Glucagon regulates lipolysis and fatty acid oxidation through inositol triphosphate receptor 1 in the liver

Glucagon increases hepatic glucose production through stimulation of glycogenolysis and gluconeogenesis. Recently, accumulating data have shown that glucagon plays pivotaly important roles in the regulation of amino acid catabolism, the product of which serves as substrates for gluconeogenesis. Glucagon also promotes lipolysis and produces glycerol, which serves as a gluconeogenic substrate. Whereas hypoglycemia is often observed in patients harboring glucagonoma syndrome with glucagon excess, hypolipidemia is not regarded as a major symptom in the syndrome. Although glucagon has been experimentally shown to stimulate lipolysis in isolated adipocytes, the expression level of the glucagon receptor in adipocytes is almost negligible compared with that in hepatocytes. In addition, glucagon concentration in the peripheral circulation is much lower than in the portal vein. Therefore, it has been questioned whether glucagon directly stimulates lipolysis in adipose tissue in the physiological condition. Nevertheless, detailed mechanisms of how glucagon stimulates catabolism of amino acids and fatty acids largely remain to be elucidated.

In a recent article published in *Nature*, Perry et al. provided novel insights into the transcription-independent mechanism of glucagon-induced lipolysis in the liver. The inositol triphosphate receptors (INSP3Rs) are Ca^{2+} channels that function to release Ca^{2+} from the endoplasmic reticulum in response to a wide array of stimuli. Type-1 INSP3R (INSP3R1) is responsible for mitochondrial calcium signaling in hepatocytes, and has been shown to be involved in glucose production in isolated hepatocytes. To characterize the role of INSP3R1 in glucagon signaling, Perry et al. analyzed the acute effect of glucagon administration in liver-specific *Insp3r1* knockout mice (INSP3R1-LKO). The mice were fasted overnight and thereby depleted of glycogen, so that an increase in glycogenolysis by glucagon was abolished. In INSP3R1-LKO, intravenous infusion of glucagon at 5 ng/kg/min increased cyclic adenosine monophosphate levels and protein kinase A activity in the liver; however, it failed to phosphorylate/activate Ca^{2+}/calmodulin-dependent protein kinase II and adipose triglyceride lipase (ATGL, also known as Pnpla2, patatin-like phospholipase domain-containing protein 2). In contrast, hormone-sensitive lipase, which is activated by protein kinase A, is phosphorylated/activated by glucagon in INSP3R1-LKO mice.

As schematically summarized in Figure 1, INSP3R1 integrates signals from protein kinase A and phospholipase C, both of which are evoked by glucagon, and release Ca^{2+} into cytoplasm and mitochondria in a manner independent of changes in gene expression. Deletion of INSP3R1 uncouples protein kinase A activation and Ca^{2+} mobilization, and hormone-sensitive lipase, but not ATGL, was activated by glucagon. Glucagon failed to increase intrahepatic lipolysis, fatty acid oxidation and glucose production in INSP3R1-LKO mice and mice treated with adeno-associated virus to knockdown liver ATGL. Therefore, the INSP3R1–ATGL pathway appears to play a central role in the regulation of hepatic lipid metabolism in response to glucagon. Under the experimental condition, the contribution of adipose tissue lipolysis appeared to be negligible, as plasma non-esterified fatty acid levels did not change significantly in both INSP3R1-LKO mice and the control mice by glucagon infusion.

The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing in parallel with that of obesity, type 2 diabetes and metabolic syndrome. Hyperinsulinemia, which is regarded as a consequence of insulin resistance, is strongly linked to these conditions. Intriguingly, hyperglucagonemia is also frequently observed under these conditions. The cause of hyperglucagonemia has often been attributed to impaired suppression of glucagon secretion from islet \(\alpha\)-cells in response to a meal, hyperglycemia and/or increased insulin secretion. In other words, disfunction of \(\alpha\)-cells has been considered as a cause of hyperglucagonemia. From this viewpoint, suppression of glucagon secretion has been considered as an option to treat these metabolic disorders. However, according to the model of action discussed herein, in which glucagon accelerates hepatic lipolysis and fatty acid oxidation, glucagon should play a beneficial role and ameliorate NAFLD. Therefore, based on the current model, an increase in glucagon secretion should be considered as a physiologically appropriate response to lipid deposition in...
hepatocytes. Based on this new point of view, suppression of glucagon, which possibly aggravates NAFLD, might result in being an inappropriate approach to treat metabolic disorders, even if blood glucose levels might be lowered.

In type 2 diabetes, islet β-cells secrete more insulin to compensate for insulin resistance, resulting in higher homeostasis model assessment for insulin resistance, a product of blood glucose levels and plasma insulin concentration. In patients with high homeostasis model assessment for insulin resistance, therapeutic intervention is directed to ameliorate insulin resistance, but never to suppress insulin secretion nor to block insulin action. If “glucagon resistance” is the cause of
hyperglucagonemia in metabolic disorders, therapeutic intervention should be directed to ameliorate glucagon resistance, but never to suppress glucagon secretion nor to block glucagon action. As response to glucagon is partially attenuated in INSP3R1-LKO mice, as discussed herein3, this model should be considered a glucagon-resistant model. Indeed, INSP3R1-LKO mice show a higher plasma glucagon concentration, which might compensate for glucagon resistance.

The glucagon receptor knockout mouse, an extreme model of glucagon resistance, shows high plasma glucagon levels and islet α-cell hyperplasia. As liver-specific glucagon receptor knockout mice, as well as liver-specific Gs α-subunit knockout mice also show a similar phenotype, hepatic glucagon resistance is sufficient to induce α-cell proliferation and hyperglucagonemia. Among animal models that show hyperglucagonemia, the glutaminase 2 knockout mouse (Gls2−/−) is of particular interest, as it suggests that impairment in amino acid catabolism or glutaminolysis in the liver is sufficient to chronically stimulate glucagon secretion1. It is also noteworthy that glucagon decreased plasma amino acid levels in the control mice, but not in INSP3R1-LKO mice3. Intriguingly, plasma glucagon concentration is significantly elevated also in knockdown liver ATGL described herein, in which hepatic lipolysis but not Ca2+ mobilization in response to glucagon is impaired3. As it is unlikely that knocking down a lipase gene, ATGL, impairs glucagon-induced changes in amino acid catabolism, impairment in lipolysis per se might be sufficient to increase glucagon secretion.

As schematically summarized in Figure 2a, glucagon stimulates glycogenolysis, gluconeogenesis, lipolysis and amino acid catabolism. Lipolysis and amino acid catabolism supplies gluconeogenic substrates under glycogen depletion. Suppression of glucagon might be beneficial in terms of blood glucose control; however, suppression of hepatic lipolysis, fatty acid oxidation and amino acid catabolism could aggravate metabolic disorders, including NAFLD and glucagon resistance (Figure 2b)5. Indeed, increases in liver fat and liver enzymes have been documented in studies with glucagon antagonism5. Further data from basic and clinical studies are required for our understanding of the benefits and disadvantages of glucagon antagonism and/or agonism.

DISCLOSURE
The author declares no conflict of interest.

Yoshitaka Hayashi*
Department of Endocrinology, Division of Stress Adaptation and Protection, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan

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