A new generation of pain medication

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Universitätsmedizin Berlin and the Zuse Institute Berlin have developed a new generation of pain medication. The researchers used computer simulations to develop new opioids that will only work at sites affected by injury or inflammation. These drugs can prevent the occurrence of brain- and gut-related side effects typically associated with conventional opioids and have been proven successful in preclinical studies. Results

from this research have been published in *Pain* and *Scientific Reports*.

Opioids are a class of drugs with powerful pain-relieving properties. They are mainly used to treat the pain associated with tissue damage and inflammation, such as that caused by surgery or cancer. Common side effects associated with their use include drowsiness, nausea, constipation, dependency and, in some cases, respiratory arrest. The research team, led by Dr. Christoph Stein of the Department of Anesthesiology and Surgical Intensive Care Medicine on Campus Benjamin Franklin, are hoping to develop new types of pain medications that will work without producing dangerous side effects. Collaborating with Dr. Marcus Weber of the Zuse Institute Berlin, the researchers used computer simulations to develop two new opioids. In both cases, the researchers used fentanyl as the starting molecule.

The researchers hypothesized that tissues that are damaged or inflamed show stronger interaction between opioid agonists—the substances that elicit the pain-relieving effect—and the opioid receptors they bind to. Their computer simulations suggested that this is due to an increased concentration of protons in inflamed tissues, which leads to lower pH values than in healthy tissues, resulting in acidic conditions. Opioid molecules need to undergo protonation before they can bind to and activate opioid receptors. The researchers used this knowledge to design two drugs that would only exist in their protonated state in the presence of inflammation. This restricts opioid receptor activation to sites of tissue damage or inflammation, rather than receptors in the brain or gut.

"Our innovative design method provides a robust basis for a new generation of pain medications," reports Prof. Stein. He adds: "These drugs could help us both to avoid the dangerous side effects of conventional opioids and to reduce complications. They would also help us stem the opioid crisis, a problem that is particularly evident in the United States."

The researchers hope to further develop these newly designed drugs in order to make them available to patients. They also plan to enhance their understanding of the molecular processes underlying the complex interactions seen in inflamed tissues, in the hope that they may be able to support opioid optimization through the insights they gain. Ideally, their insights will also be beneficial for other drugs, such as those used to treat high blood pressure.

More information: Antonio Rodriguez-Gaztelumendi et al, Analgesic effects of a novel pH-dependent μ-opioid receptor agonist in models of neuropathic and abdominal pain, *PAIN* (2018). DOI: 10.1097/j.pain.0000000000001328

Viola Spahn et al. Opioid receptor signaling, analgesic and side effects induced by a computationally designed pH-dependent agonist, *Scientific Reports* (2018). DOI: 10.1038/s41598-018-27313-4

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