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BASIC RESEARCH

Neuroimmune interactions control glucagon secretion and glucose balance

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SCIENTIFIC BACKGROUND

Maintenance of stable blood glucose levels is essential for organismal survival, particularly to sustain brain and muscle function during periods of limited nutrient availability. This balance, known as glucose homeostasis, is achieved through coordinated interactions between endocrine organs, metabolic tissues, the nervous system, and the immune system. Central to this process is the pancreas, which regulates blood glucose through the secretion of hormones from the islets of Langerhans.

Insulin and glucagon are the main hormones from the pancreas that regulate blood glucose. Insulin, made by beta cells, helps the body absorb and store glucose after eating. On the other hand, glucagon is released by alpha cells during periods of fasting, physical activity, or low blood sugar, raising glucose levels by prompting the liver to break down glycogen (glycogenolysis) and make new glucose from non-carbohydrate sources (gluconeogenesis). Although insulin resistance and poor insulin secretion are well-known causes of metabolic diseases, problems with glucagon regulation are also becoming recognized as significant yet less understood factors in these disorders.

Glucagon release has been attributed to intrinsic pancreatic mechanisms and direct neural control, particularly through sympathetic innervation of the pancreas. However, recent research has broadened this view by demonstrating that immune cells contribute actively to metabolic regulation. Both adaptive and innate immune cells influence glucose metabolism by shaping inflammation, insulin sensitivity, nutrient absorption, and energy expenditure. Among these, innate lymphoid cells (ILCs) have emerged as important regulators of tissue homeostasis and lipid metabolism.

ILCs are tissue-resident immune cells that respond rapidly to environmental and physiological signals. Type 2 innate lymphoid cells (ILC2) are best known for their roles in barrier tissues, where they contribute to host defense, tissue repair, and type 2 immune responses through the secretion of cytokines such as interleukin-5 (IL-5) and interleukin-13 (IL-13). Beyond immunity, ILC2 have been implicated in metabolic processes, including adipose tissue regulation and insulin sensitivity, suggesting that they may link immune responses to systemic metabolism.

In parallel, the nervous system plays a critical role in sensing energy status and coordinating metabolic responses. Specific brain regions detect changes in blood glucose and relay signals to peripheral organs via autonomic pathways. Importantly, neurons do not operate in isolation but interact closely with immune cells, giving rise to neuroimmune communication networks that regulate physiology across multiple organs.

Together, these observations led to the hypothesis that neuronal and immune signals may cooperate to regulate pancreatic hormone secretion during fasting. The study summarized here investigated whether such neuroimmune interactions contribute to glucagon release and glucose homeostasis, focusing on the role of ILC2 and adrenergic neuronal signaling.

RESEARCH PROJECT

To explore the contribution of immune cells to glucose regulation, the study first examined glucose homeostasis in different mouse models with selective immune deficiencies. Mice lacking both adaptive immune cells and innate lymphoid cells displayed markedly reduced fasting blood glucose levels compared with wild-type animals or mice lacking only adaptive lymphocytes. This reduction became more pronounced during prolonged fasting and was accompanied by increased hepatic glycogen stores and reduced endogenous glucose production.

Importantly, these metabolic alterations were not due to abnormalities in insulin production or action. Insulin gene expression, circulating insulin levels, insulin sensitivity, and glucose tolerance were all preserved in immune-deficient mice. Instead, the defect was linked to glucagon: mice lacking innate lymphoid cells showed reduced expression of the glucagon precursor gene in the pancreas and significantly lower circulating glucagon levels. Administration of exogenous glucagon restored blood glucose levels, indicating that glucagon responsiveness was intact but endogenous glucagon production was impaired.

These findings suggested that innate lymphoid cells play a key role in supporting glucagon secretion during fasting. Further analysis identified type 2 innate lymphoid cells as the relevant population. Under normal conditions, ILC2 were the most abundant innate lymphoid subset in the pancreas. Fasting selectively increased pancreatic ILC2 numbers, whereas other ILC subsets remained unchanged. To determine whether ILC2 were sufficient to restore metabolic function, purified ILC2 were transplanted into immune-deficient mice. This intervention restored fasting-induced glucagon secretion, normalized blood glucose levels, and corrected defects in hepatic glucose production. Conversely, selective depletion of ILC2 in otherwise healthy mice led to reduced glucagon levels, impaired gluconeogenesis, and lower fasting glucose. These complementary approaches demonstrated that ILC2 are both necessary and sufficient for maintaining glucagon-dependent glucose homeostasis during fasting.

The study then addressed how ILC2 influence pancreatic alpha cells. Transcriptomic analyses revealed that alpha cells express receptors for IL-5 and IL-13, both in mice and in humans. In vitro experiments showed that these cytokines directly stimulated glucagon secretion from isolated alpha cells and pancreatic islets. Blocking downstream signaling pathways associated with these receptors reduced glucagon release, confirming a direct functional effect. In vivo, ILC2 were identified as the primary source of IL-5 and IL-13 in the pancreas during fasting, and neutralizing these cytokines reduced glucagon levels. Together, these data established a direct cytokine-mediated pathway by which ILC2 enhance glucagon secretion.

A central question was how ILC2 accumulate in the pancreas during fasting. Analysis of ILC2 distribution across organs revealed a simultaneous decrease in intestinal ILC2, suggesting that the intestine serves as a source of pancreatic ILC2. Using cell-tracking approaches, the study showed that fasting induces ILC2

migration from the gut to the pancreas through mesenteric lymph nodes. This migration was associated with reduced expression of molecules that normally retain ILC2 in the intestinal tissue.

The study then explored the signals driving ILC2 migration. Because the nervous system is a primary sensor of energy status, they tested whether neuronal activity could influence ILC2 trafficking. Using chemogenetic approaches to activate neurons innervating the intestine, they showed that neuronal activation alone was sufficient to induce ILC2 migration to the pancreas, increase glucagon secretion, enhance hepatic glucose production, and raise blood glucose levels. Conversely, elimination of catecholaminergic neurons prevented ILC2 accumulation in the pancreas and blunted glucagon response to fasting.

Adrenergic signaling emerged as a critical mediator of this process. Activation of sympathetic neurons increased intestinal norepinephrine levels, while genetic deletion of the β2-adrenergic receptor specifically in ILC2 prevented their migration and impaired glucose homeostasis. Importantly, adrenergic stimulation reduced the expression of gut-retention molecules on ILC2, providing a mechanistic explanation for their mobilization from the intestine to the pancreas.

Together, these experiments revealed a coordinated neuroimmune mechanism in which adrenergic neuronal signals instruct ILC2 to relocate from the gut to the pancreas, where they directly promote glucagon secretion.

IN SUMMARY

This study identifies a previously unrecognized neuroimmune pathway that regulates glucose homeostasis during fasting. It shows that type 2 innate lymphoid cells are essential contributors to glucagon secretion and endogenous glucose production when energy availability is low.

In response to fasting, adrenergic neuronal signals originating in the intestine trigger ILC2 to migrate from the gut to the pancreas. This migration depends on β2-adrenergic signaling within ILC2 and involves the downregulation of intestinal retention cues. Once in the pancreas, ILC2 produce IL-5 and IL-13, which act directly on alpha cells to stimulate glucagon secretion, thereby supporting hepatic glucose production and maintenance of blood glucose levels.

These findings expand the current understanding of metabolic regulation by demonstrating that immune cells are active regulators of endocrine function, highlight a functional integration of the nervous, immune, and endocrine systems in adapting to fasting. Thus, this work suggests that dysregulation of neuroimmune communication may contribute to metabolic and endocrine disorders characterized by abnormal glucagon secretion. By revealing how neuronal signals shape immune cell behavior to control hormone release, the study opens new avenues for research and potential therapeutic strategies targeting metabolic disease through neuroimmune pathways.

ORIGINAL PAPER

Šestan M, Raposo B, Rendas M, et al. Neuronal-ILC2 interactions regulate pancreatic glucagon and glucose homeostasis. *Science.* 2025;387(6731):eadi3624. doi:10.1126/science.adi3624

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