Led by advances in chemical synthesis, scientists find natural product shows pain-killing properties

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Scientists from the Florida campus of The Scripps Research Institute have for the first time accomplished a laboratory synthesis of a rare natural product isolated from the bark of a plant widely employed in traditional medicine. This advance may provide the scientific foundation to develop an effective alternative to commonly prescribed narcotic pain treatments.

The study, published May 23, 2011, in an advanced online edition of the journal *Nature Chemistry*, defines a chemical means to access meaningful quantities of the rare natural product conolidine. Based on data from mouse models, the study also suggests that synthetic conolidine is a potent analgesic as effective as morphine in alleviating inflammatory and acute pain, with few, if any, side effects.

In recent years, there has been significant interest in developing alternatives to opiate-based pain medications such as morphine. While widely prescribed for pain, morphine has a number of adverse side effects that range from the unpleasant to the lethal, including nausea, chronic constipation, addiction, and breathing depression.

The rare natural product central to the study is derived from the bark of a widely grown tropical flowering plant Tabernaemontana divaricata (also known as crepe jasmine). Long part of traditional medicine in China, Thailand, and India, extract from the leaves has been used as an

anti-inflammatory applied to wounds, while the root has been chewed to fight the pain of toothache. Other parts of the plant have been used to treat skin diseases and cancer.

Conolidine belongs to a larger class of natural products, called C5-nor stemmadenines, members of which have been described as opioid analgesics, despite a substantial discrepancy between potent in vivo analgesic properties and low affinity to opiate receptors. Conolidine is an exceptionally rare member of this family for which no therapeutically relevant properties had ever been described. Despite the potential value of conolidine and related C5-nor stemmadenines as leads for therapeutics, efficient methods to prepare these molecules were lacking.

"This was a classic problem in chemical synthesis," said Glenn Micalizio, an associate professor in the Department of Chemistry, who initiated and directed the study, "which we were able to solve effectively and efficiently¬¬—an achievement that made subsequent assessment of the potential therapeutic properties of this rare natural product possible."

Micalizio and his colleagues began working on the synthesis of the molecule after they arrived at Scripps Florida in 2008.

Testing For Potency

Once the synthesis was complete, research shifted to pharmacology for evaluation. The pharmacological assessment, performed in the laboratory of Scripps Florida Associate Professor Laura Bohn, showed that the new synthetic compound has surprisingly potent analgesic properties.

"Her pharmacological studies confirmed that while it's not an opiate, it's nearly as potent as morphine," Micalizio said.

In various models of pain, the new synthetic compound performed

spectacularly, suppressing acute pain and inflammatory-derived pain, two key measures of efficacy. Not only that, but the new compound passed easily through the blood-brain barrier, and was present in the brain and blood at relatively high concentrations up to four hours after injection.

Bohn herself was surprised by the compound's potency and by the fact it so readily enters the brain.

"While the pain-relieving properties are encouraging, we are still challenged with elucidating the mechanism of action," she said. "After pursuing more than 50 probable cellular targets, we are still left without a primary mechanism."

So far, the compound has shown remarkably few, if any, side effects, but that is something of a double-edged sword.

"The lack of side effects makes it a very good candidate for development," Bohn said. "On the other hand, if there were side effects, they might provide additional clues as to how the compound works at the molecular level."

That remains a mystery. While the synthetic compound might be as effective as morphine, it doesn't act at any of the receptors associated with opiates. In fact, it misses most of the major neurotransmitter receptors completely, suggesting it may be highly tuned towards relieving pain while not producing multiple side effects. While still in the early stages of development, further characterizations of conolidine may suggest further development as a human therapeutic for the treatment of pain.

More information: "Synthesis of Conolidine, a Potent Non-Opioid Analgesic for Tonic and Persistent Pain," Michael A. Tarselli et al.

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