasma level of anti-body bound insulin [7], C-peptide [13] and the index of blood glucose fluctuations (M-value) [14] were determined in each patient.

Statistical analysis

Unless otherwise stated all data are given as means \pm SEM. Statistical significance was calculated by using Wilcoxon's signed rank test for paired observations.

Results

The mean blood glucose and M-value during the 24 h period prior to the studies ranged from 9.3 ± 0.3 to 9.6 ± 0.3 mmol/l and from 18.0 ± 2.8 to 21.2 ± 2.30 , respectively, with no differences between the adrenaline and the control study.

Between 08.00 and 10.30 hours, i.e. the glucose-clamp period, the blood glucose level was close to 7 mmol/l in both studies (Fig. 1) and there were no significant differences in plasma free insulin, GH, glucagon and cortisol (Fig. 2). The infusion of adrenaline raised its plasma level to 2.7 ± 0.3 nmol/l at end of the infusion at 08.30 hours; thereafter, it rapidly declined reaching the basal level within 30 min (Fig. 2). As expected, in the adrenaline study only minimal amounts of glucose had to be infused initially while glucose had to be given continuously in the study without adrenaline to keep the blood glucose close to 7 mmol/l. This difference in glucose infusion rate between the two studies decreased over time (Fig. 1). In response to the adrenaline infusion the patients recognised mild palpitation and their heart rate increased from a basal of 69 ± 3 to 76 ± 3 beats/min, $p < 0.05$.

During the SIGIT close to identical levels of plasma free insulin and counterregulatory hormones were registered (Fig. 2). The blood glucose rose significantly ($p < 0.05$) during the initial 2 h of the SIGIT in the adrenaline as compared to the control study; thereafter this difference declined and was not statistically significant from 3 h after start of the SIGIT (Fig. 3).

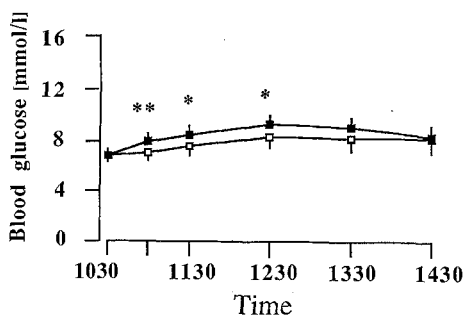


Fig. 3. The effect of the adrenalin infusion (08.00–08.30 hours) on the blood glucose level during the somatostatin-insulin-infusion test (10.30–14.30 hours) in the study with (■—■) and without (□—□) adrenaline infusion. * $p < 0.05$, ** $p < 0.01$

Discussion

The aim of the present study was to clarify whether a transient increase in plasma adrenaline alone could induce a long-standing state of insulin resistance as analysed by a somatostatin-insulin-glucose infusion test (SIGIT) [2]. The infusion of adrenaline yielded a plasma adrenaline profile similar to that seen during insulin-induced hypoglycaemia [1] and exerted a diabetogenic effect which was, however, not demonstrable 4.5 h after normalisation of the plasma adrenaline level. These findings are in accordance with the known ability of adrenaline to exert its diabetogenic action rapidly after its plasma level is raised [15].

Although data is lacking demonstrating whether the diabetogenic effect of adrenaline persists for several hours after its circulatory levels are normalised, some authors have proposed that adrenaline is the main factor behind posthypoglycaemic hyperglycaemia (the Somogyi phenomenon) [16, 17]. Thus Popp and co-workers [16] referred posthypoglycaemic hyperglycaemia to increased sympathoadrenal activation since they found that posthypoglycaemic hyperglycaemia was attenuated in Type 1 diabetic patients by the unselective beta-adrenergic blocker propranolol. Their study period was relatively short, however, not exceeding 2 h following nadir hypoglycaemia. Attvall and co-workers [17] have also reported that propranolol prevents posthypoglycaemic insulin resistance in Type 1 diabetic patients during a time period of 2.5 h following the hypoglycaemic event. Both these studies demonstrate the importance of adrenaline for the acute recovery of blood glucose but cannot evaluate the mechanism behind longstanding posthypoglycaemic insulin resistance, i.e. a time period of at least 6 h after hypoglycaemia [2, 18]. Kleinbaum and co-workers [19] have also studied the effect of propranolol on the plasma glucose homeostasis after insulin-induced hypoglycaemia in Type 1 diabetic patients. Their study period covered 5 h after nadir hypoglycaemia. The counterregulatory hormone response was similar during propranolol infusion apart from the expected potentiated secretion of GH induced by the drug. Interestingly, the recovery of plasma glucose was blunted for about 3 h by propranolol; thereafter this effect of the drug was no longer evident. The impairment of glucose recovery was due to a smaller reduction in peripheral glucose uptake, while hepatic glucose production was not modified. Thus, their study again demonstrates the importance of adrenaline for blood glucose recovery in Type 1 diabetic patients but speaks against the importance of adrenaline in causing the Somogyi phenomenon. Moreover, since unselective beta-blockers do not only counteract the action of adrenaline but also potentiate the release of GH during hypoglycaemia [19, 20], it is questionable whether the metabolic effects of adrenaline itself could be adequately assessed by beta-blockers. This may be of par-

ticular importance in prolonged studies since GH alone induces insulin resistance after a lag period of approximately 4 h [3].

It has been demonstrated that adrenaline infusion may enhance the secretion of pancreatic glucagon [21]. Against this background it is of importance to notice that in the present study adrenaline infusion did not influence the plasma levels of counterregulatory hormones or plasma free insulin significantly. Therefore the diabetogenic effect of adrenaline registered here is probably caused by its direct effects on the liver and peripheral tissues.

We conclude that a 30 min i.v. infusion of adrenaline mimicking its response to hypoglycaemia exerts a diabetogenic effect which in well-insulinised Type 1 diabetic patients subsides within 6 h. It is therefore unlikely that adrenaline is a major factor in causing long-standing insulin resistance after hypoglycaemia.

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