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# Ghrelin and Insulin Secretion in Humans: Not a Tale of Two Hormones?

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Failure of pancreatic β-cells to secrete adequate amounts of insulin is a fundamental defect in type 1 and type 2 diabetes, and the search for innovative strategies to improve β-cell mass and function is a major priority in diabetes research.

Ghrelin, a 28-amino acid peptide hormone predominantly secreted by the stomach, was identified as ligand of the growth hormone secretagogue receptor type-1a (GHSR-1a) (1). The Ser3-octanoylated ghrelin form (acylated ghrelin [AG]) also was soon recognized to act as a hypothalamic orexigenic signal (2) and to modulate tissue pathways and functions as a potential contributor to metabolic adaptation to low nutrient availability. Experimental AG administration commonly causes weight gain and hyperglycemia by enhancing food intake, fat deposition, and hepatic gluconeogenesis (3–5). A more comprehensive understanding of the metabolic impact of ghrelin has been recently allowed by the increasing appreciation of the independent, and generally more favorable, effects of its unacylated form (UAG), which does not increase food intake or circulating glucose in vivo (3,4,6). Although no specific UAG receptor has been yet identified, UAG coadministration may counteract the glucogenic effects of AG as well as AG-induced hyperglycemia (3,4,7), and positive or negative associations have been respectively reported in humans between AG or UAG and markers of whole-body insulin resistance (8). Modulating the AG–UAG balance by inhibiting the acylating enzyme ghrelin O-acyltransferase (9) or by exogenous hormone administration has therefore become an attractive therapeutic target to limit positive energy balance and altered glucose metabolism in obese and insulin-resistant states.

Importantly, both AG and UAG also contribute to regulate β-cell function and insulin secretion (10). GHSR-1a was identified in β-cells, and ghrelin expression has been described in different cell types in pancreatic islets (11). These observations introduce the concept that ghrelin is involved in a paracrine network regulating insulin release, although local hormone concentrations and interactions between systemic and pancreatic ghrelin remain poorly defined. GHSR-1a signaling may negatively modulate cAMP- and calcium-dependent glucose–stimulated insulin release (12). Indirect AG effects, including negative regulation of vagal stimulation (13), could result in additional inhibition of insulin secretion. Therefore, AG has been commonly considered an insulinostatic hormone, although it should be pointed out that reports of AG-stimulated insulin secretion are also available from experimental models (10), likely due to differences in cell lines, animal species, and hormone concentrations (10,12). Studies in humans are notably less controversial, and most of them indicate that circulating insulin is acutely reduced following bolus or continuous AG infusion (7,14,15), also at near-physiologic levels (15). On the other hand, available information indicates that UAG may counteract the negative effects of AG or directly enhance insulin secretion in vitro and in animal models (7,16,17). In healthy individuals, UAG acutely prevented the AG-induced insulin decline (7), and overnight UAG infusion transiently increased postprandial insulin (18). A comprehensive assessment of the potential positive impact of UAG in the regulation of insulin secretion is therefore of major clinical interest for treatment of declining insulin secretion in insulin resistance and diabetes.

In the current issue, Tong et al. (19) investigated the effects of bolus followed by continuous, 210-min intravenous infusions of pharmacologic AG and UAG doses (1 and 4 μg/kg/h, respectively) on circulating insulin in healthy volunteers under fasting and intravenous glucose-stimulated conditions. The key findings of the study are negative, as the inhibitory effect of AG on plasma insulin following intravenous glucose was unaffected by concomitant UAG infusion. UAG was also unable to modulate the negative impact of AG on intravenous glucose tolerance,

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while UAG alone did not alter insulin levels and responses to glucose infusion. In addition, the authors described the impact of AG and UAG on postinfusion food intake and macronutrient selection and reported novel effects of UAG to lower spontaneous total food, glucose, and fructose consumption that will deserve further investigation.

The current results provide a valuable contribution to the assessment of the acute impact of ghrelin forms on insulin secretion in healthy humans, and they strongly argue against a relevant independent stimulatory role of UAG, while further demonstrating no AG–UAG interactions at pharmacologic hormone levels (Fig. 1). To build on these novel findings, additional studies will be needed to assess the potential physiologic or clinical relevance of AG–UAG interactions under different experimental conditions (Fig. 1). In particular, the potential impact of different UAG doses on the insulinostatic effects of more physiologic AG elevations (15) remains to be determined. In terms of physiologic relevance, it also will be important to assess the impact of ghrelin forms on insulin secretion following oral glucose ingestion, when incretins contribute to modulate gut signaling to the pancreas. Moreover, AG–UAG interactions should be systematically investigated in clinical conditions characterized by insulin resistance, when a decline in circulating UAG and higher AG–UAG ratios have been reported (3,4,8). Under these conditions, potential differential modulation by AG and UAG of additional regulators of insulin secretion should be also considered, including autonomic nervous signaling (13), circulating hormones such as growth hormone and cortisol (1,6,19), and dietary carbohydrate intake as shown by Tong et al. (19). Finally, the well-demonstrated positive impact of both AG and UAG on β-cell survival and proliferation, leading to enhanced β-cell mass and higher circulating insulin in streptozotocin-induced type 1 diabetes models (10,20), poses important questions; longer-term interactions between altered insulin release and beneficial changes in β-cell mass should be directly investigated during long-term modification of ghrelin profile.

In summary, Tong et al. (19) provide a model for the challenging investigation of AG–UAG interactions in vivo in humans, and they show no independent effect of UAG

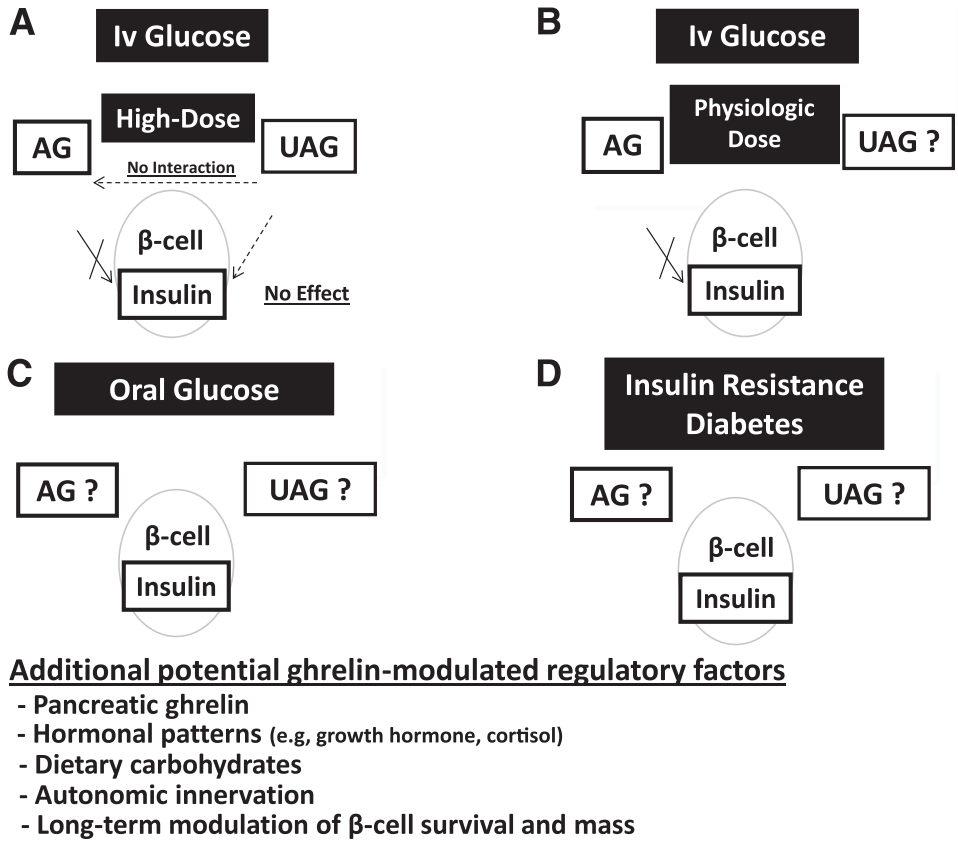


**Figure 1**—Relevant experimental or clinical conditions with well-defined or poorly defined effects of exogenous AG, UAG, or their interactions on insulin secretion in humans. *A*: Inhibitory effects of high-dose AG on intravenous (Iv) glucose-induced insulin secretion, unaffected by high-dose UAG; no independent effects of high-dose UAG on insulin secretion (14,19). *B*: Inhibitory effects of physiologic AG dose on intravenous glucose-induced insulin secretion (15); no information on potential physiologic UAG interactions. *C–D*: No or limited information on potential effects of AG, UAG, or AG–UAG interactions on insulin secretion during oral glucose intake or in insulin-resistant and diabetic conditions. Additional factors potentially contributing to modulate the impact of changes in circulating ghrelin profile on insulin secretion are listed in the lower section of the figure.

to acutely modulate insulin secretion. Future studies should aim at fully elucidating the pathophysiologic relevance of AG–UAG interactions, as well as the potential therapeutic role of modulating the ghrelin profile to optimize β-cell function in insulin-resistant and diabetic people.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

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