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Researchers identify new compound that takes aim at neuropathic pain

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A new compound discovered by a team of UC Davis investigators has potent actions against production of a chemical that which is implicated in the development of chronic pain following a peripheral nerve injury in the spinal cord.

The compound, a molecule named 6-chloro-8-(glycinyl)-amino-β-carbolin, or 8-Gly carb, provides an important new avenue of research for developing drugs to prevent the severe pain that sometimes remains long after an injury or infection has healed.

The findings are published in *The Journal of Pharmacology and Experimental Therapeutics*.

"We have discovered a new compound that is 43 times more potent in inhibiting nitrous oxide production than the current reference compound known to have this action," said Fredric Gorin, professor and chair of the UC Davis Department of Neurology and co-principal investigator for the study. "That makes 8-Gly carb a potentially very fruitful focus for new drug development against neuropathic pain syndromes."

Neuropathic pain is a disorder characterized by often severe pain that sometimes develops following nerve damage resulting from conditions such as shingles, injury, amputation, autoimmune inflammation and cancer. Months or even years after the initial trauma, the area can remain extremely painful, a condition believed to result from the brain misinterpreting nerve signals from the area. The pain can be completely

spontaneous or triggered by something normally as innocuous as a light touch or temperature change. Traditional pain treatment with non-steroidal anti-inflammatory drugs and even opioids such as morphine is usually ineffective.

The condition is believed to develop from immune cells called microglia, a type of macrophage that resides in the spinal cord and provides an important defense against injury and infection. Following a trauma to a peripheral nerve, microglia release a host of chemicals, among them cytokines that are important for recovery, and nitrous oxide, which is believed to be a key factor in initiating and sustaining inflammation associated with the establishment of neuropathic pain. Inhibiting the production of nitrous oxide at the time of a nerve injury may be an important mechanism to prevent the later development of a chronic pain syndrome, Gorin said.

The class of drug to which 8-Gly carb belongs is known as β-carbolines, a large group of natural and synthetic organic compounds, some of which are known to reduce nitrous oxide production. Previously characterized β-carbolines block a precursor—tumor necrosis factor α—in the nitrous oxide production pathway, also resulting in the reduction of the expression of the cytokine interleukin -1β; however, experiments show that 8-Gly carb does not reduce levels of tumor necrosis factor α or the cytokine. The exact mechanism of nitrous oxide by the new compound is poorly understood and will be a focus of future research, according to Gorin.

"A compound like 8-Gly carb that selectively targets nitrous oxide production and does not block cytokine expression makes a promising candidate for drug development aimed at preventing a neuropathic pain syndrome without interfering with recovery," Gorin said. "We look forward to extending this research by developing and testing this compound and related ones in the laboratory and eventually in clinical

trials."

Gorin noted that this research resulted from a fruitful collaboration between the UC Davis Schools of Medicine and Veterinary Medicine, as well as with the University of Louisville, Kentucky. Pamela Lein, professor in the Department of Molecular Biosciences of the UC Davis Veterinary School of Medicine, is co-principal investigator and another study author.

Provided by UC Davis