Insulin and NPR-1 Neuropeptide Signaling Mutants Are Defective in the Enhanced Slowing Response Induced by Food Deprivation

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To identify mutants that might perceive a constitutive state of food deprivation, we screened for mutants that behave as if they had been food-deprived when well fed. Well-fed C. elegans animals that encounter a bacterial lawn slow their locomotion in the basal slowing response. Acutely food-deprived animals slow more upon entering a bacterial lawn, in the enhanced slowing response. Deletion of mod-5, which encodes a serotonin reuptake transporter, confers increased slowing on food in both conditions. Using a mod-5(n3314) deletion background, we screened for mutants that exhibited enhanced slowing in the well-fed state.

From this screen we isolated an allele of mrp-1 (multidrug resistance protein family), a member of a large family of ABC transporters. mrp-1 is the C. elegans ortholog of the human sulfonyleurea receptor SUR1, which attenuates ATP-dependent inward-rectifying potassium currents in pancreatic beta cells, thus stimulating insulin secretion. The SUR1/K\textsubscript{ir}6.x complex is sensitive to changing ATP/ADP levels and is thought to be an important component in glucose homeostasis in many cell types, including neurons. daf-2 encodes a C. elegans insulin-like receptor. Like mrp-1 mutants, daf-2(e1370) mutants display a constitutive enhanced slowing response in a mod-5(n3314) background, consistent with the hypothesis that both mutants perceive a constitutively food-deprived state. We propose that, analogous to the function of SUR1 in humans, mrp-1 may act as a metabolic sensor in the insulin signaling pathway in C. elegans.

Tangential to this study, we discovered that wild strain CB4856 has a greatly reduced enhanced slowing response and that this defect maps to the X chromosome. Work by DeBono et al. (Cell 94: 679-689, 1998) led us to identify npr-1 as the gene responsible for this modulation defect. npr-1 encodes a putative neuropeptide Y-like receptor. The mammalian neuropeptide Y receptor functions in energy homeostasis to stimulate increased food consumption in response to a deficit in stored energy. We postulate that npr-1 acts similarly in C. elegans and is involved signaling a food-deprived state. We are currently attempting to identify NPR-1 ligands involved in enhanced slowing and the circuit in which npr-1 acts in the enhanced slowing response.

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