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Morphine dependency blocked by single genetic change

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Morphine's serious side effect as a pain killer – its potential to create dependency – has been almost completely eliminated in research with mice by genetically modifying a single trait on the surface of neurons. The study scientists think a drug can be developed to similarly block dependency.

The research was published online January 17 by "Current Biology" and appears in the journal's January 23 print edition. The scientists were led by Jennifer Whistler, PhD, an investigator in the UCSF-affiliated Ernest Gallo Clinic and Research Center, and associate professor of neurology at UCSF.

Millions of people in the U.S. are given the opiate drug morphine for extreme pain caused by cancer, surgery, nerve damage and other conditions. It remains the pain killer of choice for many types of short-term pain, such as surgery, according to Whistler, but it is less useful for the treatment of chronic pain because its effectiveness decreases with continued use in a process called tolerance. As a consequence, an increasingly larger dose is required to treat the pain, thereby increasing the chance of addiction.

The body's natural pain killers, such as endorphins, ease pain by first binding to receptors on the surface of neurons. The receptors cycle on and off "like a light switch," Whistler says, regulating the intake of endorphin. This crucial control is absent when the neurons encounter morphine. The researchers' strategy in their study was to try to trick

neurons into responding to morphine in the more regulated way.

Strong evidence suggests that the natural on-off cycling occurs because the endorphin receptor withdraws from the cell surface, toward the cell's interior, Whistler says. The migration from the cell surface is called endocytosis.

When the neuron receptors encounter morphine the light switch is broken, and the nervous system responds by becoming more tolerant of the drug, making the recipient more dependent on the drug.

To demonstrate their hunch that morphine's unwanted effects were caused by the failure of its receptor to withdraw from the cell surface, the researchers genetically engineered mice with a single difference from normal mice: Receptors that encounter morphine in these mice can undergo endocytosis, as they normally do in the presence of endorphins. The researchers showed that with this single change, morphine remained an excellent pain killer without inducing tolerance and dependence.

"As more pain medications are being removed from the market, new strategies to overcome chronic pain become crucial," Whistler says. "If new opiate drugs can be developed with morphine's pain killing properties but also with the ability to promote endocytosis, they could be less likely to cause the serious side effects of tolerance and dependence."

The research is the first direct demonstration that this single cellular change can block the body's tendency to become tolerant of the drug, she points out.

Several strategies are now being tested to counter morphine addiction, Whistler says. These include development of morphine derivatives such as oxycontin, that are delivered in a time released manner or only once they have been processed in the digestive system. Other approaches seek

to develop morphine derivatives that target only certain opioid receptors but not others.

“The most promising aspect of these other approaches is that they have the potential to prevent or delay dependence and addiction to morphine, but few of them address the development of tolerance,” Whistler said.

Source: University of California - San Francisco