

Hypothalamic Insulin Signaling is Required for Inhibition of Glucose Production

Insulin has many energy modulating actions that take place in the hypothalamus, such as inhibition of feeding. The investigators studied the effects of infusing insulin, an insulin mimetic, and inhibitors of insulin action. Infusion was done in the intra-third cerebral ventricle (ICV). Hepatic glucose production and peripheral glucose consumption were determined. Steady state of serum insulin concentrations were achieved by using systemic pancreatic-insulin clamps.

ICV infusion of insulin/insulin mimetic at basal insulin concentrations led to a 7-fold increase in glucose infusion rate to maintain euglycemia. Thus, ICV glucose enhanced peripheral insulin action. Employing radiolabeled glucose and kinetic glucose studies, the investigators demonstrated that ICV insulin decreased the rate of hepatic glucose production by 40+% while not altering peripheral glucose consumption. Inhibition of insulin action in the hypothalamus by co-infusion of insulin antibodies or an antisense disrupter of insulin receptor synthesis antagonized the effect of insulin on glucose production. Further studies demonstrated that the intracellular mechanism(s) through which hypothalamic insulin exerted its effect on glucose production involved the phosphoinositide-3-kinase signal transduction pathway and ATP sensitive potassium channels. However, the manner in which

hypothalamic insulin impaired hepatic glucose production was not identified by these studies. The authors suggest that hypothalamic insulin (as well as other factors such as leptin and melanocortins) may monitor and modulate exogenous energy intake relative to endogenous energy consumption. Failure of hypothalamic insulin function may lead to peripheral insulin resistance and may be a factor in the pathogenesis of the dysmetabolic syndrome and type 2 diabetes mellitus.

Obici S, et al. *Nature Med* 2002;8:1376-1382.

Editor's Comment: *The physiological importance of insulin action within the central nervous system is well described in the content of this manuscript. The demonstrations reported open yet another site at which a metabolic error may lead to clinical illness. It is crucial to determine the specific mechanisms by which the hypothalamic action of insulin is recognized at the hepatic level and to develop a method(s) by which one may assess hypothalamic insulin function in the intact human.*

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Hyperzincemia and Hypercalprotectinaemia: A New Disorder of Zinc Metabolism

The authors describe five patients (including a mother and her son) who had a multidimensional illness comprised of recurrent infections, rash, arthritis/vasculitis, hepatosplenomegaly, and growth retardation in infancy and childhood. Although these findings were consistent with zinc deficiency, the patients had marked hyperzincemia due to its binding to greatly elevated amounts of a zinc-binding protein called calprotectin. Calprotectin is a calcium and zinc binding protein complex of two S100 plasma proteins termed S100A8 and S100A9 (also termed proteins MRP8 and MRP14, respectively). It is present in the cytosol of phagocytes and is released into plasma as phagocytic neutrophils are destroyed. In these patients, plasma zinc concentrations were 5-10 times higher than the upper normal range (18 $\mu\text{mol/L}$), while calprotectin concentrations were 1000 fold greater than the upper normal value (850 $\mu\text{g/L}$), suggesting that free plasma zinc concentrations were likely to be low. Individual patients were anemic, thrombocytopenic, and had low numbers of monocytes and B lymphocytes.

Chromatographic analysis of S100A8 and S100A9 proteins was normal, suggesting no major mutations or post-translational modifications of calprotectin. Since there was no evidence of increased neutrophil turnover rate, the investigators hypothesized: (1) that the increased plasma concentrations of calprotectin reflected its decreased rate of degradation; (2) that the patients were zinc deficient because of the high affinity of calprotectin for zinc; and (3) that calprotectin itself may have been cytotoxic to neutrophils and other tissues.

Sampson B, et al. *Lancet* 2002;360:1742-1745.

First Editor's Comment: *The new syndrome comprises patients with an apparent "functional zinc deficiency" despite high plasma concentrations of this element. Although "free zinc" concentrations were not measured, they were thought to be low. In addition, the authors did not report the effects of a trial of therapy with supplemental zinc in these subjects. Thus, the*