Genes Involved in Serotonergic Neurotransmission

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Wild-type animals that have been acutely food-deprived slow their locomotory rate upon encountering bacteria more than do well-fed animals. This behavior, called the enhanced slowing response, is partly serotonin (5-HT) dependent. Animals mutant for the 5-HT reuptake transporter gene *mod-5* slow even more than wild-type animals, presumably because 5-HT signaling is potentiated. We call this behavior the hyperenhanced slowing response. *mod-5* mutants are hypersensitive to immobilization by exogenous 5-HT. To identify additional genes involved in 5-HT signaling and possibly in the enhanced slowing response, we screened for suppressors of the 5-HT hypersensitivity of *mod-5* animals. We also used a candidate gene approach, testing for 5-HT resistance of strains containing deletions in genes that encode proteins similar to metabotropic 5-HT receptors.

We screened 105,000 genomes for suppressors of the 5-HT hypersensitivity of *mod-5* mutants. We isolated 26 mutants, which define at least 8 genes. 19 of these mutants also suppress the hyperenhanced slowing response of *mod-5* animals. We identified 7 alleles of *goa-1,* which encodes an alpha subunit of a G-protein, and two alleles of *mod-1,* a 5-HT-gated Cl^- channel. Both of these genes were known to suppress the 5-HT hypersensitivity and the hyperenhanced slowing response of *mod-5* mutants. In addition, we identified one allele of *eat-16*, an RGS (Regulator of G-protein Signaling) protein, one allele of a gene similar to bicarbonate transporters, and two alleles of a gene on LGIV. We are further mapping the mutations on LGIV and characterizing all mutants isolated for other defects to better understand the functions of the disrupted genes.

Using a candidate gene approach, we found that two independent deletions, *ser-4(ok512)* and *ser-4(n4577),* confer resistance to 5-HT and defects in the enhanced slowing response. *ser-4* encodes a metabotropic 5-HT receptor (Olde and McCombie, *J. Mol. Neurosci.*, 8: 53-62, 1997). Like other mutations known to disrupt the enhanced slowing response (*goa-1, mod-1, dgk-1* and *eat-16*), *ser-4* mutations suppress the hyperenhanced slowing response of *mod-5* mutants. These data suggest that *goa-1, mod-1, dgk-1, eat-16* and *ser-4* act postsynaptically to one or more 5-HT synapse(s) that mediate(s) the enhanced slowing response. We are now testing genetic interactions among these mutations to determine whether these genes act in the same or parallel pathways in the enhanced slowing response.