Putting the fire out with light

July 25 2013

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Chili peppers contain an activator of heat-sensitive pain receptors. An LMU team has now converted an antagonist to the compound into a light-sensitive regulator of such receptors that can differentially modulate the effects of various stimuli.

Bite into a flaming red chili pepper and you really do feel like a fire-eater – you very soon experience a sharp burning sensation in your mouth. This perception is due to the binding of capsaicin, a chemical present in peppers, to a class of cell-surface proteins on sensory neurons that react to a variety of noxious physical and chemical stimuli including heat. The receptor is referred to as TRPV1 (for "Transient Receptor Potential Vanilloid 1") and is sensitive not only to capsaicin and heat, but

also electrical potential, certain spider toxins and acidic pH.

TRPV1 is a member of one of the largest families of ion channels, proteins that play a central role in sensory physiology. "TRP channels are also involved in visual responses and may be required for the regulation of circadian rhythms in mammals. Nevertheless, although TRPV1 reacts to many different kinds of stimuli, it is not inherently sensitive to light," says Dirk Trauner, Professor of Chemical Biology and Genetics at LMU and a member of the Center for Integrated Protein Science Munich (CIPSM), a Cluster of Excellence.

Cheating the chili

Trauner's specialty is the design and synthesis of chemicals that act as light-regulated switches to trigger activation of receptors that do not naturally respond to light. He and his team, in collaboration with Professor Thomas Gudermann's research group at the Walther Straub Institute for Pharmacology and Toxicology, have now produced a ligand that allows TRPV1 to be controlled by light. To do so, they chemically modified a known synthetic molecule called capsazepine, which blocks the site on TRPV1 at which capsaicin normally binds, without activating the receptor. It thus acts as a so-called competitive inhibitor and prevents opening of the TRPV1 channel. "By creating a photosensitive derivative of capsazepine, we have effectively turned TRPV1 channels into receptors that respond to light," says Marco Stein, the lead author on the new study.

The researchers accomplished this feat by coupling so-called azobenzenes to the inhibitor. Azobenzenes are chemical building blocks that have characteristic double bonds whose conformation can be altered by light. Depending on the wavelength of the light to which they are exposed, they exist either in a bent "cis" configuration or an extended "trans" form. One of the capsazepine derivatives obtained (AC4), turned

out to be a particularly versatile regulator of TRPV1, because binding of AC4 alters the response of the ion channel in two ways. In the trans form, AC4 binds to TRPV1 in such a way that it inhibits the voltage-dependent activation of the receptor. The cis form inhibits activation of the channel by capsaicin. "And by preventing capsaicin from binding to TRPV1, it essentially turns chili from a pungent into a bland and innocuous taste experience," Trauner explains.

New dimensions in photopharmacology

Thanks to its dual mode of action, AC4 further extends the applicability of the concept of photopharmacology – the use of light-sensitive chemicals to regulate the activity of ion channels and other receptor proteins. "Since AC4, as a photosensitive antagonist, can inhibit the action of an agonist (capsaicin in this case) in response to light, one can employ an agonist and a photoswitchable antagonist simultaneously," says Trauner. In addition, as AC4 can block the effects of specific stimuli in a wavelength-dependent manner, it provides a tool with which to dissect how the receptor is differentiate between various sensory inputs.

The next step in the project will be to explore ways of using AC4 – and related compounds – to elucidate other aspects of sensory physiology. But possible medical applications of the new substance also suggest themselves. As Marco Stein explains, "We also want to check whether these compounds are capable of inducing some kind of visual perception in the retina. If so, they could potentially be used to treat certain forms of blindness."

More information: onlinelibrary.wiley.com/doi/10 … e.201302530/abstract

Provided by Ludwig Maximilian University of Munich