

TITLE

**The role of
hypothalamic
glucose-inhibited
neurons in
hypoglycaemia
detection and counter
regulation**

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Tight glycemic control with intensive insulin therapy significantly improves diabetic-related complications. However, it has a major side effect: hypoglycemia. Recurrent hypoglycemia (RH) impairs the neuro-endocrine counter-regulatory responses (CRR) that normally restore euglycemia. This impairment is a component of the life threatening syndrome known as hypoglycemia-associated autonomic failure (HAAF). It is clear that the central nervous system plays a key role in hypoglycemia detection and the regulation of the CRR. However, the mechanisms by which the brain senses glucose and how these mechanisms are impaired during HAAF are not clearly understood. Specialized neurons whose activity is regulated by changes in ambient glucose stand out as prime candidates for central glucose sensors. These neurons exist in key areas involved with the regulation of glucose homeostasis. One such region is the ventromedial hypothalamus (VMH). The VMH detects decreases in blood glucose concentration and initiates the CRR. We have recently shown that nitric oxide (NO) produced in the VMH in response to hypoglycemia is necessary for both neuronal glucose sensing and full initiation of the CRR through a mechanism involving the NO receptor soluble guanylate cyclase (sGC). However, when NO is produced in the presence of reactive oxygen species, sGC undergoes S-nitrosylation. S-nitrosylation of sGC leads to decreased affinity for NO and impaired NO signaling. Insulin-hypoglycemia increases VMH ROS levels. Moreover, prevention of ROS generation during RH prevents HAAF. This talk will focus on the role of NO and itrosylation in impaired glucose sensing and CRR initiation.

Biography

Dr. Vanessa H. Routh received her Ph.D. from the University of California at Davis in 1993 in Physiology/Neurophysiology. She joined the faculty at the New Jersey Medical School in 1998, received tenure in 2003 and was promoted to Full Professor in 2010. She is the author of over 40 papers related to central nervous system glucose sensing mechanisms in health and diabetes and is an editorial board member for the Journal of Diabetes and Metabolism. She is serving or has served on grant review panels for the NIH, Juvenile Diabetes Research Foundation and the Veterans Administration.