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New research may help to develop effective pain killers

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The nerve cells that transmit pain signals in the body are called nociceptors. When activated they release pro-inflammatory neuropeptides. In order to recognise harmful external influences, nociceptors are equipped with a wide range of receptors. The capsaicin receptor channel, for example, reacts strongly to the spicy substance in chili peppers. Another receptor is sometimes called the mustard oil receptor as it is activated by a substance found in mustard, horseradish and onions. This receptor, whose scientific name is TRPA1, plays a key role in painful inflammation of the bowel and the pancreas, as well as in asthma.

A team led by FAU researchers Dr. Matthias Engel, Chair of Internal Medicine I, and Prof. Dr. Peter Reeh, Institute of Physiology and Pathophysiology, have recently examined a substance called capsazepine that partially blocks the capsaicin receptor in more detail. In previous studies by other researchers this substance prevented ulcerative colitis, a form of inflammatory bowel disease, in mice. However, an unknown side effect of capsazepine must have been responsible for this, as Dr. Engel's own experiments had shown that the capsaicin receptor is not involved in the pathogenesis of this inflammatory disease. In these studies, a synthetic inhibitor of the mustard oil receptor not only prevented bowel disease but actually healed it. This led the FAU researchers to suspect that capsazepine could have a similar inhibiting effect on the mustard oil receptor. They were surprised to find that capsazepine did not inhibit the receptor but instead activated it very effectively. This caused the receptor to become insensitive to the

stimulus - a phenomenon that has also been observed with many other receptors. The protective effect of capsazepine was therefore due to the fact that the nociceptors responded less to their stimuli and no longer released neuropeptides.

The researchers also discovered that although capsazepine was administered locally in the bowel, the skin also more or less stopped releasing neuropeptides. They therefore concluded that capsazepine can effectively reach all nociceptors in the body via the bloodstream and potentially desensitize them. Could this be the first step towards a new medication for severe pain? Researchers have known for some time that nociceptors can in principle be desensitized in any area of the body and that this can be achieved with large doses of capsaicin. The problem with this is that it means that the body is no longer able to regulate its temperature properly, the patient no longer feels pain due to heat, and the blood supply to certain organs suffers. All of these effects are permanent and irreversible. For this reason, capsaicin is only used to treat humans in the form of patches placed on specific skin areas or creams with a very low dose.

In the study, when mice were administered a high but tolerable dose of capsazepine over the course of several days the sensitivity towards chemical and heat stimuli gradually decreased in the whole body, while inflammation in the bowel was prevented at the same time. This is a very promising result, as in the long term it could lead to the development of highly effective pain killers for diseases in which the mustard oil receptor plays an important role. In addition to chronic inflammatory bowel disease, this includes joint arthrosis, chronic pancreatitis, Crohn's disease and chronic asthma.

More information: Katrin Kistner et al, Systemic desensitization through TRPA1 channels by capsazepine and mustard oil - a novel strategy against inflammation and pain, *Scientific Reports* (2016). DOI:

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