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A new strategy to treat chronic pain targets a Toll-like receptor in touch fibers.

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HIGHLIGHTS

Chronic pain affects millions of people worldwide and remains a challenge to treat. A new study presents a promising new strategy that specifically targets this form of pain.

ARTICLE

Pain in response to acute insult serves as a warning system to protect us from harm. People who suffer from congenital insensitivity to pain experience auto-mutilation, increased injury and have a shorter life expectancy. Though acute pain is necessary, persistent pain syndromes, which affect more than 30% of the general population, often become pathological, debilitating and are a major reason people seek medical attention. Many conditions give rise to persistent pain, including post-operative injury, migraine, diabetes, arthritis and cancer, which manifests as ongoing (spontaneous) or touch-induced (mechanical allodynia) pain. Despite intense efforts, success in alleviating this form of pain has remained elusive, as current therapies, such as opioid analgesics, anti-inflammatory drugs, antidepressants and anticonvulsants often lack efficacy, are highly addictive or show other serious side effects¹. Clinicians and pain researchers thus continue to aggressively search for more effective and specific treatment strategies. In this issue, Ru-Rong Ji and colleagues² report a provocative new therapeutic strategy that specifically targets persistent pain.

The story begins nearly a decade ago, when Clifford Woolf and colleagues developed a clever strategy to selectively block nociception by introducing the local anesthetic QX-314 specifically into pain-sensing neurons³. QX-314 is a sodium channel blocker derived from lidocaine that is positively charged and membrane impermeable, but can enter cells through non-selective cation channels, such as the Transient Receptor Potential (TRP) channels. To target pain-sensing neurons, Woolf and colleagues co-applied QX-314 with the TRPV1 receptor agonist capsaicin, the noxious ingredient in chili peppers. Entry of QX-314 through TRPV1 stopped action potential

generation and eliminated the behavioral response to acute, noxious stimuli, while leaving other modalities intact (see Fig. 1). In a subsequent study, Woolf and colleagues silenced itch-sensing neurons using a similar TRP-mediated QX-314-anesthetic strategy confirming that the approach could be extended to other modalities of the somatosensory system⁴. The question then arose as to whether this powerful approach could be used to block chronic pain syndromes.

Mechanical allodynia is one of the most common symptoms of chronic pain. It results, at least in part, from neuronal plasticity within the dorsal horn that permits activation of the nociceptive spinal cord circuit by innocuous sensory neurons, thus turning touch into pain⁵. The A β class of mechanosensory neurons have long been suggested to convey touch-induced pain based on human studies⁶, although A δ - and C-fibers also possess mechanosensory properties⁷. Could a TRP-mediated QX-314-anesthetic strategy be used to silence A β -fibers and alleviate the pain? To date, no TRP channels specific to only innocuous sensory neurons have been reported. To overcome this issue, Xu et al.² considered a different approach. Ru-Rong Ji's group previously showed that activation of the Toll-like receptor, TLR7 in a subset of nociceptors leads to action potential generation via the opening of TRPA1⁸. TLRs initiate immune responses in rodents and humans and recently have been implicated in pain and itch⁹. Could a TLR be used to specifically target QX-314 to A β -fibers?

Xu et al.² followed this path and now report that in both rat and human sensory neurons, TLR5 is expressed almost exclusively by medium-large A-fibers, including A β mechanoreceptors. The authors further show the presence of TLR5 in axon terminals that innervate touch-related sensory organs in the skin and centrally, primarily in the

deep dorsal horn, where A β -fibers project. Importantly, co-application of QX-314 and flagellin, a highly potent TLR5 ligand, specifically blocks A-, but not C-fiber conduction *in vitro* in both rodent and human primary sensory neurons. The currents are not blocked by QX-314 or flagellin applied alone, confirming that the anesthetic effect of QX-314 in A-fibers depends on TLR5 activation. Additionally, when injected into the plantar surface of the hindpaw, flagellin/QX-314 specifically blocks action potentials generated in A β -, but not A δ - or A α -fibers measured at the sciatic nerve *in vivo*. Next, the authors asked whether blockade of TLR5-expressing A β -fibers could reverse mechanical allodynia.

Using the flagellin/QX-314 strategy, the authors reversed mechanical allodynia induced by chemotherapeutic agents, diabetic neuropathy and nerve constriction in wild-type, but not TLR5 knockout mice. The analgesic effect was dose-dependent, lasted up to three hours and did not show side effects or anti-nociceptive tolerance after repeated application. While the authors mainly focused on mechanical allodynia, they were also able to reverse paclitaxel-induced ongoing pain. Lastly they demonstrated that flagellin/QX-314-induced A-fiber, but not capsaicin/QX-314-induced C-fiber blockade, is effective in relieving the allodynia in these pain models (see Fig. 1).

While Xu et al² present an intriguing, potential breakthrough therapeutic strategy, several issues still need to be addressed before moving from bench to bedside. The nature of the QX-314 makes it highly membrane impermeable, and therefore resistant to skin penetration, and intradermal delivery of flagellin/QX-314 has limited surface area coverage. Application of the compounds with a dermal penetration enhancer may solve this issue. Although not observed in rodents, the flagellin/QX-314 treatment may alter A-fiber-mediated normal touch or proprioception in humans. Also of note, mechanical

hypersensitivity was induced by application of the compounds in uninjured animals². While initially counter-intuitive, this effect could be explained by the “gate control theory” which predicts that touch (A-fibers) inhibits pain under normal conditions⁵. Interestingly, flagellin has been extensively used in preclinical studies for its ability to protect against lethal doses of ionizing radiation and its cytotoxic actions against tumors. The recombinant flagellin derivative Entolimod (previously known as CBLB502), which is being developed for these indications in humans due to its lower toxicity^{10,11}, may also be useful for treating persistent pain.

The authors show flagellin/QX-314 diminished pain in several clinically-relevant models of both mono- and polyneuropathies. Although different types of injuries often produce the same chronic pain symptoms, the mechanisms and circuits that encode the pain likely differ by etiology. This more complex biology can hinder drug development efforts, as drugs that are efficacious across a range of different pain conditions have greater clinical value, but are more difficult to identify. If the effectiveness of flagellin/QX-314 across pain models holds similarly in humans, it would suggest the existence of a common, critical peripheral mediator.

The Xu et al² study also raises new questions. How does QX-314 enter A-fibers with TLR5 activation? Woolf’s group has shown that QX-314 can enter neurons through the opening of TRP channels^{3,4} which are preferentially expressed by nociceptors¹². Could a TRP channel be uniquely expressed *de novo* by touch-sensing neurons after injury? Additionally, the authors show that the canonical MyD88 pathway, known to be activated downstream of TLR activation, is not involved in the flagellin/QX-314-mediated A-fiber blockade, leaving open the question of what pathway is activated by

TLR5. Overall, the study by Xu et al² introduces a promising new therapeutic strategy to treat persistent pain and will likely shed light on the biology of the A-fibers responsible for conveying touch as painful.

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The authors declare no competing financial interests.

FIGURE LEGEND

Figure 1. Selective blockade strategy. Above, activation of the TRPV1 channel by capsaicin allows entry of the sodium channel blocker QX-314 specifically in nociceptive C-fibers resulting in acute pain inhibition. Below, activation of the TLR5 receptor by flagellin allows entry of the sodium channel blocker QX-314 specifically in A β -fibers producing an inhibition of touch-induced pain after injury.

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