An Ionotrophic Serotonin Receptor and a Serotonin Reuptake Transporter Are Involved in Experience-Dependent Modulation of Behavior

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Hermaphrodites respond to the presence of a bacterial lawn by slowing their locomotion rate. Animals deprived of bacteria for 30 minutes exhibit enhanced slowing when they encounter a bacterial lawn. This modulatory response is mediated by serotonin (5-HT)¹. Mutations in mod-1 and mod-5 (modulation of locomotion defective) affect both the modulatory response and 5-HT neurotransmission¹, but in opposite manners.

mod-1(n3034) mutants display a dominant phenotype of reduced slowing in the modulation assay and 5-HT resistance in liquid assays of locomotion (exogenous 5-HT inhibits locomotion of wild-type animals). We have cloned mod-1 and found that it encodes a ligand-gated ion channel. Electrophysiological studies of MOD-1 in Xenopus oocytes show that the MOD-1 channel is an ion channel gated specifically by 5-HT and has a pharmacological profile distinct from its mammalian counterparts. Channels carrying the mod-1(n3034) missense mutation behave in a dominant-negative manner in oocytes, as predicted by the phenotype of two mod-1 deletion mutants.

mod-5 encodes a protein similar to mammalian 5-HT reuptake transporters, which are the proposed sites of action of the tricyclic antidepressants and the selective 5-HT reuptake inhibitors (SSRIs), such as Prozac. A defect in 5-HT re-uptake is consistent with the characteristics of mod-5 mutants: defective 5-HT loading of the NSM neurons², more pronounced slowing than the wild type in the modulatory response, and hypersensitivity to exogenous 5-HT in liquid assays of locomotion.

An understanding of how mod-1 and mod-5 function within a neural circuit should provide insights into how the processes of ionotrophic 5-HT neurotransmission and reuptake are involved in experience-dependent modulation of C. elegans behavior. Small molecules that manipulate 5-HT neurotransmission include drugs of major importance in the clinic. Our studies of the 5-HT pathway in C. elegans may define analogous human neural circuits and may suggest novel means of manipulating such circuits.