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Involvement of steatosis-induced glucagon resistance in hyperglucagonaemia

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ABSTRACT

For more than a century type 2 diabetes has been looked upon mainly as an insulin-related disease and it is well-acknowledged that insulin resistance and beta cell dysfunction play important roles in the pathophysiology of the disease. During the last couple of decades, glucagon has also been recognised to play a significant role in type 2 diabetic pathophysiology. However, the mechanisms underlying disturbances in the regulation of glucagon remain unclear. Glucagon constitutes the primary stimulus for hepatic glucose production and, thus, upholds adequate blood glucose levels during fasting conditions. Many – but not all – patients with type 2 diabetes are characterised by inappropriately elevated plasma levels of glucagon contributing to their hyperglycaemic state. We believe that phenotypical dissimilarities within this group of patients may determine the presence and degree of hyperglucagonaemia. Results from our group show that both normoglycaemic individuals and patients with type 2 diabetes with non-alcoholic fatty liver disease (NAFLD) exhibit fasting hyperglucagonaemia compared to similarly grouped individuals without NAFLD. Therefore, we speculate that NAFLD – and not type 2 diabetes *per se* – is the main driver behind fasting hyperglucagonaemia. We hypothesise that in the majority of type 2 diabetic individuals hepatic sensitivity to glucagon is compromised due to hepatic steatosis, and that this provides a feedback mechanism acting at the level of pancreatic alpha cells, leading to elevated levels of glucagon. Here we present our hypothesis and propose a way to test it. If our hypothesis holds true, hepatic glucagon resistance would constitute a parallel to the obesity-induced insulin resistance in muscle and liver tissue, and underpin a central role for glucagon in the pathogenesis of type 2 diabetes. This would provide a crucial step forward in understanding the interaction between NAFLD and the alpha cell in the pathophysiology underlying type 2 diabetes.

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Introduction

For more than a century type 2 diabetes has been looked upon mainly as an insulin-related disease and it is well acknowledged that insulin resistance and dysfunction of the insulin-secreting beta cells in the pancreas play important roles in the pathophysiology of the disease. Several drugs targeting these defects have been developed and applied in the treatment of type 2 diabetes. During the last couple of decades glucagon, the other major pancreatic gluco-regulatory hormone, has also been recognised to play a significant role in type 2 diabetic pathophysiology [1,2]. This has heightened the interest in developing drugs targeted glucagon, which in turn demands detailed knowledge of the mechanisms underlying dysregulated glucagon secretion in type 2 diabetes. Here we present a new hypothesis on the mechanisms underlying disturbed glucagon physiology in type 2 diabetes (see Fig. 1).

Glucagon constitutes the primary stimulus for hepatic glucose production [3], which is essential to uphold adequate blood glucose levels during fasting conditions and maintain vital functions. Thus, under normal circumstances, glucagon secretion from the pancreatic alpha cells is stimulated during low blood glucose levels (e.g. during fasting) and suppressed during conditions of carbohydrate abundance (e.g. during carbohydrate-rich meals). Many patients with type 2 diabetes are characterised by elevated fasting plasma levels of glucagon and inadequate suppression of glucagon following carbohydrate ingestion [4]. This, in turn, stimulates hepatic glucose production and contributes to the hyperglycaemic state of the patients. Interestingly, many obese and/or prediabetic individuals are also characterised by fasting hyperglucagonaemia [5,6] and increased hepatic glucose production [7], supporting the view that hyperglucagonaemia constitutes an early part of type

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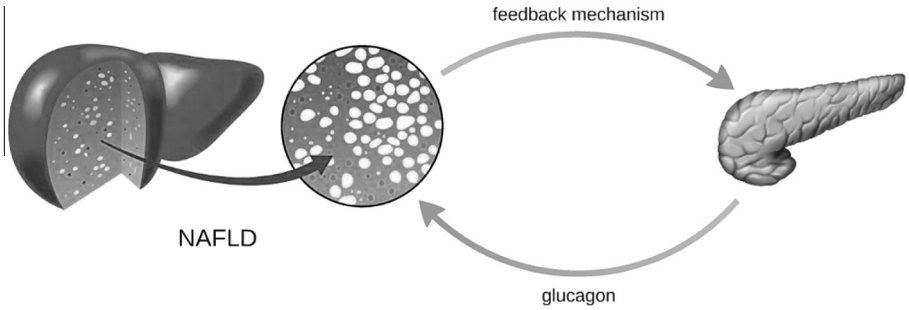

Fig. 1. We hypothesise that steatosis-induced glucagon resistance affects a feedback mechanism acting on the pancreatic alpha cells, leading to increased glucagon secretion, and that this liver-pancreas axis might contribute to explain hyperglucagonaemia in type 2 diabetes.

2 diabetic pathophysiology. Additionally, recent studies have shown that hyperglycaemia and ketosis in rodent models of type 1 diabetes and type 2 diabetes, respectively, can be abrogated by knocking out the glucagon receptor [8,9]; stressing the importance of glucagon in the pathophysiology of diabetes. Furthermore, Lee et al. showed that – in the glucagon receptor knock-out version of their type 2 diabetes mouse model – the 'original' type 2 diabetic phenotype (i.e. hyperglycaemia and hyperinsulinaemia) emerged when glucagon receptor cDNA was introduced by adenovira [9]. These findings place glucagon centrally in the pathogenesis of diabetes. However, despite decades of intense investigations, the mechanisms underlying the hyperglucagonaemic state remain unclear. In this paper we provide the rationale behind a novel hypothesis to explain the occurrence of elevated plasma glucagon levels in patients with type 2 diabetes, offer an approach to test it and outline the potential implications of our hypothesis.

Hypothesis

We hypothesise that in the majority of individuals with type 2 diabetes hepatic sensitivity to glucagon is compromised due to hepatic steatosis, and that this provides a feedback mechanism acting at the level of pancreatic alpha cells, leading to hyperglucagonaemia. This would explain the hyperglucagonaemia often seen in diabetic subjects as a compensatory mechanism.

Rationale for the hypothesis

Hyperglucagonaemia in diabetes is commonly ascribed to alpha cell resistance to the glucagon-suppressive effect of insulin and/or glucose combined with reduced secretion of insulin and other pancreatic beta cell products (including amylin, Zn^{2+} and gamma-Aminobutyric acid (GABA)) known to suppress the secretion of glucagon [1]. Disturbances of these factors may indeed contribute to the dysregulation of glucagon levels in type 2 diabetes. However, studies of the incretin effect in patients with type 2 diabetes suggest that glucose and insulin may not be as important as previously believed and that other mechanisms could constitute main drivers of diabetic hyperglucagonaemia [10]. In these studies plasma levels of glucagon are significantly higher, and even paradoxically increase, after oral ingestion of glucose compared to intravenous (iv) glucose infusion, despite identical plasma glucose curves under the two conditions and significantly lower plasma levels of insulin during the latter due to the lack of gut-derived incretin hormone potentiation of beta cell secretion. This clearly indicates that circulating glucose and insulin may not represent the hitherto-considered major determinants of postabsorptive glucagon secretion and suggests that other yet undiscovered mechanisms may play important roles in the understanding of postabsorptive hyperglucagonaemia. Like postabsorptive hyperglucagonaemia, fasting hyperglucagonaemia is common in type 2 diabetes and it is well-established that it contributes significantly to the fasting hyperglycaemia of the patients when present [11,12]. Nevertheless, fasting hyperglucagonaemia is not pathognomonic for the disease – some patients have normal fasting levels of circulating glucagon. The reason for differences in fasting glucagon levels among patients with type 2 diabetes has not been elucidated and, thus, the pathophysiology underlying fasting hyperglucagonaemia in patients with type 2 diabetes needs further clarification.

It is widely believed that obesity-related peripheral insulin resistance leads to compensatory hypersecretion of insulin after e.g. a carbohydrate-rich meal [13]. Additionally it is well acknowledged that hepatic insulin resistance gives rise to fasting hyperinsulinaemia. A similar mechanism could account for the observed hyperglucagonaemia in type 2 diabetes. However, since hyperglucagonaemia characterises most, but not all patients with type 2 diabetes, we believe that phenotypical dissimilarities within this group of patients may determine the presence and degree of hyperglucagonaemia. In particular we propose that hepatic steatosis, i.e. non-alcoholic fatty liver disease (NAFLD), could be of importance. Thus, in patients with fasting hyperglucagonaemia, the hepatic sensitivity to glucagon may be compromised due to hepatic steatosis and perhaps provide a feedback mechanism acting on the level of pancreatic alpha cells, leading to increased secretion of glucagon.

Cirrhosis, the end-stage of NAFLD, is – not surprisingly – associated with reduced hepatic responsiveness to glucagon, i.e. hepatic glucagon resistance, most likely due to reduced functional liver tissue mass [14,15]. Type 1 diabetes, too, has long been known to be associated with glucagon resistance [16] and recent evidence suggest that NAFLD is common in patients with this disease. In the light of this, it might be that disruption of normal liver structure is involved in the development of glucagon resistance, even in the early and reversible stages of NAFLD. Notably, studies in mice with hepatocyte-specific elimination of the glucagon receptor suggest that a circulating factor generated after disruption of hepatic glucagon receptor signalling can increase alpha cell proliferation independently of direct pancreatic input [17]. We believe that a similar liver-pancreas axis in humans could be a significant contributor to fasting hyperglucagonaemia in patients with type 2 diabetes. This effect could either be mediated by the generation of a circulating factor, as suggested by Longuet et al., or via attenuation of a negative feedback mechanism from the liver, normally acting to control pancreatic alpha cells.

Interestingly, preliminary results from our group show that both normoglycaemic individuals and patients with type 2 diabetes with NAFLD exhibit significantly higher fasting plasma glucagon levels compared to normoglycaemic and type 2 diabetic control subjects without NAFLD [18]. Therefore, we speculate that the fasting hyperglucagonaemia observed in the majority of obese

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