Zinc Regulation of Food Intake: New Insights on the Role of Neuropeptide Y

The role of neuropeptide Y (NPY) in feeding behavior and zinc deficiency–induced anorexia has been controversial because hypothalamic NPY levels are elevated in both zinc deficiency and food restriction. A recent report shows that while NPY is released from terminals in the paraventricular nucleus of the hypothalamus of food-restricted animals, this release is significantly impaired in zinc-deficient animals. Zinc deficiency may therefore cause anorexia by inhibiting the release of NPY that is required for receptor activation.

Key words: anorexia, eating disorders, zinc, NPY, hypothalamus

© 2003 International Life Sciences Institute

Appetite and weight loss have been associated with cancer, aging, and various affective disorders, including bipolar disorder and major depressive disorder. Anorexia nervosa (AN), a well known eating disorder, is also characterized by reduced food intake and weight loss, and is accompanied by an intense fear of gaining weight, disturbances in body image, and altered perceptions of weight and body size. The prevalence of AN and the associated eating disorder bulimia nervosa has been estimated to be between 1 and 4% of the population, with 90 to 95% of cases occurring in females, largely in 15- to 24-year-olds. The clinical consequences of AN, including hormonal alterations and amenorrhea, dermatologic abnormalities, electrolyte imbalances, osteoporosis, and cardiac arrhythmias, can be serious and even life threatening.

Because the neurobiologic regulation of appetite is complex, we do not yet understand the mechanisms that are responsible for the development of anorexia. This unfortunate gap in our knowledge limits treatment not only of AN, but also of other clinical situations (e.g., cancer) in which loss of appetite may complicate treatment and contribute to increased mortality. Investigators have recently been exploring the possible role of micro-nutrients in the regulation of appetite and the development of AN. In one study, women between the ages of 18 and 35 with AN were significantly more likely than healthy, age-matched control subjects to have intakes below the recommended dietary allowance for riboflavin, niacin, vitamin B₆, vitamin B₁₂, phosphorus, and selenium. Zinc (Zn) deficiency has also been identified as a possible contributor to loss of appetite. Urinary Zn excretion in patients with AN was approximately half that of controls. Zinc supplementation has been shown to correct Zn excretion rates and serum Zn levels in patients with AN, and to enhance weight gain in double-blind clinical trials in which subjects were randomized to zinc treatment and placebo control groups. Others have reported no differences in serum Zn levels, suggesting that Zn deficiency cannot be the cause of all cases of AN. One study even reported serum Zn levels in AN that were 123% of control subjects. In the same subjects, however, activities of the serum Zn-dependent enzymes lactate dehydrogenase and alkaline phosphatase were reduced in AN by 38% and 21%, respectively. Thus, a shift in Zn pools could result in normal serum values, whereas other functional measures of Zn activity are impaired. Zinc deficiency may also be a sustaining factor in which the deficiency occurs secondary to self-starvation. The difficulty in determining a causative relationship between Zn deficiency and reduced food intake may be in part due to the lack of sensitive measures of Zn status in humans. This is especially problematic in mild and moderate Zn deficiency in which the typical clinical measures of urinary and serum zinc are likely to be inadequate to assess Zn status.

Because dietary Zn can be tightly controlled in the laboratory, and more precise measures of zinc status (i.e., femur Zn) can be made, the relationship between Zn deficiency and appetite in the laboratory rat is much more clear. When young rats are provided a diet low in Zn, reductions in total food intake are observed within approximately 3 to 5 days. Sustained Zn deficiency can
result in food intakes that are less than 50% of normal, and body weights that are abnormally low compared with Zn-adequate controls. Anorexia associated with Zn deficiency results in a characteristic feeding cycle in which rats will transiently increase their consumption every 3 or 4 days. Whereas Zn-adequate rats will generally consume food soon after the onset of the dark cycle, Zn-deficient rats appear to delay the timing of their first meal. They also eat fewer meals than Zn-adequate control rats. When Zn-deficient rats were given a choice between carbohydrate, fat, and protein, intake of fat and protein remained constant, whereas carbohydrate intake fell significantly. In fact, 100% of the reduction in food intake can be explained by a reduction in carbohydrate intake. Re-feeding with a Zn-adequate diet resulted in a reversal of carbohydrate intake within 1 day. During the first several days of re-feeding, protein intakes appeared to be transiently increased. Thus, Zn not only regulates food intake, but appears to regulate nutrient selection as well.

The mechanisms responsible for the role of Zn in food intake and macronutrient selection have been the subject of some controversy. Although investigators have examined the possible role of neurotransmitters and neuroendocrine substances such as norepinephrine, gamma-aminobutyric acid, dopamine, leptin, dynorphin, and galanin over the past two decades, a comprehensive picture has not yet emerged. Recently, the possibility that neuropeptide Y (NPY) participates in Zn-regulated feeding mechanisms was evaluated. This highly abundant neuropeptide is expressed in most regions of the central nervous system, including the cortex, hypothalamus, thalamus, olfactory bulb, amygdala, and hippocampus. It is also highly expressed in peripheral neurons of the sympathetic nervous system. NPY regulates a wide variety of physiologic functions including reproductive behavior, circadian rhythms, the cardiovascular responses, memory, and the response to stress. It is also known to be a powerful regulator of feeding behavior, and is a particularly good candidate for study in Zn deficiency and anorexia because it acts as an orexigen (i.e., stimulator of food intake) when administered centrally, is increased in the hypothalamus by food restriction, and appears to specifically stimulate carbohydrate intake.

Studies were therefore designed to test the hypothesis that Zn deficiency induces anorexia by preventing NPY gene expression and/or peptide synthesis. The initial report showed that NPY mRNA was elevated in the hypothalamus of Zn-deficient rats. After 3 weeks on a Zn-deficient diet, relative NPY mRNA abundance was more than 1.5-fold higher than Zn-adequate controls (P < 0.01), and 1.2-fold higher than pair-fed rats that were consuming the same amount of food as the Zn-deficient animals (P < 0.05). Despite the elevations in NPY mRNA, NPY peptide levels in the hypothalamus were not increased by Zn deficiency, suggesting that Zn deficiency impairs NPY translation. However, later work clarified the regulation of NPY translation by examining the effect of Zn deficiency in the arcuate nucleus (ARC) and paraventricular nucleus (PVN) of the hypothalamus. This anatomic distinction is important because NPY mRNA is synthesized in the ARC, but NPY peptide is abundant in the PVN. When these specific regions were examined, investigators found that not only did Zn deficiency increase NPY mRNA abundance in the ARC, but also NPY peptide levels in the PVN were 1.6-fold higher in Zn-deficient rats. This appeared to be the effect of reduced food intake rather than Zn deficiency, however, because pair-fed animals also had elevated NPY levels in the PVN.

The finding that NPY levels in the PVN are equally high in Zn-deficient and pair-fed rats initially called into question the role of NPY in Zn deficiency–induced anorexia, but when pair-fed rats are provided with food they immediately engage in feeding behaviors. Zn-deficient rats, despite high levels of NPY in the PVN, are anorexic. This suggests that Zn-deficient rats are insensitive to increases in NPY. Given the possibility of NPY resistance, this led to the reasonable hypothesis that NPY is unable to stimulate feeding behavior in Zn-deficient rats owing to a receptor abnormality preventing NPY binding, or to a defect in signaling downstream from NPY receptor binding. This hypothesis has now been tested; it appears that the central administration of NPY to Zn-deficient rats increases food intake. Increasing doses of synthetic NPY infused directly into the PVN 30 minutes before the onset of the dark phase normalized food intake, even when animals were fed the Zn-deficient diets for more than 3 weeks and were severely Zn deficient. Another group recently reported similar results. Whereas in this study feeding was not completely normalized, possibly because the peptide was infused intracerebroventricularly rather than directly into the PVN, NPY did induce feeding behavior in Zn-deficient rats. These two studies both suggest that NPY receptor mechanisms are intact in Zn-deficient animals.

So we are left with a question: Why are Zn-deficient animals anorexic despite normal increases in NPY and apparently functional receptor mechanisms? A recent study has shed some new and interesting light on this question by testing the hypothesis that anorexia persists in Zn-deficient animals because the deficiency prevents NPY release. Normally, NPY is co-released from terminals in the PVN with the catecholamine norepinephrine (NE). NE is a neurotransmitter that, similar to NPY,
participates in feeding behavior and carbohydrate intake. The effects of NPY on behavior are mediated by receptor binding. To date six different subtypes of NPY receptors have been identified (Y1–Y5 and y6). NPY also modulates the release and function of NE. Mechanisms of NPY function may therefore include independent receptor-mediated actions and neuromodulatory roles that regulate the function of other neurotransmitters such as NE.

To assess the possible role of Zn in these mechanisms, microdialysis (push-pull perfusion system) was used to measure changes in extracellular NPY and NE in the PVN of control, Zn-deficient, and pair-fed rats. At the onset of the dark phase, when feeding normally occurs, extracellular NE increased in control animals as expected. In pair-fed and Zn-deficient animals, however, there was no release of NE from PVN terminals. This suggests that the reduction in NE release is not specific to Zn deficiency and is not responsible for Zn deficiency–induced anorexia.

Measurement of NPY release from the PVN was more revealing. As expected, in pair-fed animals there was a marked increase in the release of NPY from the PVN during the hour before and the hour after the onset of the dark phase. In Zn-deficient animals, however, there were no significant increases in NPY release. Rather than disrupting NPY synthesis, processing, or receptor function as previously hypothesized, therefore, Zn deficiency appears to impair NPY release from the PVN. This is a significant step forward in our understanding of the Zn-dependent mechanisms that are responsible for feeding behavior and macronutrient selection. Clearly, the next step is to explore the role of Zn in the mechanisms that are responsible for the release of NPY from the PVN and possibly other terminals in the central nervous system. Given the long list of known NPY functions, and the possibility that Zn regulates NPY release, this work has potential impact on our fundamental understanding of the role of Zn in neurophysiology.
