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Glucagon's yin and yang effects on hepatic glucose production

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Abstract

New insights into the actions of the hormone glucagon are provided by a recent study in rodents, which shows that glucagon can suppress hepatic glucose production by acting through the mediobasal hypothalamic region of the brain. This central regulatory mechanism is impaired in rats fed a high-fat diet, suggesting that hypothalamic glucagon resistance may be relevant to the hyperglycemia observed in obesity, diabetes or both (pages 766–772).

Surprising new evidence suggests that glucagon, a peptide hormone secreted by pancreatic alpha cells, inhibits hepatic glucose production through effects on the brain, in addition to its well-known direct stimulatory effect on the liver. In this issue of *Nature Medicine*, Mighiu *et al.*¹ provide data from rodent studies showing that glucagon suppresses hepatic glucose production through actions mediated by the mediobasal hypothalamus (MBH), thereby limiting the direct stimulatory effect of this hormone on the liver. The suppression required activation of protein kinase A in the MBH and intact vagus nerves. It also occurred independently from changes in circulating glucose, insulin or glucagon. Remarkably, glucagon's central inhibitory effect on glucose production was defective in high fat-fed rats, suggesting that this negative feedback loop may have regulatory value and that its absence may contribute to the hyperglycemia associated with obesity, diabetes or both.

Despite being discovered nearly 90 years ago, glucagon has had a controversial history^{2,3}. It was not until the last few decades that its role in coupling hepatic glucose production to the body's needs during fasting, exercise, infection, trauma and hypoglycemia was clearly established⁴. Likewise, recognition that the plasma concentration of glucagon is absolutely or relatively increased in individuals with type 1 or type 2 diabetes has occurred slowly. Even now, the extent of glucagon's contribution to the diabetic phenotype is debated^{2,3}.

The appreciation of the importance of glucagon in glucoregulation has been slowed, in part, by the lack of a highly specific assay for its measurement (in current assays ~50% of measured basal 'glucagon' is actually non-specific, cross-reacting material). This means that changes in arterial plasma glucagon are more substantial than they might appear, an issue made worse by the fact that assessment of glucagon concentration in arterial plasma (where it is usually measured) underestimates its concentrations within the hepatic portal vein and liver sinusoids (where it acts). Skepticism about the physiological and pathophysiological

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role of this hormone was also triggered by the observation that the hepatic effect of a square-wave rise in glucagon wanes with time, such that after a few hours it seems to be gone⁵. In fact, however, if glucagon concentrations are then returned to baseline, there is a significant decrease in glucose production⁵. This indicates that the hormone is, in fact, still active, but with reduced potency. Numerous suggestions have been put forward to explain glucagon's evanescence⁴, including hyperglycemia, hyperinsulinemia, depletion of hepatic glycogen, decline in the amount of hepatic cAMP, phosphodiesterase activation and desensitization of hepatic glucagon receptors, but the cause remains unclear. Mighiu *et al.*¹ now shed new light on this important topic, drawing the conclusion that the downregulation of glucagon action at the liver is, at least in part, neural in origin and an important characteristic of glucagon's normal biology.

The authors' initial data¹ showed that infusion of glucagon directly into the MBH of rats inhibited glucose production in the presence of a pancreatic clamp. The physiological relevance of these experiments, however, is unclear for several reasons. First, somatostatin was used to inhibit insulin and glucagon secretion, whereas glucagon was not replaced and insulin was infused into a peripheral vein, rather than the hepatic portal vein, to clamp the arterial insulin level at a basal value. The portal vein plasma insulin concentration is normally three times greater than the arterial concentration, but when insulin is clamped by infusion into a peripheral vein, the portal vein insulin concentration falls to about one-third of its basal level. This means that glucose production was studied under conditions in which the liver was deficient in both glucagon and insulin. In addition, it has been argued that glucagon exposure resulting from targeted infusion into specific nuclei in the brain (for example, the MBH) is more relevant than administration by the intracerebroventricular route. It is unlikely, however, that either method actually replicates the level or extent of central nervous system (CNS) exposure that occurs when the hormone enters from the circulation. Issues such as these may explain why there have been conflicting results in other studies on this topic using paraventricular⁶ or intracerebroventricular⁷⁻¹¹ glucagon delivery. Nevertheless, the data of Mighiu *et al.*¹ clearly demonstrate that MBH glucagon action can suppress glucose production in rodents.

Mighiu *et al.*¹ also performed experiments to address the physiological relevance of this finding. They showed that antagonism of the MBH glucagon receptor prevented the time-dependent waning of glucose production seen in response to peripheral glucagon infusion. Although this observation was made during hepatic insulin deficiency, both the amount and the distribution of glucagon in the brain were appropriate because the hormone entered the CNS from the blood. Furthermore, in the absence of a pancreatic clamp the authors showed that intravenous glucagon infusion caused greater hyperglycemia when MBH glucagon action was blocked than when it was not. These loss-of-function experiments are more convincing than the gain-of-function experiments because they are not confounded by the potential nonphysiological effects of direct MBH glucagon administration. The authors also reported that MBH glucagon infusion did not suppress glucose production in rats that had been fed a high-fat diet. Thus, the emerging concept (Fig. 1) is one in which glucagon is responsible for the direct stimulation of hepatic glucose production, as well as for an autoregulatory inhibitory signal originating in the CNS. This would allow glucagon to mediate a burst of glucose production while limiting the likelihood of it causing

overproduction of glucose. In certain states this centrally driven downregulation may be overridden to provide the desired rate of glucose production (for example, during prolonged fasting or exercise). By contrast, in pathological conditions, it could become dysfunctional, thereby causing unwanted hyperglycemia.

It will be important going forward to further understand the signaling pathways and mechanisms (that is, glycogenolysis, gluconeogenesis or both) involved in brain glucagon's effect on the liver. Most importantly, however, it will be crucial to establish the physiological relevance of glucagon's effects in the brain in nonrodent species, particularly in humans. Although rodents offer powerful advantages over other species (for example, genetic manipulation and the precise delivery of hormones and compounds to specific brain nuclei), findings from such models often do not translate to humans^{12–14}. With regard to glucose metabolism there are considerable differences between small and large animals. For example, glucose production is five- to tenfold greater in rodents, and glycogen depletion during fasting occurs more rapidly (several hours versus several days); thus they have a greater dependence on gluconeogenesis. Interestingly, hepatic denervation did not prevent evanescence of glucagon's hepatic effect in dogs¹⁵. Variation in the importance of liver innervation across species may also contribute to differences in insulin-mediated CNS regulation of hepatic glucose production¹⁶. If the observations of Mighiu *et al.*¹ extend - to humans, it will be important to determine whether central glucagon resistance can explain any of the metabolic abnormalities associated with obesity, type 2 diabetes or both.

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Figure 1.

Glucagon infusion rapidly stimulates hepatic glucose production, but the effect wanes with time. New data from Mighiu *et al.*¹ indicate that glucagon action in the MBH can inhibit glucose production in rodents and that this neural circuit contributes to the evanescence of glucagon's direct hepatic effect. Feeding rats a high-fat diet results in MBH glucagon resistance, suggesting that impairment of this negative feedback loop may contribute to hyperglycemia in obesity, diabetes or both.