

Researchers Unlock the Key that Could Lead to the Development of Non-Opioid Painkillers to Treat Chronic Pain

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Neuropathic pain is a type of chronic pain that can occur if your nervous system is damaged or not working correctly, and can be caused by injury, virus infection or cancer treatment, or be a symptom or complication of conditions such as multiple sclerosis and diabetes.

The new study, led by world-renowned drug researchers, has demonstrated a new mode of targeting the adenosine A1 receptor protein, which has long been recognised as a promising therapeutic target for non-opioid painkillers to treat neuropathic pain but for which the development of painkillers had failed due to a lack of sufficient on-target selectivity, as well as undesirable adverse effects.

In the study, researchers used electrophysiology and preclinical pain models to demonstrate that a particular class of molecule, called a 'positive allosteric modulator' (PAM), can provide much more selective targeting of the A1 receptor by binding to a different region of the protein than traditional, previously investigated, activators.

Another breakthrough in the study was facilitated by the application of cryo electron microscopy (cryoEM) to solve the high-resolution structure of the A1 receptor bound to both its natural activator, adenosine, and an analgesic PAM, thus providing the first atomic level snapshot of where these drugs bind.

Chronic pain remains a widespread global health burden, with lack of current therapeutic options leading to an over-reliance on opioid painkillers, which provide limited relief in patients with chronic (particularly neuropathic) pain, while exhibiting severe adverse effects, such as respiratory depression and addiction.

The new researcher discovery provides the opportunity for researchers to develop non-opioid drugs that lack such side effects.

Researchers stated "This study has helped us to better understand mechanisms underpinning allosteric drug actions. One of the exciting things we found is that not only were the PAMs able to decrease neuropathic pain with minimal unwanted effects, but they actually increase their level of effectiveness as the pain signals in the spinal cord get stronger ~ thus highlighting the potential for allosteric medicines that are uniquely sensitive to disease context."

Professor added: "This multidisciplinary study now provides a valuable launchpad for the next stage in our drug discovery pipeline, which will leverage structure-based insights for the design of novel non-opioid allosteric drugs to successfully treat chronic pain."

Some patients with chronic pain will simply not find relief with non-opioid medications or treatments like physical therapy. For them, there are new techniques being developed that may relieve their pain and, in some cases, keep it from coming back.

Some of the latest high-tech methods for relieving chronic pain include:

Radio waves: Radiofrequency ablation involves inserting a needle next to the nerve responsible for the pain and burning the nerve using an electric current created by radio waves. This short-circuits the pain signal. Pain relief can last for up to one year.

Nerve blocks: Using X-ray imaging, pain medicine physicians can inject numbing medication that blocks or dampens pain and might even stop chronic pain from developing. The location of the injection depends on the source and type of pain. For example, pain in the arm or face can be relieved by blocking nerves in the neck. Relief may require a series of injections and repeated treatment.

Electrical signals: Transcutaneous electrical nerve stimulation can provide short-term pain relief, especially for various types of muscle pain, by sending low-voltage electrical signals from a small device to the painful area through pads attached to the skin. While researchers aren't sure why it works, they think it may either interrupt the nerve signals to the brain or stimulate the production of "feel good" endorphins, the body's natural painkillers.

Spinal cord stimulation: When other methods fail, a pain medicine specialist might recommend spinal cord stimulation (SCS), which uses a pacemaker-like device that replaces the pain with a more tolerable sensation, typically a tingling or massage-like feeling. The physician implants the device in the lower back, attaching it to tiny wires that are located in the spinal canal. When patients feel pain, they can use a remote control to send signals to the painful area. This technique can help with back pain as well as neuropathy –

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nerve damage in the legs that causes numbness and pain – which is common in people with diabetes. New forms of SCS show promise in relieving pain without the tingling.

As research on these substances continues, physician anesthesiologists and other pain management specialists can work with people in pain to develop a safe, effective pain management plan that doesn't include marijuana, cannabinoids, or opioids.