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Glucagon and insulin hypoglycaemia

Dear Sir,

In their recent report Lager et al. [1] have tested the hypothesis that blunted responses of plasma glucagon to hypoglycaemia in patients with Type 1 (insulin-dependent) diabetes wholly account for their impaired rates of plasma glucose recovery. They conclude that replacement of glucagon in sufficient quantities to normalize portal plasma venous glucagon concentrations does not restore normal glucose counter-regulation in Type 1 diabetes mellitus.

For several reasons these conclusions appear to be questionable. First, recalculation of overall glucose recovery rate from their Figure 1 indicates that the diabetic patients examined after glucagon replacement had values greater than those of non-diabetic controls (0.025 versus $0.017 \text{ mmol} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$). Secondly, the difference in plasma glucose concentration between glucagon-infused diabetic patients and non-diabetic controls soon after the end of the insulin infusion appears to be negligible, i.e. approximately 0.2 mmol/l . Thus, Lager et al. have shown not only improvement but full normalization of glucose counter-regulation following glucagon replacement in the diabetic patients examined under the experimental conditions of their study.

However, they have replaced glucagon only after the end of the insulin infusion and not in the very early phase of plasma glucose fall [2], as would seem more appropriate, since plasma glucagon increases significantly in response to trivial decrements in plasma glucose [3] and glucagon has powerful effects in the prevention of hypoglycaemia [4]. Thus, the study by Lager et al. shows that supra-physiological increases in plasma glucagon after severe insulin-induced hypoglycaemia in diabetes mellitus succeed in restoring normoglycaemia, but cannot address the question of whether loss of A-cell response to hypoglycaemia accounts totally for disrupted counter-regulation in diabetes.

Clearly, in addition to loss of plasma glucagon responses, blunted responses of other hormones, such as plasma adrenaline, noradrenaline, growth hormone and cortisol [5], contribute to impaired counter-regulation in diabetes. Finally, in diabetic patients with even modest antibody binding [2], inappropriate hyperinsulinaemia is an additional factor in impairment of counter-regulation [5].

Yours sincerely,

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Reply from the authors

Dear Sir,

The main point raised by Dr. Bolli is whether infusion of glucagon at a rate sufficient to produce physiological levels in the portal blood during experimental hypoglycaemia leads to a complete or only partial normalization of the glucose recovery process in Type 1 diabetes. If a complete normalization is seen, this would support the concept that the impaired glucose recovery can be ascribed to the insufficient glucagon release. Bolli et al. have recently suggested this to be the case [2] and they have now also interpreted the results of our study [1] to support this. We feel, however, that our results show that glucagon infusion certainly improves, but does not completely normalize, the recovery process.

This discrepancy in the interpretation of our results depends on how the glucose recovery rate is calculated. Dr. Bolli has calculated

the overall recovery rate, i.e., the increase in glucose from the end of the insulin infusion to the end of the observation period [1, Fig. 1] divided by the time (140 min). We did not calculate our data in this way since we feel that it is not appropriate and may, in fact, be distinctly misleading since it does not take into account the various aspects of the recovery process as outlined below.

The impairment in glucose recovery in normal Type 1 diabetic patient following intravenous insulin infusion is mainly due to two abnormalities [1, Fig. 1]; in contrast to non-diabetic subjects, glucose levels continue to decline for some time even after the insulin infusion is stopped; and the initial, rapid phase of recovery is markedly attenuated (15 min after nadir, glucose increased by 1.1 mmol/l in the control subjects but only by 0.4 mmol/l in the diabetic patients). The later phase (15 min and later after nadir) is, however, similar (0.015 versus $0.013 \text{ mmol} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$ in control and diabetic subjects, respectively, using the same calculations as Dr. Bolli).

It is quite clear that glucagon infusion prevented a decline in the glucose levels after the insulin was stopped. Thus, glucagon completely normalized this abnormality documenting its importance as a counter-regulatory hormone. However, the rapid increase after the nadir, characteristic of normal subjects ($+1.1 \text{ mmol/l}$), was still clearly attenuated and essentially unchanged in the diabetic patients even when glucagon was infused ($+0.4 \text{ mmol/l}$) and high physiological portal levels likely to have been present. Consequently, this part of the glucose recovery process was *not* normalized.

The high overall recovery rate calculated by Dr. Bolli in the glucagon-infused diabetic patients is mainly due to the presence of high glucagon levels throughout the observation period [1, Fig. 3] even at a time when the free insulin levels were normal clearly a non-physiological over-compensation which we also pointed out (p.341, paragraph 3). Even so, the glucose recovery rate was less than half of that occurring shortly after nadir in the control subjects (0.033 versus $0.073 \text{ mmol} \cdot \text{l}^{-1} \cdot \text{min}^{-1}$, respectively) when similar portal glucagon levels should have been present.

Taken together we feel that our interpretation of the data is the most appropriate at the present time, i.e., glucagon clearly plays an important role, but it is not the only factor accounting for the attenuated recovery from hypoglycaemia in Type 1 diabetes. We are glad that Dr. Bolli now also seems to agree with the complexity of glucose counter-regulation in diabetes and the importance of other factors than glucagon.

Yours sincerely,

I. Lager and U. Smith

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