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# How Glucagon Impacts Type 1 Diabetes and Vice Versa

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# How Glucagon Impacts Type 1 Diabetes and Vice Versa

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Glucagon is such an important hormone when it comes to blood glucose management in everyone—and it both impacts and is impacted by type 1 diabetes (T1D). A recent mini-review in *Physiological Reports* (1) focused on altered glucagon responses brought up some interesting points that are worth discussing further.

We have known for a while that people with T1D have blunted or absent glucagon release when their blood glucose levels drop too low (2, 3). The five glucose-raising hormones—of which glucagon is one—are released and regulated by a variety of metabolic stressors like fasting, exercise, anxiety, illness, and more. In adults with T1D, even a single prior hypoglycemic event or a workout can blunt the hormonal response (including glucagon, epinephrine, and more) to the next low the same day or the next (4-6). Even in adults without diabetes, several bouts of hypoglycemia can impact the hormonal responses to the next low somewhat; however, their glucagon release is normal (7). So, why is glucagon so impacted by T1D and how?

In answering this, let's revisit the main points of the recent mini-review (1):

- The regulation of pancreatic alpha cells leading to the release of glucagon is complex and may involve several feedback loops (where the rise and fall of things can interplay).
- Glucagon secretion from alpha cells is regulated by amino acids (the building blocks of protein), glucose (directly and/or indirectly), the central (autonomic) nervous system, incretins (gut hormones released into the blood after eating that stimulate insulin release), and signaling from beta and delta cells in the pancreas.
- During hypoglycemia, glucagon signals the liver to release glucose, which is does either by breaking down glycogen or creating new glucose from precursors (like amino acids).
- Pancreatic alpha cells are less responsive to changes in blood glucose than they are to certain amino acids; ones like alanine can cause a greater release of glucagon.
- Glucagon release during hypoglycemia is absent in individuals with T1D, but it still responds to many other stimuli including fasting, physical and mental stress, and exercise, all of which may rely on different mechanisms to release glucagon.
- Whatever is causing the absent glucagon secretion in T1D in response to hypoglycemia appears to reside within the pancreatic islets (of Langerhans) themselves.

- Abnormal glucagon secretion is not confined to hypoglycemia as individuals with T1D secrete extra glucagon after meals, which can contribute to insulin resistance.

As I discussed in a recent article, part of why glucagon release is altered in T1D is the lack of insulin in the circulation around the liver when insulin has to be delivered under the skin or inhaled. Functioning beta cells normally make insulin while the alpha cells of the pancreas make glucagon, but T1D removes the insulin release, thus altering the one typical check and balance on glucagon. Both a lesser storage of glycogen in the liver and an excess release of glucose after meals and overnight is the result.

However, as the mini-review reveals, the interactions and feedback loops are potentially a lot more complicated than that. Even youth with T1D have impaired plasma glucagon responses to hypoglycemia during their first year after diabetes onset, and older individuals with T1D still making a little of their own insulin also have defective and absent glucagon responses to hypoglycemia (8). The mini-review also suggests that the absence of glucagon secretion after hypoglycemia is irreversible and specific to lows since other stimuli—including administration of amino acids, insulin withdrawal, exercise, and more—can cause glucagon release. Perhaps this is why doing some high-intensity (glucagon-releasing) exercise often raises blood glucose or can be used to manage blood glucose during activities (9, 10).

So, is there anything people can do to compensate for the lack of glucagon release during blood glucose lows? Maybe when glucose goes low, doing a short sprint can help. Also, consuming some amino acids (via protein) may improve their glucagon responses and how well they can think during lows (11). Some groups are working on creating mini-dosing with glucagon with a pen (like an insulin pen but with glucagon in it). Whatever the answer, it is abundantly clear that anyone with T1D needs a workaround to raise glucagon by other means to treat hypoglycemia until a cure for diabetes is found.

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