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 sulfonylurea receptor SUR1, which attenuates ATP-dependent inward-rectifying potassium currents in pancreatic beta cells, thus stimulating insulin secretion. The SUR1/K_{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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