Researchers separate analgesic effects from addictive aspects of pain-killing drugs

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For the first time, pain researchers at Washington University School of Medicine in St. Louis have shown that it's possible to separate the good effects of opiate drugs such as morphine (pain relief) from the unwanted side effects of those drugs (tolerance, abuse and addiction).

The investigators, led by Zhou-Feng Chen, Ph.D., associate professor of anesthesiology, psychiatry and molecular biology and pharmacology, report their results online in the *Proceedings of the National Academy of Sciences*. They found that opiates like morphine don't relieve pain as well in mice genetically engineered to lack neurons that produce a neurotransmitter called serotonin in the central nervous system. In fact, some opiates completely lost their analgesic, or pain-relieving, effects in the mutant mice. But to the surprise of the investigators, those mice still developed tolerance to the drugs and actively sought them out.

Serotonin is involved in a wide range of behavioral and psychological processes including cognition, circadian rhythm and mood. Serotonin also is an important regulator for pain sensation, and abnormal levels of serotonin can contribute to painful events such as migraine headaches.

"The number of serotonin-producing neurons, which also are know as 5-HT neurons, is relatively small, and they are found in a very restricted area of the hindbrain," Chen explains. "Importantly, however, these neurons make extensive connections to other parts of the brain and are able to release serotonin almost everywhere in the central nervous system. These neurons have been implicated in almost every aspect of physiological function and in psychiatric disorders including anxiety and depression."

For several decades, scientists have been interested in the role these 5-HT neurons play in the analgesic effects of opiate drugs such as morphine. Studies done in the 1970s and the 1980s determined that the serotonin system was involved in the pain-killing effects of these drugs. But other studies have contradicted that "classical" view. As a result, the involvement of 5-HT neurons in the analgesic effects of opiates has remained uncertain.

In 2003, Chen's research team found that mice missing a gene called Lmx1b were completely unable to produce serotonin in the brain. But those mice could not be used for behavioral studies because they died soon after birth. To overcome that problem, Chen and his collaborators developed a line of mice lacking Lmx1b only in 5-HT neurons. Remarkably, despite the loss of all 5-HT neurons in the central nervous system, the mutant mice live to adulthood with apparently normal motor function.

Earlier this year, Chen's team reported in the Journal of Neuroscience that the mutant mice had increased pain when they encountered a painful stimulus. In this new study, Chen's team compared the pain-relieving effects of opiate drugs in normal mice to the effects in the mice without 5-HT neurons. "We performed a number of tests to measure the response of the mice to different opiate drugs," he says. "In contrast to previous studies that used drugs to destroy or disable 5-HT neurons, our study provides the first genetic evidence to support the 'classical' view that 5-HT neurons are a very important component of the neural circuits required for the analgesic effects of these drugs."

They also compared unwanted side effects such as tolerance and morphine-induced drug-seeking behaviors in mice with and without serotonergic neurons, and they found no differences. "These findings demonstrate that opiates exert their analgesic effects through a serotonin mechanism but that serotonin is not responsible for the negative, addictive side effects associated with those pain-killing drugs," Chen says. "That was

unexpected because serotonin has been known to interact with other neurotransmitters like dopamine or to modulate the levels of these neurotransmitters in the forebrain, which is important for reward-seeking behaviors." Chen says the finding raises the possibility that serotonergic neurons or opiate receptors on those neurons could be potential targets for opiate drugs that might suppress pain without risk of tolerance and drug addiction.

Source: Washington University in St. Louis