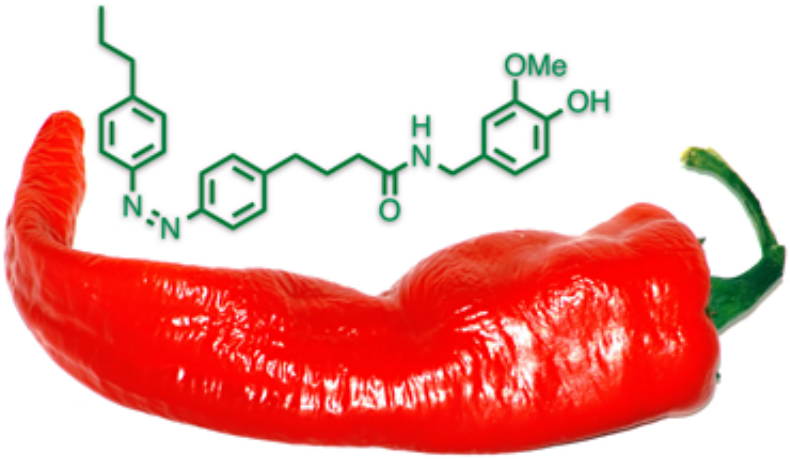
Controlling the function of nerve cells that mediate perception of painful stimuli

June 3 2015



Chemical biologists at LMU have synthesized a set of molecules which make it possible to optically control the function of nerve cells that mediate perception of painful stimuli.

A thoughtless brush with a hotplate and an encounter with the fiery taste of a vindaloo curry are both painful experiences. These apparently very different stimuli provoke the same burning sensation because they both activate the same cell-surface receptor, TPRV1. TRPV1 is ultimately responsible for the perception of the pain evoked both by high temperatures and by the chemical irritants found in many spicy foods. The receptor is mainly expressed by nerve fibers in sensory epithelia,

and it responds not only to high temperatures and compounds present in chilis and other types of pepper, but also to electrical potentials, spider toxins and acids. "One stimulus it does not respond to is light," says Dirk Trauner, Professor of Chemical Biology and Genetics at LMU. But recent work by his research team has now changed that.

TRPV-1 is a pore-shaped integral membrane protein and, when activated, it allows positively charged ions to percolate into the cell. This influx of cations alters the balance of charge across the nerve-cell membrane. The resulting change in electrical potential is propagated along the membrane, initiating a nerve impulse that is transmitted to the brain, where it evokes the sensation of pain. "TRPV-1 is also activated by a variety of lipids, in particular by fatty acids that are coupled to a particular structural element called a vanilloid headgroup," Trauner explains. "In this case, the efficacy of activation depends both on the length of the fatty acid and its degree of saturation, and is consequently very variable." This versatility also means that such fatty acids can provide ideal precursors for the construction of light-sensitive switches that can activate TRPV-1 to varying extents.

A box of tricks

Trauner's team succeeded in inserting into the fatty-acid chain a functional group whose structure can be altered by exposure to light of a certain wavelength, allowing one to change the conformation of the chain at will. "Using this strategy, we have designed a set of light-sensitive fatty acids, which can serve as building blocks for complex photo-activatable fat molecules," says Trauner. "By modifying these building blocks through the addition of a vanilloid head group, we have synthesized a series of six compounds, which we call AzCAs. These agents make it possible to accurately tune the level of activity of the pain receptor."

Thus, with the aid of the new molecules, pain-receptor function can be regulated with unprecedented precision. They may therefore provide new leads in the search for more effective therapies for the alleviation of acute and chronic pain. They could, for instance, be used to enable short-term opening of ion channels for local anesthetics, or to depress the sensitivity of pain receptors by sporadic exposure to long-term stimulation. In animal studies carried out in collaboration with Gary Lewin's group at the Max-Delbrück Centrum in Berlin, Trauner and his colleagues have already shown that the propagation of pain signals can indeed be controlled in whole tissues. "In addition to the precision offered by this system, we were also impressed by the speed with which the receptors reacted," says Trauner. Capsaicin, the TRPV1 activator found in chili peppers, stimulates the receptor rather slowly and detaches from the receptor only when the ambient concentration of the compound has fallen below a certain threshold. In contrast, AzCAs can be administered in the deactivated state, activated with ultraviolet light, and deactivated in a flash with a pulse of blue light. By this means, the ability to perceive pain can be rapidly turned on and off.

The researchers now plan to test the effects of their light-controlled switches in more complex neuronal model systems and in vivo. "In addition, we are working on agents that respond to illumination with red light, which would make cells located in deeper tissue layers accessible to optical control," says Trauner. "And in a further project, we want to incorporate our diverse light-sensitive fatty acids into more complex lipids, aiming to controlling other proteins and cell functions with light. And, finally, we have paved the way for photogastronomy."

More information: "Photoswitchable fatty acids enable optical control of TRPV1" *Nature Communications* 6, Article number: 7118 DOI: 10.1038/ncomms8118