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Chemical Dissection of Brain Glucoregulatory Circuitry

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INTRODUCTION

Glucose is the essential substrate for brain energy metabolism *(1)*. Although glycogen, the major storage form of glucose, contributes dynamically to brain energy metabolism, it is present in very limited quantities *(2)*. Thus, the brain requires continuous delivery of glucose by the blood. Clearly, then, the control of blood glucose is of fundamental importance for brain metabolism. Work in our laboratory has focused on the neural organization of controls that maintain blood glucose concentrations. The immunotoxin, antidopamine β-hydroxylase (anti-DβH) conjugated to saporin (anti-DβH-sap) *(3–7)*, has been an invaluable tool for establishing the importance of hindbrain catecholamine neurons for coordinated arousal of critical behavioral, autonomic, and neuroendocrine responses to glucose deficit. The goal of this review is to describe our use of anti-DβH-sap in demonstrating the essential roles of hindbrain catecholamine neurons in glucoregulation.

To date, we have concentrated primarily on three key responses to a glucose deficit (glucoprivation). These are increased adrenal medullary catecholamine secretion, increased corticosterone secretion, and stimulation of food intake. These responses can be readily elicited by hypoglycemic doses of insulin or by central or systemic administration of nonmetabolizable glucose analog, such as 2-deoxy-D-glucose (2DG) or 5-thio-D-glucose (5TG) *(8–12)*, which competitively inhibit intracellular utilization of glucose *(13,14)*. Adrenal medullary catecholamine secretion increases hepatic and muscle glycogenolysis, decreases insulin secretion, and increases lipolysis.

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These responses almost immediately elevate blood glucose while reducing its uptake by peripheral tissues. Corticosterone promotes gluconeogenesis by several mechanisms and directs peripheral metabolism away from glucose and toward utilization of fat. Finally, glucoprivic stimulation of food intake elevates blood glucose directly on absorption of ingested carbohydrates and provides calories for replenishment of depleted energy stores.

Control of Glucoregulatory Responses by Hindbrain Glucoreceptor Cells

The first and most definitive attempts to localize glucoreceptor cells involved in systemic glucoregulation focused on those controlling feeding and adrenal medullary responses. Early cannula-mapping studies showed that glucoprivic feeding could be elicited by injection of 2DG into the forebrain ventricles but not by localized glucoprivation of a variety of forebrain tissue sites *(15,16)*. Later studies using chronically maintained decerebrate rats showed that neural circuits sufficient to detect glucoprivation and stimulate hyperglycemic and feeding responses are present within the midbrain or hindbrain *(17,18)*. Also pivotal were experiments showing that acute obstruction of the mesencephalic aqueduct completely blocked feeding and hyperglycemic responses to lateral ventricular, but not to fourth ventricular, 5TG injection *(19),* demonstrating that glucoreceptors controlling feeding and hyperglycemic responses most likely are restricted to the hindbrain.

In more recent cannula-mapping studies, we have been able to localize glucoreceptors controlling feeding and hyperglycemic responses to distinct areas of the ventrolateral and dorsomedial hindbrain (Fig. 1) *(20).* We have also found that corticosterone secretion and glucagon secretion can be elicited by localized glucoprivation of these same hindbrain sites but not by localized glucoprivation of the hypothalamus (unpublished data).

Although the phenotype of hindbrain glucoreceptor cells and the transduction mechanism by which they monitor glucose availability are not yet known, the cannulation maps indicating their localization within specific hindbrain regions has allowed us to make substantial progress in defining the circuitry through which they evoke glucoregulatory responses.

The Neural Circuitry for Glucoregulatory Responses Includes Hypothalamic and Spinal Sites

Although receptor cells that elicit glucoprivic feeding and corticosterone secretion are not located in the hypothalamus, there is abundant evidence that the hypothalamus contains circuitry important for these responses. Glucoprivic feeding is impaired by acute administration of neuropeptide Y (NPY) antibodies into the paraventricular nucleus of the hypothalamus