Glucagon and hyperglycaemia in diabetes

Philip E. CRYER
Division of Endocrinology, Metabolism and Lipid Research, Washington University School of Medicine, St Louis, 660 South Euclid Ave, MO 63110, U.S.A.

ABSTRACT

Glucagon, in the setting of absolute or relative insulin deficiency, is thought to contribute to the pathogenesis of hyperglycaemia in diabetes, but much of the evidence is extrapolated from short-term studies to the long-term condition. In the present issue of Clinical Science, Li and co-workers report that infusion of glucagon raised fasting plasma glucose concentrations and impaired glucose tolerance over 4 weeks in mice, thus demonstrating a sustained glycaemic effect of hyperglucagonemia. Nonetheless, compelling evidence that glucagon contributes to the pathogenesis of hyperglycaemia in diabetes awaits long-term selective reduction of glucagon secretion or action in humans.

The existence of a second pancreatic hormone, one that raises plasma glucose concentrations, in addition to the glucose-lowering hormone insulin was deduced early in the 20th century and fully documented, and named glucagon, by the mid-20th century [1]. Since then, a great deal has been learned about the physiology of glucagon, but understanding of the roles of the hormone in the pathophysiology of diabetes mellitus remains incomplete [1].

Glucagon is a 3500 Da peptide secreted from pancreatic islet α-cells into the hepatic portal venous circulation. The hormone increases hepatic glucose production by stimulating glycogenolysis and, particularly when glucoseogenic precursors are abundant, gluconeogenesis [1,2].

Glucagon secretion in vivo is stimulated by decreased glucose and increased amino acid levels; it is inhibited by increased glucose, insulin and non-esterified fatty acid levels as well as by somatostatin. It is also stimulated by β2-adrenergic receptor activation [by sympathetic neural noradrenaline (norepinephrine)] and by muscarinic cholinergic receptor activation (by parasympathetic neural acetylcholine), but at least the glucagon response to hypoglycaemia is not critically dependent on pancreatic innervation [2]. Findings, ranging from elegant studies of isolated rat α-cells [3] to studies in healthy humans [4], have provided renewed interest in the concept of Samols et al. [5] that β-cell insulin, perhaps among other secretory products, acting via the islet microcirculation, regulates α-cell glucagon secretion in a reciprocal fashion: a decrease in insulin signals an increase in glucagon secretion and an increase in insulin signals a decrease in glucagon secretion. However, the relative contributions of β-cell products, such as insulin [3–5], and of direct effects of signalling molecules, such as glucose, on α-cells [6,7] in the regulation of glucagon secretion remain to be determined.

The role of glucagon in the physiological defence against hypoglycaemia is well established [8]. Although the first defence against falling plasma glucose concentrations is a decrease in insulin secretion, the second defence is an increase in glucagon secretion [8]. Loss of the glucagon response to falling plasma glucose concentrations, probably the result of β-cell failure [4], is a key feature of the pathophysiology of glucose counter-regulation, and thus the pathogenesis of iatrogenic hypoglycaemia, in Type 1 diabetes and advanced (i.e. absolutely endogenous insulin deficient) Type 2 diabetes [9].

On the other hand, a role of glucagon, in the setting of absolute or relative insulin deficiency, in the pathogenesis of hyperglycaemia in diabetes, proposed by Unger and Orci [10] more than three decades ago, remains to be established conclusively [1]. Plasma glucagon levels have been found to be elevated in patients with diabetes in some studies but not others [1]. Therefore the

Key words: glucagon, glucose tolerance, insulin deficiency, kidney, microalbuminuria, Type 2 diabetes.

Abbreviation: GLP-1, glucagon-like peptide-1.

Correspondence: Professor Philip E. Cryer (email pcryer@wustl.edu).
general concept is that of relative hyperglucagonaemia in diabetes, since glucagon levels might be expected to be reduced in the setting of hyperglycaemia. Given a body of physiological evidence that glucagon supports the postabsorptive and postprandial plasma glucose concentrations [1,2,11] and an array of studies, including but not limited to those of glucagon suppression with somatostatin in experimental animals and humans without and with diabetes by Gerich and co-workers and by others (reviewed in [1]), the involvement of glucagon in the pathogenesis of hyperglycaemia in diabetes is plausible, perhaps even probable. However, much of the supportive evidence is from short-term studies extrapolated to the long-term condition. For example, it is assumed that chronic hyperglycaemia suppresses glucagon levels and that glucagon, despite its transient short-term glycaemic effect [1], continues to increase glucose production in the long term. With respect to the latter, in the present issue of Clinical Science, Li and co-workers [12] report that an infusion of glucagon raised fasting blood glucose concentrations and impaired glucose tolerance over 4 weeks in mice and that those effects of glucagon were prevented by co-infusion of the glucagon antagonist [Des-His1-Glu3]glucagon. Thus the results document a sustained glycaemic effect of hyperglucagonaemia. Interestingly, probably because of the resulting hyperglycaemia, the glucagon-infused animals had features of diabetic nephropathy: increased kidney weight/body weight ratios, albuminuria and glomerular mesangial expansion.

Long-term administration of drugs that suppress glucagon secretion, such as GLP-1 (glucagon-like peptide-1) receptor agonists and dipeptidyl peptidase-IV inhibitors, lowers plasma glucose concentrations to some extent in patients with Type 2 diabetes [1]. However, those drugs have additional glucose-lowering actions, including enhancement of glucose-stimulated insulin secretion and, with GLP-1 receptor agonists, delayed gastric emptying and weight loss. Thus compelling evidence that glucagon contributes to the pathogenesis of hyperglycaemia in diabetes awaits the development of safe and effective drugs that selectively reduce glucagon secretion or action in the long term in humans. With respect to safety, effective glucagon antagonism would be expected to impair defence against hypoglycaemia [8]; however, that might not be a clinically important problem if the first defence against falling plasma glucose levels, a decrease in insulin secretion [8], were intact as it is early in the course of Type 2 diabetes [9]. With absolute β-cell failure, in Type 1 diabetes and advanced Type 2 diabetes, both the insulin and the glucagon responses to falling plasma glucose levels are already lost [1,9].

ACKNOWLEDGMENTS

The author’s work cited was supported, in part, by National Institutes of Health grants R37 DK27085, MO1 RR0036 and P60 DK20579, and a fellowship award from the American Diabetes Association. Ms Janet Dedele assisted in the preparation of this manuscript.

REFERENCES


10 Unger, R. H. and Orci, L. (1975) The essential role of glucagon in the pathogenesis of diabetes mellitus. Lancet i, 14–16
