Hypoglycemic Detection at the Portal Vein
Absent in Humans or Yet to Be Elucidated?

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With the advent of more intensive glucose management, hypoglycemia has emerged as a primary limitation in the treatment of insulin-dependent diabetes. It is now recognized that the increased incidence of hypoglycemia derives not only from imperfect insulin replacement but also from impaired counterregulation and hypoglycemic unawareness (1). The latter two observations have led to a renewed interest in the mechanisms underlying hypoglycemic detection. As a result of intensive research over the past decade, the traditional hypothalamocentric model of glucose sensing has been replaced with one emphasizing a widespread neural network involving numerous aspects of the central nervous system, as well as peripheral sensory input. Thus, in addition to the ventromedial hypothalamus, the paraventricular hypothalamus, arcuate nucleus, area postrema, nucleus of the solitary tract, and dorsal motor nucleus all appear to play important roles (2,3). In the periphery, important glucose sensors have been identified in the carotid bodies (4), gastrointestinal tract (5), and portal-mesenteric vein (6). For hypoglycemic detection, the glucose sensors of the portal-mesenteric vein have garnered the most attention. Animal studies have repeatedly demonstrated that blocking portal glucose sensing via portal glucose infusion (7) or denervating the portal vein (8) substantially suppresses the sympathoadrenal response to hypoglycemia. More recently, it was shown that portal-mesenteric vein glucose sensing is particularly important when hypoglycemia develops slowly and, under these conditions, modulates over 90% of the sympathoadrenal response to hypoglycemia (9).

While portal vein glucose sensing appears to be conserved across several species (7,9,10), demonstration of consistent findings in humans has proven elusive. An obvious limitation for human studies is the lack of direct access to the portal vein, which severely constrains experimental interventions. To circumvent this problem, Rossetti et al. (11) employed an oral glucose load to elevate portal glucose concentration during a hyperinsulinemic-hypoglycemic clamp. Oral glucose was administered before the clamp to establish a portal-arterial gradient before the onset of hypoglycemia. Hypoglycemia was then allowed to develop slowly—an important aspect of this study considering the previously mentioned animal experiments and the clinical relevance. Despite these efforts, they observed no effect of the oral glucose load on counterregulatory or symptomatic responses to hypoglycemia. The authors conclude that the portal glucose sensor plays no significant role in hypoglycemic detection for humans. This is not the first time such an approach has been employed in an attempt to elucidate the potential role of portal glucose sensing in humans (12–14). While all previous reports demonstrated a significant impact of an oral glucose load on the hormonal responses to hypoglycemia, results have been anything but consistent.

In addition to the negative findings for Rossetti et al., oral glucose during a hyperinsulinimic-hypoglycemic clamp has been shown to suppress (14), augment (13), and initially suppress and then augment (12) the sympathoadrenal response to hypoglycemia in humans. As noted by Rossetti et al. (11), subtle differences in the respective protocols (e.g., rate of fall in glycemia, the timing and/or mass of the oral glucose load) may explain some of the observed differences. However, critical to the interpretation of these findings is the assumption that the oral glucose load actually elevates the portal vein glucose concentration above the glycemic threshold for the duration of the experiment. Because portal glucose concentration cannot be measured directly in humans, it must be based on estimated rates of glucose appearance and portal blood flow. A number of sophisticated modeling approaches employing multiple tracers have been developed for estimating the appearance of an oral glucose load (15,16) but, to date, have not been used in studies of portal glucose sensing in humans. Further confounding estimates of portal glucose concentration is the wide range of values reported for human portal blood flow, ($10–18\ ml \cdot kg^{-1} \cdot min^{-1}$ [17]), which may increase substantially in response to oral glucose ingestion.

Alternatively, the disparate findings for these human studies may result from the complexity of introducing an oral glucose load, as opposed to simply infusing glucose in the portal vein (Fig. 1). As noted in one recent review (3), glucose sensing of an oral glucose load begins in the oral cavity and continues in the gut, the portal-mesenteric vein, and, finally, the systemic circulation. In particular, the gastrointestinal tract is now recognized as an important locus for glucose detection. The ability to sense glucose in the luminal contents of the gut not only allows for intrinsic control but also provides important sensory feedback to the central nervous system via extrinsic afferent nerves and blood-borne peptides (5). Many of the peptides secreted by the enteroendocrine cells of the gut (e.g., glucagon-like peptide 1 [GLP-1], glucose-dependent insulinotropic peptide, and peptide YY) are now well recognized for their impact on glucose and energy homeostasis. While considerable insight has been gained regarding their role

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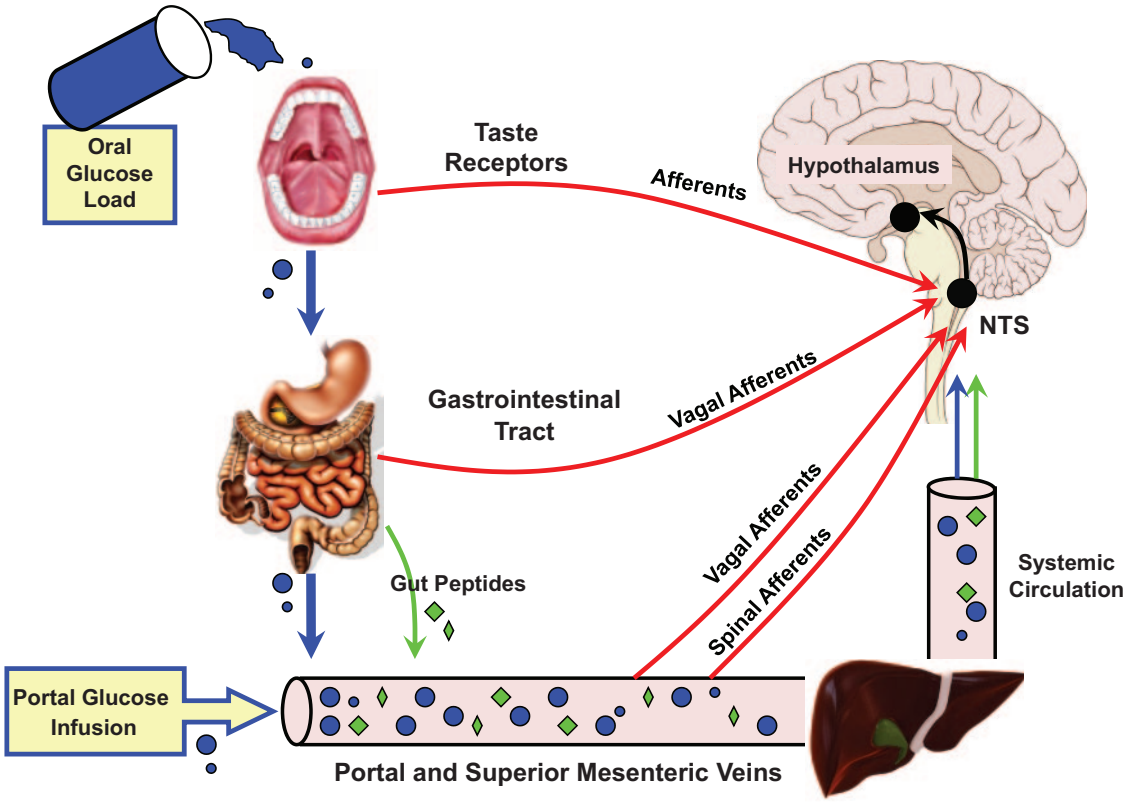

FIG. 1. Glucose sensory input: For an oral glucose load, afferent inputs include the oral cavity, gastrointestinal tract, and portal-superior mesenteric veins (vagal and spinal), all of which converge on the nucleus of the solitary tract (NTS). In addition, gut peptides released by an oral glucose load can activate sensory neurons in the gastrointestinal tract and portal vein, as well as activate the central nervous system directly. For portal vein glucose infusion during a hyperinsulinimic-hypoglycemic clamp, input is restricted to glucose sensing afferents in the portal-mesenteric vein.

in hyperglycemic and euglycemic states, their impact under hypoglycemic conditions is poorly understood and not always obvious. For example, the ability of GLP-1 to suppress glucagon secretion is apparently lost under hypoglycemic conditions (18). Also, the vagal glucose-sensitive afferents of the portal vein, which are inhibited by glucose, are activated by GLP-1 (19), a peptide released in response to oral glucose (5). While vagal afferents are apparently not involved in hypoglycemic detection at the portal vein (20), if the spinal glucose-sensitive afferents (8) demonstrate similar reciprocal responses to glucose and GLP-1, this might explain some of the observed disparity in these human studies. It is also important to recognize that all peripheral glucose sensory input, i.e., gut, portal-mesenteric, and gustatory, converges on the nucleus of the solitary tract, where local glycemic conditions are likely to impact on the eventual efferent response (3).

Given the marked disparity in findings for humans, it is perhaps premature to conclude that hypoglycemic detection at the portal vein is not important for humans as proposed by Rossetti et al. (11). Beyond the substantial technical obstacles faced by such studies, there is the fundamental question of whether glucose introduced to the portal circulation via the gut is equivalent to a direct glucose infusion. As our understanding of the neural network underlying glucose sensing improves, it is likely that at least some of the apparent differences in human and animal hypoglycemic detection will be resolved.

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