# The Welcome Resurgence of the α-Cell: A Pro Glucagon Commentary

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Of late an increasing number of publications about glucagon, a hormone that once enjoyed center stage with insulin but for several decades has been sitting in the wings, have appeared. The primary function of this islet α-cell product is to regulate hepatic glycogenolysis to supply increased endogenous glucose production. Clinically, this is a critical role. Release of this hormone is triggered by hypoglycemia, and it rescues patients with type 2 diabetes from hypoglycemia when too much insulin is used for glycemic control. Sadly, patients with type 1 diabetes do not have this luxury. In the absence of functional β-cells, the α-cell does not respond to hypoglycemia. The central relationship between these two cells is that the β-cell, by its own response to stop secreting insulin during hypoglycemia, provides an essential signal to the α-cell to release glucagon. This chain reaction only happens during hypoglycemia, so it takes both signals (hypoglycemia and an insulin decrement) to activate the α-cell. This phenomenon has been variably termed the intraislet insulin hypothesis (1) or the insulin switch-off signal (2).

A major stimulus for refocusing on glucagon has been an increasing number of intriguing studies from basic electrophysiological, biochemical, and animal physiology laboratories involving other regulators of α-cell function, including zinc, GABA, glutamate, somatostatin, ghrelin, and the autonomic nervous system (rev. in 3 and reference list of 1). These studies cause consideration of the concept of synergistic activation of the α-cell by forces other than low glucose and insulin levels. This general line of thinking is reasonable because we have long appreciated that the human body is replete with redundant regulation of its many important functions. Stimulated by the potential role of zinc as a regulator, Cooperberg and Cryer (4) set out to evaluate their hypothesis that "an increase in insulin per se, i.e., in the absence of zinc, suppresses glucagon secretion during euglycemia and that a decrease in insulin per se stimulates glucagon secretion during hypoglycemia in humans," as reported in this issue of *Diabetes*. One of the recent zinc studies was our own (5) in which glucagon secretion in rodents was suppressed by zinc and stimulated by a combination of hypoglycemia plus the switch off of a zinc or insulin infusion that had been started before hypoglycemia was induced. We later suggested that the mechanism whereby zinc exerts influence over α-cells involves the SUR1 subunit of ATP-sensitive $K^+$ ($K_{ATP}$) channels (6) (Fig. 1). The surprise in these experiments was that an infusion containing zinc-free insulin was not successful in suppressing glucagon, and switch-off of zinc-free insulin was not successful in stimulating glucagon secretion during hypoglycemia. Yet, this same preparation of zinc-free insulin was active in providing the anticipated insulin effect of increasing glucose uptake by L6 muscle and HepG23 hepatic cell lines (5). This led to our hypothesis that it is zinc bound to insulin within native β-cells, which dissociates (because of higher pH of blood) from the extruded insulin granules in islet portal blood to travel downsteam to α-cells, that is the active principle suppressing glucagon secretion, not the insulin molecule itself. On the other hand, Cooperberg and Cryer have now demonstrated that systemic intravenous infusion of a zinc-free insulin preparation in type 1 diabetic humans suppressed glucagon levels and that switching off the zinc-free insulin infusion during hypoglycemia activated glucagon secretion. These data clearly confirmed their hypothesis.

An essential consideration is whether confirmation of a hypothesis using one paradigm necessarily disproves an antithetical hypothesis using another paradigm. Would that science were so simple! A comparison of the two studies (4,5) turns up obvious differences (rats vs. humans, anesthesia vs. no anesthesia, and systemic vs. retrograde intrapancreatic venous infusions). There are other more complex methodological problems, such as absence of confirmation that the zinc-free insulin infused intravenously in the antecubital vein of humans was still zinc-free by the time it underwent circulation in zinc-containing blood and through zinc-containing tissues before it reached the pancreatic artery and α-cells. Another consideration is that regulation of α-cells in this human study might have been due to effects of the zinc-free insulin infusion on the central nervous system, which is known to directly regulate glucagon secretion (3). What is left unexplained by the human studies is why zinc-free insulin was ineffective in the animal studies. Clearly, the infusion technique via the pancreatic artery that we used in the animal studies, which provided intimate contact between the infusate of zinc-free insulin and α-cells, cannot be used in humans. So, as often happens when comparing animal studies and human studies, more work and deeper thought must be expended before the two data sets can be reconciled. Put another way, scientists who respect and believe each others' data not infrequently disbelieve their hypotheses—which certainly keeps us busy and hard at work . . . a good thing in general, and specifically a good thing for the current resurgence of interest in glucagon research.

But, in closing, one might ask, "Who cares?" Of what value is raising new basic questions in physiology or any

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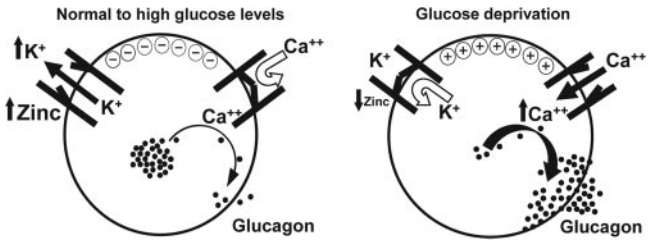


**FIG. 1. Regulation of glucagon secretion by zinc. *Left panel*: α-cell electrical and hormonal status in states of physiological and elevated glucose conditions. β-cells release zinc and insulin hexamers into the intraislet periportal circulation. Zinc dissociates from insulin and reaches downstream α-cells where it binds to and opens the $K_{ATP}$ channels. $K^+$ ions leave the cell and hyperpolarize the α-cell, thus preventing voltage-dependent calcium channels from opening. Glucagon granules are not mobilized and remain stored inside the cell. *Right panel*: When blood glucose levels decrease in response to exogenous insulin, β-cell insulin and zinc secretion decrease as well. $K_{ATP}$ channels on α-cells close, $K^+$ remains in the cell, and the α-cell depolarizes, which induces calcium channels to open, and calcium enters the cell. Intracellular calcium rises, which induces glucagon exocytotic granules to migrate to the plasma membrane where they fuse and release glucagon into the portal venous system. (Reproduced from Slucca et al. [6]).**

branch of science when a pragmatic clinical fact is, after all, a fact pure and simple. Insulin suppresses glucagon. Benjamin Franklin is reputed to have made a quip in which he defended scientific inquiry with a gentle smile and an alternative question, "Of what possible value is a newborn infant?"

## ACKNOWLEDGMENTS

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