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Sensing hypoglycemia: the ventromedial hypothalamus

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Hypoglycemia as a limiting factor in the treatment of diabetes mellitus with insulin was apparent even before the hormone was administered to patients. A passage in a biography of Banting notes: 'The pace picked up as Banting and Best began adjusting extract... On December 2, 1921 ... the injections threw the longevity dog, number 27, into repeated convulsions.... It finally died, killed by the extract.' (1). It is acknowledged that the organism has an intricate control mechanism to regulate glycemic levels within a narrow range; insulin as the hypoglycemic agent, and an array of mechanisms as a control against potentially fatal hypoglycemia. The central nervous system (CNS) plays a major role in sensing glucopenia and triggering hormone release during imminent hypoglycemia (2–4). As previous studies have demonstrated, selective perfusion of the cranial arteries with glucose abrogate counterregulation elicited by insulin-induced hypoglycemia, but hepatic glucoreceptors have also been reported to sense hypoglycemia and to activate the sympathoadrenal system (5). This mechanism is regarded to be secondary to the dominant role of the CNS.

Several lines of evidence localize the specific region which is responsible for activation of counterregulatory mechanisms to the ventromedial hypothalamus (VMH): focal lesioning of this region abolishes the hormonal response to systemic hypoglycemia (6) and production of local hypoglycemia by perfusion of 2-deoxy-glucose into the VMH is able to trigger the release of counterregulatory hormones despite systemic normoglycemia (7). Alternatively one may ask: when peripheral hypoglycemia is induced by insulin, does continued supply of glucose to the VMH prevent the peripheral neurohumoral counterregulatory response? This question has been studied in a recent and most remarkable piece of work in which the authors were able to demonstrate the central role of the VMH in sensing and responding to hypoglycemia (8). Indeed, they showed that in awake rats, local perfusion of glucose to the VMH by a microdialysis technique blocks counterregulation during systemic hypoglycemia (8). Most of the counterregulatory responses were abrogated. At this point it is important to note that counterregulatory mechanisms normally come into play well before hypoglycemia ensues (4), such that it may be assumed that the VMH is usually active in physiologic situations. Glucagon – an important counterregulatory hormone – is an exception since it appears to be regulated normally regardless of the state of the VMH, suggesting that ambient glucose levels directly or indirectly regulate glucagon secretion independent of the above mentioned mechanisms.

Let us now turn to the pathophysiology of hypoglycemia when it arises from prolonged fasting or strenuous exercise. During these situations circulating ketone bodies and lactate levels increase severalfold. In both situations certain signs and symptoms of hypoglycemia are diminished. In experimental situations, hyperketonemia and hyperlactacidemia lowered responses to hypoglycemia in humans (9–11). One of these studies reported that lactate infusions protect cerebral function during hypoglycemia suggesting a potential therapeutic application of lactate during hypoglycemia in patients with insulin overdosage (11). Another important finding of these studies is that, during glucopenia, ketone bodies and lactate can serve as an immediate energy substitute to the CNS.

Future studies will reveal whether – similar to glucose – local infusion of ketone bodies and lactate to the VMH will abrogate the hormonal response to hypoglycemia. Moreover, the sensing at the molecular level of hypoglycemia and/or adequate alternative energy supplies to the brain remain to be investigated.

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