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RESEARCH NEWS

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New Brain-Signaling Chemical Identified in C. elegans

Researchers have discovered that a new neurotransmitter—a chemical message sent by neurons—exists in the roundworm *C. elegans*. The studies show that the chemical tyramine controls neurons responsible for important behaviors in the roundworm.

Neurotransmitters such as acetylcholine, glutamate, GABA, dopamine, serotonin, norepinephrine and octopamine are key signaling molecules among neurons in the brain and nervous system. Disruptions in their functions can underlie a multitude of neurological diseases and psychiatric disorders. Most drugs that aim to treat these disorders by influencing brain function act by altering the levels or actions of specific neurotransmitters. The identification of a new neurotransmitter is a substantial contribution.

The researchers, Mark Alkema, Melissa Hunter-Ensor, Niels Ringstad, and Howard Hughes Medical Institute investigator H. Robert Horvitz, published their findings in the April 21, 2005, issue of the journal *Neuron*. All were at the Massachusetts Institute of Technology when the experiments were conducted.

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- H. Robert Horvitz

“Many researchers long considered tyramine simply to be the biosynthetic precursor of the neurotransmitter octopamine,” Horvitz said. “Then receptors that respond to tyramine were discovered, which caused some to suspect that tyramine might have a more direct nervous system function. What we have done is show that there are specific cells in the nematode that contain tyramine but not octopamine and that tyramine controls behaviors that are

distinct from those controlled by octopamine. Thus, tyramine is clearly a neurotransmitter on its own."

Alkema, Horvitz and their colleagues began their studies of tyramine in the context of their analysis of the role of octopamine in *C. elegans* behavior.

C. elegans is an excellent model organism for such studies, said Alkema, because researchers can manipulate its genes easily to perturb production of a particular neurotransmitter, such as octopamine. Also, since the roundworm has only 302 well-characterized neurons, the behavioral consequences of genetic manipulations can be traced to the responsible neurons, he said.

To investigate the role of octopamine in controlling *C. elegans* behavior, the researchers generated mutant worms that lacked the two enzymes required first to convert the amino acid tyrosine to tyramine and then to convert tyramine to octopamine. They found that the worms that could not produce tyramine and octopamine had two behavioral deficits distinct from those of worms that could not produce octopamine: Such worms showed hyperactive egg-laying, and, when touched with an eyelash and caused to move backwards, they failed to suppress exploratory head movements. Normally head movements are suppressed in response to touch, possibly as a survival technique to avoid being trapped by natural fungal predators.

When the researchers tried to identify where the tyramine-producing enzyme was active in the worms, they found specific neurons specialized for producing tyramine but not octopamine. When the researchers destroyed these neurons with pinpoint bursts of laser light, they found the same behavioral changes as seen in the tyramine-deficient mutants. Given the known "wiring diagram" of the worm's nervous system, the researchers were able to show with single-cell precision how tyramine links the animal's locomotor movement to its head movements. "Our studies," noted Alkema, "exemplify how a single neurotransmitter can act to generate complex coordinated behaviors."

According to Alkema, genome database searches of the fruit fly, honeybee, and mosquito identified versions of the enzyme responsible for tyramine production similar to the one they discovered in *C. elegans*. "Since these enzymes seem to be invertebrate-specific, they might be worth exploring as targets for nematode and insect pest management by seeking chemicals that inhibit the enzymes and disrupt egg-laying," he said.

"It is also interesting," he continued, "that tyramine receptors have been characterized in mammals, including humans. And trace amounts of tyramine have been found in the human brain. Although tyramine had been thought of as just a by-product of synthesis of mammalian neurotransmitters, these findings suggest that tyramine might also have a role in the mammalian nervous system."

Several studies have linked the family of chemicals that includes tyramine to human neurological and neuropsychiatric disorders. "It has been known that in psychiatric disorders there are imbalances of these trace amines, like tyramine and octopamine," said Alkema. "At this point, however, there is no causal relationship whatsoever," he emphasized.