Neuropathic pain

Developing a Nobel Prize winning target in pain

Chronic pain is very common and includes conditions like arthritis and chronic lower back pain. Neuropathic pain is primarily a chronic disease caused by a dysfunction or an injury to the sensory nervous system. This could be diabetic neuropathy, or a consequence of shingles, or nerve injury from an accident or surgery.

Current therapeutic options for neuropathic pain give relief to only 15 to 20% of patients – at best.[1] In spite of not being a recommended treatment, more than 50% of patients with chronic neuropathic pain have received prescriptions for opioids with the subsequent risk of withdrawal symptoms and dependency.

In this article, we describe research by our company AlzeCure Pharma AB, on a candidate topical treatment for the treatment of peripheral neuropathic pain which targets TRPV1, a capsaicin receptor that is widely expressed in sensory nerve fibers and non-neuronal cells. TRPV1 is understood to play an important role in a number of pathological conditions. Its role in drug research and development is likely to increase following the award in October of the Nobel Prize in Physiology or Medicine to David Julius and Ardem Patapoutian for their discoveries of receptors for temperature and touch. Prof Julius is credited with discovering TRPV1.

The sensation of our close environment is a crucial function for the survival of our species. It is not surprising therefore that the mechanisms underlying our senses have continued to fascinate man for thousands of years. Prior to the seminal discoveries of this year's Nobel Prize laureates, a fundamental unsolved question was: how can we sense temperature and mechanical stimuli in the nervous system? Through the use of pressure-sensitive cells, Prof Patapoutian discovered novel sensors that respond to mechanical stimuli in the skin and internal organs. Prof Julius used the notion that capsaicin, a compound present in chilli peppers, induces a burning sensation to try and find the responsible endogenous sensor system. He was subsequently able to show the presence of a capsaicin and heat activated sensor in the nerve endings of the skin, TRPV1.

TRPV1 is a so-called non-selective cation channel and is also commonly known as the Vanilloid receptor (VR1) or Capsaicin receptor. The receptor is present almost everywhere in the body, but abundant in our sensory nerve endings, e.g. where sensory sensations are initiated. TRPV1 is activated by noxious heat (>45°C), low pH and by capsaicin, the active ingredient in chili peppers. It can also be activated by inflammatory mediators released by a tissue injury, e.g., prostaglandin E2, bradykinin, and nerve growth factor as a response to an acute injury causing acute pain, like burning your hand on a hot plate.

However, in chronic pain and particularly in chronic neuropathic pain, the TRPV1 receptor becomes 'sensitised' to heat, making it constantly activated at normal body temperature, and whilst being activated, it also activates other pain systems, making pain signaling mechanisms more sensitive to painful stimuli, such as light touch or needle-sharp objects.

When this happens, the pain signaling becomes continuous, and may even become worsened by additional sensory input. Therefore, modulating TRPV1 function may have profound effects on nociceptive processing in inflamed tissue. TRPV1 is also involved in initiating pain signaling in general. In chronic pain it has a wider scope in maintaining increased pain sensitivity to not only temperature, but also to sharp objects (pinprick) and touch, a common feature in peripheral neuropathic pain.

Blocking the TRPV1 receptor is therefore a highly interesting target for the development of new analgesics. Using a local administration to avoid the systemic effects on normal temperature sensation, would give any future compound a significantly improved risk- benefit ratio, i.e., with improved efficacy and/or safety profile compared with existing therapies for neuropathic pain.

Many previous TRVP1 antagonist projects using oral formulations have failed due to significant effects on normal temperature regulation and insensitivity to heat, e.g. subjects not sensing how hot their coffee was. This was all due to the blocking of normal TRPV1 receptor function. The effects of blocking the TRPV1 receptor will of course also be affected when treating pain, so therefore these systemic effects cannot be avoided when taking the TRPV1 blockers as oral analgesics.

We believe a more promising idea is to target the specific nerves that carry sensory information from the injured tissue, and in the case of peripheral neuropathic pain, from the skin to the spinal cord and brain where the pain is perceived. These sensory nerves are normally silent, but under conditions like neuropathic pain, they are known to be sending pain signals spontaneously and independently of any provoking stimuli. Further, in many types of peripheral neuropathic pain, the nerve fibers containing TRPV1 receptors are more abundant and more superficial than in normal skin. This is an important cause of increased sensitivity maintaining chronic pain. In neuropathic pain patients, stimuli in the form of touch from a bed sheet, pressure from a sock or waist elastic, low or high temperature or even a draft of wind may increase the pain signaling. This then leads to additional attacks of worsening pain, which is extremely disruptive for pain patients, especially those suffering from neuropathic pain.

A topical antagonist for neuropathic pain

AlzeCure Pharma is developing ACD440, a potent and selective TRPV1 antagonist for the treatment of peripheral neuropathic pain. The ACD440 project focusses on affecting the TRPV1 target where it is possible to reach by local administration. In peripheral neuropathic pain, the TRPV1 receptors in the skin are directly affected by the disease,

so local treatment with a topical gel where the active drug can reach the nerves without causing systemic side effects is a very attractive approach. It has long been known that peripheral nerve blocks with local anesthetics reduce or eliminate the pain signaling and reduce the pain intensity. Reducing the input of painful nerve signaling by applying the ACD440 gel is thus expected to also reduce overall pain in neuropathic pain patients.

We have found that ACD440 has a limited effect on temperature regulation even after oral dosing. It is thus well suited to test the hypothesis that TRPV1 antagonists could be a future treatment for chronic neuropathic pain, in particular since topical use gives very low blood concentrations. A recently conducted Phase Ib study of our compound in healthy volunteers demonstrated that it is efficient in blocking the TRPV1 receptor in the skin of healthy volunteers without causing any side effects. To the best of our knowledge, there is only one other topical TRPV1 antagonist product under development. This is for corneal pain after surgery and for more long-term eye treatment.

An oral formulation of ACD440 has been investigated in an extensive Phase I programme involving not only clinical pharmacology studies, but also various proof-of-mechanism model studies in healthy volunteers. Multiple oral administration of ACD440 with a treatment duration of up to four weeks have also been studied in Phase 2 studies including in patients with acute post-operative pain following molar extraction and patients with chronic osteoarthritis pain. The compound has gone through extensive preclinical testing and there are no identified safety risks in the full preclinical package. The current development programme is studying the effects of ACD440 gel as a topical product for the treatment of peripheral neuropathic pain and we are currently planning a Phase 2 study in neuropathic pain patients.

Summary

Neuropathic pain is a very common and disabling disease, affecting one in 10 individuals globally who consequently, have difficulty leading a normal life. A vast majority of these people are not helped by existing therapies. We believe that targeting the TRPV1 receptor is a promising approach. It captures a fundamental discovery by two Nobel laureates on how we sense heat, cold and touch which are essential for human survival.

Reference:

1. Finnerup NB, Attal N, Haroutouian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice ASC, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: systematic review, meta-analysis and updated NeuPSIG recommendations. Lancet Neurol. 2015; 14(2): 162–173.

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Non-opioid treatments – the path forward

Treatment with opioids is often commonly viewed as 'the strong pain medication.' Not only is this not true for neuropathic pain, where strong opioids are not considered efficacious and therefore not a recommended treatment. Opioid treatment and misuse also have a high risk for dependence and abus. Still over 50% of patients with neuropathic pain have at some occasion during their course of disease been prescribed opioids as treatment. The current opioid crisis has put focus on the development of new and much needed pain treatments that do not lead to dependence and abuse. The TRPV1 receptor is not involved in the systems potentially leading to dependence and abuse. An effective TRPV1 receptor antagonist could potentially be a first line treatment - free from abuse potential.