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An 'off' switch for pain: Chemists build light-controlled neural inhibitor

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Pain? Just turn it off! It may sound like science fiction, but researchers based in Munich, Berkeley and Bordeaux have now succeeded in inhibiting pain-sensitive neurons on demand, in the laboratory. The crucial element in their strategy is a chemical sensor that acts as a light-sensitive switch.

The notion of a pain switch is an alluring idea, but is it realistic? Well, chemists at LMU Munich, in collaboration with colleagues in Berkeley and Bordeaux, have now shown in laboratory experiments that it is possible to inhibit the activity of pain-sensitive neurons using an agent that acts as a photosensitive switch. For the LMU researchers, the method primarily represents a valuable tool for probing the neurobiology of pain.

The system developed by the LMU team, led by Dirk Trauner, who is Professor of Chemical Biology and Genetics, is a chemical compound they call QAQ. The molecule is made up of two functional parts, each containing a quaternary ammonium, which are connected by a nitrogen double bond (N=N). This bridge forms the switch, as its conformation can be altered by light. Irradiation with light of a specific wavelength causes the molecule to flip from a bent to an extended form; exposure to light of a different color reverses the effect.

One half of QAQ closely resembles one of the active analogs of lidocaine, a well-known local anesthetic used by dentists. Lidocaine blocks the perception of pain by inhibiting the action of receptors found

on specific nerve cells in the skin, which respond to painful stimuli and transmit signals to the spinal cord.

Neuroreceptors are proteins that span the outer membrane of nerve cells. They possess deformable pores that open in response to appropriate stimuli, and function as conduits that permit electrically charged ions to pass into or out of the cells. The ion channel targeted by the lidocaine-like end of QAQ responds to heat by allowing positively charged sodium ions to pass into the cells that express it. This alters the electrical potential across the membrane, which ultimately leads to transmission of the nerve impulse.

In their experiments, the researchers exploited the fact that QAQ can percolate through endogenous ion channels to get the molecule into nerve cells. This is a crucial step, because its site of action is located on the inner face of the targeted ion channel.

Furthermore, the lidocaine-like end of QAQ binds to this site only if the molecule is in an extended conformation. When the cells were irradiated with 380-nm light, which bends the bridge, signal transmission was reactivated within a matter of milliseconds. Exposure to light with a wavelength of 500 nm, on the other hand, reverts the molecule to the extended form and restores its inhibitory action. The analgesic effect of the switch was confirmed using an animal model.

Trauner's team has been working for some considerable time on techniques with which biologically critical molecular machines such as neuroreceptors can be controlled in living animals by means of light impulses. The researchers themselves regard the new method primarily as a tool for neurobiological studies, particularly for pain research. Therapeutic applications of the principle are "a long way off", says Timm Fehrentz, one of Dirk Trauner's PhD students and one of the two equal first authors on the new paper. For one thing, the monochromatic

light used to isomerize the QAQ molecule cannot penetrate human skin sufficiently to reach the pain-sensitive neurons. The researchers hope to address that problem by looking for alternatives to QAQ that respond to red light of longer wavelength, which more readily passes through the skin.

More information: Rapid optical control of nociception with an ion-channel photoswitch, A. Mourot, T. Fehrentz, Y. Le Feuvre, C.M. Smith, C. Herold, D. Dalkara, F. Nagy, D. Trauner & R.H. Kramer, *Nature Methods*, doi: 10.1038/nmeth.1897

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