Commentary

MOLECULAR METABOLISM

The D-Day of ghrelin

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Ghrelin has emerged as an important player in the regulation of glucose homeostasis. During caloric restriction, the presence of acyl ghrelin (the active isoform) is necessary for the defense against hypoglycemia and survival [1]. In fasted humans, ghrelin administration enhances growth hormone (GH) secretion, suppresses insulin release and promotes insulin resistance to maintain normoglycemia [2]. The exact mechanism for the insulinostatic effect of ghrelin is not known. Ghrelin is secreted primarily by gastric endocrine cells, although a novel endocrine cell type (ε cells) in the pancreatic islet [3] also produces ghrelin raising the possibility of intra-islet regulation. Ghrelin has been shown to activate its receptor, the GH secretagogue receptor (GHSR) 1a, on β cells to inhibit glucose-stimulated insulin secretion (GSIS) through a $G\alpha_{i2}$ signaling pathway [4] and acts directly on α cells to stimulate glucagon secretion by elevating intracellular calcium and promoting ERK phosphorylation [5]. Another major inhibitor of insulin secretion from β cells is somatostatin (SST) through the SST receptor subtype-5 (SSTR5). Park and colleagues reported collaborative actions between ghrelin and SST via their receptors in INS-1 β cells to modulate GSIS during low- and high-energy balance states [6]. The close proximity of islet cells makes it difficult to distinguish between direct and indirect effects of hormones on β cells. However, the recent advances in molecular genetic techniques and next-generation sequencing allows for unbiased evaluation of gene expression in individual cells and provides a unique opportunity to intercept cross talk between pancreatic islet cells. In this issue of *Molecular Metabolism*, DiBruccio et al. [7] report a novel insulinostatic mechanism of ghrelin by acting directly on δ cells to promote SST release.

Little is known about the factors that regulate δ cell function despite these being the third most prevalent islet cell type. DiGruccio and colleagues generated a triple transgenic reporter mouse that enabled FACS purification of α, β and δ cells from the same islets. Comprehensive transcriptomes for each of the three islet cell types was performed. Static and perifusion assays were performed in both mouse and human islets to measure SST secretion from δ cells. Using RNA sequencing, fluorescent in situ hybridization (FISH), and qPCR analyses, they found that the Ghsr gene was abundantly and selectively expressed in δ cells. Stimulation of mouse and human islets with ghrelin produced a robust increase in glucose-stimulated SST secretion, and stimulation of calcium responses in δ cells in intact mouse islets. Des-Acyl-ghrelin, which does not activate the GHSR-1a, did not potentiate SST secretion or block ghrelin-induced SST release. Furthermore, the authors showed that ghrelin inhibited GSIS from β cells in a SST-dependent manner.

The SST-secreting δ cells provide essential negative feedback to the maintenance of glucose homeostasis by inhibiting the secretion of insulin and glucagon from their neighboring β and α cells, respectively. Disruptions in this intra-islet feedback loop contribute to the imbalance of insulin and glucagon release and the development of diabetes mellitus. The authors previously found that Urocortin3 (Ucn3) mediates SST inhibition of insulin secretion by amplifying SST release from δ cells [8]. In this new study, they uncovered a novel paradigm in which ghrelin acts directly on δ cells independently of Ucn3 to stimulate SST secretion. This finding may also be relevant to the *in vivo* effect observed in humans. Ghrelin cells are present in most islets in the human pancreas. It has been reported that 35–45% of the circulating ghrelin comes from tissues outside of the stomach in humans as compared to only 20% in rats [3]. More than a decade ago, Arosio et al. observed that acute ghrelin administration significantly increased circulating GH, SST, and pancreatic polypeptide levels in healthy individuals, accompanied by a decrease in plasma insulin level and an increase in plasma glucose [9]. However, the contribution of the intra-islet ghrelin regulation of islet hormone secretion to glucose homeostasis is far from being established.

Findings from this research also raise questions and controversies. Several groups have reported that GHSR was expressed by β cells [10] and α cells [5] and that ghrelin inhibited insulin release and promoted glucagon secretion via actions on the GHSR in these cells [5,11]. In the present study, GHSR expression is reported to be absent from primary β and α cells. This suggests that any effect of ghrelin on insulin and glucagon secretion is indirect and likely occurs through a paracrine or neural mechanism. These discrepancies may be attributed to the use of whole islets and (β- and α-) cell lines in the previous publications as opposed to sorted primary islet cells in the current study. Islet glucagon secretion was not measured in the present study. One would expect glucagon secretion to be reduced if the suppressive effect of SST dominates the stimulatory effect of the falling insulin on the α-cell. This hypothesis will need to be directly tested in future studies. It is worth noting that while the SSTRs are an integral part of the intra-islet

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signaling system, they only account for a small fraction (3.5%) of the whole islet transcriptomes. It is possible that ghrelin may engage other molecular signals or other receptors within the islet to coordinate its effects on insulin and glucagon secretion.

In summary, the data reported here make a strong case that δ cells are the primary site of islet regulation by ghrelin. Future studies are needed to confirm the current findings and to elucidate the complex interplay between islet hormones under physiological and pathological conditions. However, the present findings add to a growing body of experimental evidence for the importance of intra-islet regulation.

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