Targeting the brain for the treatment of type 1 diabetes

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Michael W. Schwartz, MD, explains the role played by the brain as a cause of elevated blood sugar and related metabolic derangements in type 1 diabetes, and how therapeutic targeting of this brain system can eliminate the need for insulin therapy in animal models

What is type 1 diabetes?

There are two primary forms of diabetes, referred to as type 1 and type 2. While the latter is associated with obesity and is more common in adults, type 1 diabetes (T1D) is an autoimmune disease that typically begins in childhood. The disease is caused by an immune attack on the cells that make the hormone insulin, known as pancreatic beta cells. Apparently, the immune system misidentifies these beta cells as foreign invaders and proceeds to destroy them. The resulting state of severe insulin deficiency, if left untreated, is incompatible with life. Indeed, afflicted patients were condemned to an early death until insulin was discovered in the early 1920s. It is no surprise, therefore, that the discovery that insulin prolongs the life of afflicted patients was heralded as a miracle and, in 1923, was rewarded with a Nobel Prize. To this day, T1D simply cannot be treated without insulin – or so we thought.

How does insulin lower the blood sugar level?

Pancreatic beta cells are equipped with a specialized system for sensing glucose, the primary sugar in the bloodstream, and a key source of fuel for cells and tissues throughout the body. Detection of a rising blood glucose level by this glucose-sensing system in beta cells triggers the secretion of insulin into the circulation. Insulin, in turn, lowers the blood glucose level in two ways: by reducing glucose entry into the blood (primarily from the liver) and promoting its uptake out of the blood (into tissues such as muscle, heart, and fat cells [adipocytes]). As blood glucose levels begin to fall, so too does insulin secretion, closing a negative feedback loop.

What else does insulin do?

Insulin plays another role that, while less widely recognized, is crucial to our understanding of ‘diabetic ketoacidosis,’ the most lethal consequence of untreated T1D. This condition results from unrestrained mobilization of glucose and other fuels that effectively flood the bloodstream (discussed below). Because insulin prevents this from happening, even when present at very low levels, it does not occur except in patients with

diabetes. Stated differently, insulin's function to prevent unrestrained fuel mobilization is crucial to survival because diabetic ketoacidosis occurs when insulin is unable to perform this function.

How is this fuel mobilization process governed?

In some ways, diabetic ketoacidosis can be viewed as a pathological extension of the normal adaptive response to fasting. When there is no longer any food remaining in the GI tract, the energy needs of virtually all tissues in the body must still be met, namely, by mobilizing fuels from within the body. These fuels include glucose and ketones, which are released from the liver, and free fatty acids and glycerol, which are mobilized from stored fat. Failure to mobilize these fuels when they are needed can threaten survival, but excessive or unrestrained fuel mobilization can also have catastrophic consequences.

So, how does the body ensure that fuels are mobilized in amounts that meet but do not exceed ongoing bodily requirements? This balancing act is achieved by a kind of Kabuki dance between the brain, which orchestrates fuel mobilization when energy stores are threatened, and the pancreas, which secretes enough insulin into the bloodstream to keep things from spinning out of control (returning to the flood analogy, the brain and pancreas are the 'up' and 'down' levers on the dam's floodgate).

What does all this have to do with type 1 diabetes?

Because the complete absence of insulin releases the brake on fuel mobilization, the circulation becomes flooded with glucose, ketones (released from the liver as ketoacids), free fatty acids, and glycerol, i.e., ketoacidosis. The underlying process is essentially identical to what occurs during fasting, except that because the brake normally provided by insulin is missing, there's no way to close the floodgate.

If untreated, diabetic ketoacidosis causes dehydration, electrolyte disturbance, and destabilization of the body's carefully controlled acid-base balance. In its effort to respond to this very stressful constellation of events, the brain mistakenly turns on the secretion of adrenaline, which has the unfortunate effect of further activating fuel mobilization. This vicious cycle cannot be broken without insulin – or so we thought.

Where does the brain fit in?

As noted above, the brain's ability to respond when fuel stores are threatened is essential for survival. But how is this message delivered to the brain? Here's the crazy part: the brain relies on the detection of insulin and another hormone called leptin (made by fat cells) to gauge the amount of stored fuel that is available. When these two hormones are present at sufficiently high levels, the brain will not perceive fuel deficiency, regardless of how much-stored fuel actually exists. Conversely, the brain perceives the absence of these hormones as an urgent, 'all hands on deck' situation requiring maximal fuel mobilization.

Complicating matters further, leptin production is dependent on insulin.
So, in untreated T1D, insulin deficiency rapidly causes leptin deficiency, and the brain gets busy mobilizing fuel. And because the brake normally provided by insulin is missing, the circulation is soon flooded with glucose, ketoacids, fatty acids, and glycerol – diabetic ketoacidosis.

Targeting the brain to treat T1D

How do we know this scenario is true? Because in animal models of T1D, this vicious cycle can be blocked by silencing neurons that trigger fuel mobilization (located in a brain area called the ventromedial hypothalamic nucleus). Stated differently, if the brain is unable to respond to the perception that fuel stores are depleted, diabetic ketoacidosis is stopped in its tracks.

Remarkably, related work in animal models has shown that T1D can be rescued by infusing small amounts of leptin directly into the brain. It's as if the brain, under the influence of leptin, says, "No need to mobilize fuel here!" and the powerful cascade of metabolic decompensation described above simply fails to materialize. ***Even more impressive is that in these animals, the brain not only lowers the blood sugar level but also restores normal control of blood sugar without the need for insulin or frequent blood sugar monitoring – something previously considered impossible.***

Implications for the future treatment of type 1 diabetes

The profound implications of these findings have motivated a proposed human study to formally test whether leptin infusion into the brain can normalize blood sugar in T1D without the need for insulin. A positive outcome from this study would open entirely new avenues for the treatment of this disease – without the burden of insulin therapy (and the ever-present and dangerous risk of insulin-induced hypoglycemia) or regular blood sugar monitoring.