A new promising approach in the therapy of pain

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The treatment of inflammatory pain can be improved by endogenous opioid peptides acting directly in injured tissue. Scientists at the Charité – Universitätsmedizin Berlin and the Université Paris Descartes showed that pain can be successfully treated by targeting immune and nerve cells outside the brain or spinal cord. The study is published in the current issue of the *FASEB Journal*.

Inflammatory pain is the most common form of painful diseases. Examples are acute pain after surgery, and chronic pain as in the case of rheumatoid arthritis. However, the treatment of inflammatory pain is often difficult because it rarely responds to conventional therapies. Furthermore, opiates, such as morphine, produce serious side effects including addiction mediated in the brain, while drugs, such as ibuprofen, may cause stomach ulcers, internal bleeding, and cardiovascular complications. The activation of opiate receptors in nerve cells outside the brain or spinal cord can alleviate pain without serious side effects. This can be achieved by synthetic opiates or endogenous opioid peptides, e.g. enkephalins and endorphins. However, these peptides are rapidly inactivated by two major enzymes, aminopeptidase N (APN) and neutral endopeptidase (NEP), which limit their analgesic effects.

The aim of the research group of Prof. Halina Machelska-Stein from the Klinik für Anästhesiologie at Campus Benjamin Franklin was to prevent the breakdown of endogenous opioid peptides directly in the inflamed tissue. In an animal model, the group has shown that inflammatory pain

can be alleviated if the two enzymes (APN and NEP), responsible for the inactivation of the opioid peptides, were blocked by the selective inhibitors. In preparations from immune or nerve cells, which express these enzymes, the opioid peptides were quickly broken down. This was prevented by the enzyme inhibitors, bestatin, thiorpan and P8B. As a result, the sensation of pain was either markedly reduced or completely disappeared. "Targeting of endogenous opioid peptides directly in injured tissues might be a promising strategy to treat inflammatory pain without serious side effects," states Prof. Machelska-Stein, explaining the results of the investigation. Furthermore, blocking pain at the site of its origin may prevent excitatory mechanisms in the nervous system, which lead to the development of chronic pain.

More information: Schreiter A, Gore C, Labuz D, Fournie-Zaluski MC, Roques BP, Stein C, Machelska H. Pain inhibition by blocking leukocytic and neuronal opioid peptidases in peripheral inflamed tissue. *FASEB J.* doi: 10.1096/fj.12-208678

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