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

R Ranganathan[1], SC Cannon[2], HR Horvitz[1]

[1] HHMI, Dept. Biology, MIT, Cambridge, MA 02139.
[2] Dept. Neurobiology, Harvard Medical School, Boston, MA 02114.

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 neurotransmission[1], 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 neurons[2], 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.

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1. Sawin, E., (1996), Ph. D. Thesis, MIT.

2. Trent, C., (1982), Ph. D. Thesis, MIT.