

# A step forward in targeted pain therapy

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Our bodies sense painful stimuli through certain receptors located in the skin, in joints and many internal organs. Specialized nerve fibers relay these signals coming from the periphery to the brain, where pain becomes conscious. “The spinal cord is placed between these structures as kind of a pain filter”, says Hanns Ulrich Zeilhofer, Professor at the Institute of Pharmaceutical Sciences at ETH Zurich and at the Institute of Pharmacology and Toxicology of the University of Zurich.

That filter assures that pain is not evoked by everyday stimuli like light touch. This is accomplished by inhibitory nerve cells located in the spinal dorsal horn that release the messenger molecule  $\gamma$ -amino butyric acid (GABA) at specialized contacts between neighboring nerve cells, so-called synapses. GABA then activates chloride channels on those neighboring cells which relay the pain signals to the brain.

## Activating pain inhibiting factors

In patients with chronic inflammatory diseases, such as rheumatoid arthritis or after nerve damage, for example following injuries, the pain inhibiting action of GABA becomes severely compromised. Pain signals are then conducted to the brain nearly unfiltered. Benzodiazepines, such as the sedative drug Valium<sup>®</sup>, which enhance the action of GABA, alleviate chronic pain when they are applied directly to the spinal cord via an injection into the spinal canal. In practice, however, such injections can only be done in very selected cases.

More often benzodiazepines are administered systemically, such as with

tablets. In this instance, the benzodiazepines not only act in the spinal cord but also in the brain where they can have undesired, sometimes deleterious, effects on pain patients. The drugs cause sedation, impair memory, and can even lead to addiction. In addition, during prolonged treatment their effect often fades with time. Classic benzodiazepines should therefore be avoided in chronic pain patients.

## **GABAA receptors as pain targets**

It had been acknowledged for some time that GABA serves important functions in pain control. That benzodiazepines act on at least four different subtypes of GABA receptors was also known. Nonetheless, these receptors were largely neglected as potential targets for pain treatment.

The research team led by Ulrich Zeilhofer used genetically altered mice in experiments to target the GABA receptors that control spinal pain relay. They first induced a slight inflammation in one hind paw or irritated the sciatic nerve to induce pain. A few days later the mice received an injection of a benzodiazepine close to the spinal cord. Experiments with the mice allowed the researchers to identify two subtypes of GABAA receptors which mediate spinal pain control.

## **A challenge for drug design**

For experiments with animals, drugs with the proposed receptor specificity are already available. Such experiments have confirmed that the pharmacological enhancement of spinal GABA receptor function inhibits the relay of pain signals to the brain. Further studies have also shown that these compounds did not lose their analgesic effects during prolonged treatment and did not lead to addiction.

Successful design of a drug that targets only those two subtypes of GABA receptors would be a big step forward in pain therapy. Chronic pain could be treated specifically and with fewer side effects. “The challenge is now for pharmaceutical companies to develop drugs that specifically target these receptors in humans”, says Zeilhofer.

Source: Swiss Federal Institute of Technology

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