Antidepressant found to extend lifespan in C. elegans

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A team of scientists led by Howard Hughes Medical Institute (HHMI) investigator Linda B. Buck has found that a drug used to treat depression can extend the lifespan of adult roundworms.

Buck and colleagues Michael Petrascheck and Xiaolan Ye report in the November 22, 2007, issue of the journal *Nature*, that the antidepressant drug mianserin can extend the lifespan of the nematode Caenorhabditis elegans by about 30 percent.

Intriguingly, the drug may act by mimicking the effects of caloric restriction, which has been shown to retard the effects of aging in a variety of animals ranging from worms and flies to mammals.

“Our studies indicate that lifespan extension by mianserin involves mechanisms associated with lifespan extension by dietary restriction,” said Buck, a member of the Basic Sciences Division of the Fred Hutchinson Cancer Research Center in Seattle. “We don't have an explanation for this. All we can say is that if we give the drug to caloric restricted animals, it doesn't increase their lifespan any further. That suggests the same mechanism may be involved.”

Researchers don’t yet understand exactly how mianserin staves off the effects of aging. But the drug appears to act the same way in both C. elegans and humans: by blocking certain receptors for the neurotransmitter serotonin. Serotonin is a chemical that cells use to communicate, helping them regulate many functions, including mood,

appetite, and sensory perception.

Buck said it was a surprise to find that a drug used to treat depression in humans could extend lifespan in worms. The researchers in Buck's lab found that in addition to inhibiting certain serotonin receptors in the worm, it also blocked receptors for another neurotransmitter, octopamine.

A number of observations support the idea that serotonin and octopamine may complement one another in a physiological context, Buck explained, with serotonin signaling the presence of food and octopamine signaling its absence or a state of starvation. C. elegans, for instance, usually only lays eggs when food is on hand. But serotonin stimulates egg laying in the absence of food, while octopamine inhibits egg laying even when food is nearby. Another example of interplay between the two chemicals is that pharyngeal pumping, the mechanism by which worms ingest food, is jump-started by serotonin and thwarted by octopamine.

"In our studies, mianserin had a much greater inhibitory effect on the serotonin receptor than the octopamine receptor," she said. "One possibility is that there is a dynamic equilibrium between serotonin and octopamine signaling and the drug tips the balance in the direction of octopamine signaling, producing a perceived, though not real, state of starvation that activates aging mechanisms downstream of dietary restriction."

Buck and her colleagues chose to focus on the effects of mianserin based on the results of a search through 88,000 chemicals for agents that extended the lifespan of nematodes. They found 115 such chemicals. In follow-up studies of one chemical, they found four additional compounds, including mianserin, that extended lifespan by 20-33 percent. All four compounds inhibit certain types of serotonin receptors

in humans.

“We screened a wide variety of chemicals without knowing anything about them except that they were small molecules,” Buck noted. “By screening adult animals with this extremely varied panel of compounds, we hoped to identify drugs that could increase lifespan in adults, even though some might have a deleterious effect on the developing animal.”

By identifying drugs that influence lifespan, Buck added, it may be possible to home in on how those drugs act and contribute to a growing body of knowledge about the genetic mechanisms of aging.

“Other researchers have done beautiful work using molecular genetic approaches to identify genes involved in aging,” she said. “We decided to take a chemical approach. By finding chemicals that enhance longevity, and then finding the targets of those chemicals, it may be possible to identify additional genes important in aging. In addition, the chemical approach could point to drugs suitable for testing in mammals.”

Buck said that her group has yet to identify what kinds of cells are affected by the drug, because while the serotonin receptors involved are only found on neurons, many types of cells -- not just cells of the nervous system -- have receptors for octopamine.

Source: Howard Hughes Medical Institute