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Studies of Worms that Fail to Brake for Food Yield New Serotonin Receptor

Researchers studying the roundworm *Caenorhabditis elegans* have identified a new type of serotonin receptor. If this type of receptor is found in humans, it may become an additional target for drugs designed to treat a wide range of disorders caused by serotonin imbalance, including mood disorders, migraine headaches and obesity.

The identification of the new serotonin receptor began with experiments designed to probe why certain strains of the roundworm, *Caenorhabditis elegans*, fail to slow down when they encounter food. When well-fed worms are presented with food, their rate of locomotion slows in what scientists call the "basal slowing response." In contrast, worms that have been deprived of food for 30 minutes before encountering food exhibit an "enhanced slowing response." In an article published in the November 23, 2000, issue of the journal *Nature*, Howard Hughes Medical Institute (HHMI) investigator H. Robert Horvitz and colleagues at the Massachusetts Institute of Technology (MIT) report that they have isolated one of the genes responsible for the enhanced slowing response.

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— H. Robert Horvitz

Earlier this year, Horvitz and his colleagues, including former MIT graduate student Elizabeth R. Sawin, identified 17 worm strains that showed a defective enhanced slowing response. Extending this work, graduate student Rajesh Ranganathan, an HHMI predoctoral fellow and lead author of the *Nature* paper, sought to identify one key gene responsible for controlling the enhanced slowing response. Ranganathan and his colleagues isolated the *mod-1* gene and showed that it encoded a serotonin receptor cell membrane protein that binds to the neurotransmitter serotonin.

"Although we had evidence that serotonin is involved in the enhanced slowing response," said Ranganathan, "we did not expect the mod-1 protein

to represent an entirely new kind of serotonin receptor." There are two basic types of serotonin receptor, those that trigger fast responses in neurons and those that trigger slow responses. While the "slow" receptors can either excite or inhibit the firing of neurons, the "fast" receptors discovered to date can only excite neurons.

"With the identification of the mod-1 protein, we have discovered the first fast serotonin receptor that can lead to inhibition," said Ranganathan. "This was quite surprising, since in mammals there are six types of the slow serotonin receptor, but only one subtype of the fast receptor."

Additional understanding of the serotonin receptor's properties came in experiments carried out in collaboration with Stephen C. Cannon of Harvard Medical School. The investigators inserted *mod-1* RNA into frog eggs, which then expressed the MOD-1 protein in the cell membrane. The scientists conducted electrical and chemical studies on these altered frog eggs to determine the function of the receptor. They discovered that the receptor acts as a selective ion channel that opens to allow the influx of chloride ions. Negatively charged chloride ions alter the electrical properties of neurons, making them more refractory to excitation that would trigger transmission of a nerve signal.

According to Horvitz, many questions remain for future studies, not the least of which is determining whether such a receptor exists in mammals. "The sequence of the MOD-1 receptor protein looks quite different from the fast serotonin receptors known to exist in humans," he said. "However, the discovery that *C. elegans* has a fast serotonin receptor that is likely to be inhibitory raises the possibility that a receptor with such properties will likely be found in mammals."

If this type of receptor exists in humans, it could become an important target of therapeutic drugs, said Horvitz. Serotonin function is already targeted in the treatment of mood disorders, migraine headaches, obesity and other problems.