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Silencing TRPV1 containing sensory neurons to treat bone cancer pain

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Nearly half of all cancer patients will experience pain during the course of their disease. Pain that occurs when primary tumors are present in or metastasize to bone is the most common and severe type of cancer pain reported in 75–90% of late stage cancer patients. Cancer induced bone pain consists of ongoing pain that is dull in character, persistent and progressive. Bone cancer pain can also be triggered by movement and produce episodes of intense pain that breakthrough a standard opioid-based regimen significantly limiting daily activity and overall quality of life. Current therapies used to manage bone cancer pain including radiotherapy, opioids, bisphosphonates, and nonsteroidal anti-inflammatory drugs are not completely effective and may be associated with adverse side effects that limit their use. Thus, new analgesic approaches are desperately needed. In this issue of *Anesthesiology*, Fuseya et al. present data from a rodent study to suggest a novel approach for treatment and relief from metastatic bone pain involving systemic administration of the sodium channel blocking agent QX-314¹.

QX-314 is a positively charged quaternary lidocaine derivative that has limited permeability through neural membranes. At relatively high concentrations (10–70mM) QX-314 diffuses through neural membranes to produce sensory and motor blockade in mice². Several years ago, Woolf and colleagues developed an approach to selectively silence nociceptive sensory neurons that involves perineural administration of lower concentrations (5.8mM) of QX-314 with transient receptor potential vanilloid type 1 (TRPV1) agonists³ leading to long term sensory selective nerve block without impairment of motor function or touch sensation. TRPV1 is a large pore cation channel expressed on nociceptive sensory neurons that is activated by multiple pain producing stimuli including noxious heat, extracellular protons (pH < 6.0), membrane derived lipids and capsaicin, the noxious ingredient in hot chili peppers. Perineural administration of capsaicin with QX-314 opens the TRPV1 channel pore allowing entry of QX-314 for maximal long term sodium channel blockade. Fuseya and colleagues hypothesize that in pathological conditions in which TRPV1 is activated,

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Editorial refers to:

Systemic QX-314 reduces bone cancer pain through selective inhibition of TRPV1-expressing primary afferents. (ALN-D-15-01053).

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systemic administration of QX-314 alone would be sufficient to silence nociceptors and reduce bone cancer pain.

To test this hypothesis, the authors use a model of bone cancer pain that involves injection of osteosarcoma cells into the mouse femur. Following tumor inoculation, mice develop spontaneous flinching of the tumor bearing limb. Mice also display movement-evoked pain evident as observable impairment while walking. Previous studies in this model established that bone cancer pain is multifactorial. Cancer and associated immune cells within the bone release algogenic mediators (e.g. nerve growth factor, prostaglandins) that activate and sensitize nociceptive neurons that innervate the bone. Factors released from tumor cells also activate osteoclasts which release extracellular protons producing an acidic environment that drives excessive bone resorption and osteolysis. The resulting acidic environment within the tumor bearing bone is believed to be a primary factor driving bone cancer pain through direct activation of acid sensing ion channels, including TRPV1, on nociceptive neurons. In support of this idea, previous studies in the mouse osteosarcoma model by the authors⁴ and others⁵ have shown that pharmacological inhibition or genetic knockdown of TRPV1 in tumor-bearing mice reduces ongoing bone pain.

In the current study, the authors demonstrate profound reduction of spontaneous flinching of the tumor-bearing limb in mice following acute bolus and continuous (48 hour) administration of QX-314. Interestingly, QX-314 was without effect on movement-evoked pain as QX-314 did not reverse impaired mobility observed during voluntary or involuntary walking in tumor-bearing mice. The authors provide two pieces of evidence that suggest the analgesic efficacy of QX314 is dependent on TRPV1 containing afferents. The authors assess the levels of phosphorylated cyclic AMP response element binding protein (pCREB) in the ipsilateral dorsal root ganglia (DRG) as an indicator of neuronal activation. While bone cancer increased pCREB in TRPV1 and nonTRPV1 containing neurons, QX314 selectively reduced pCREB only in TRPV1 positive neurons. Further, ablation of central terminals of TRPV1 containing afferents in mice prior to tumor inoculation mimicked the results achieved with systemic QX-314, abolishing ongoing pain but failing to reduce movement-evoked pain. These findings raise an interesting question. Are subsets of sensory neurons responsible for driving ongoing versus movement-evoked bone cancer pain?

Sensory neurons are classified based on size, neurochemical phenotype, functional properties, and pattern of innervation. Thickly myelinated A β fibers predominantly detect non-noxious tactile or mechanical sensation. Thinly myelinated A δ fibers detect predominantly noxious mechanical stimuli. Unmyelinated C fibers detect multiple types of noxious stimuli (thermal, mechanical, chemical) and are further subdivided into peptidergic and non-peptidergic subsets containing calcitonin gene related peptide or binding isolectin B4, respectively. Cutaneous tissues contain virtually all sensory neuron subtypes. Skeletal tissue including mineralized bone, bone marrow, and periosteum (the thin layer of cells that surround bone) are innervated by a more restrictive population of only thinly myelinated A δ fibers and unmyelinated peptidergic C fibers⁶ a majority of which express TRPV1 in mice. So what are the afferents responsible for movement evoked pain? The authors posit that it is driven by a small subset of TRPV1 negative A δ or C fibers that innervate the bone. Alternatively, mechanical hypersensitivity has been reported in the plantar aspects of the

paw following intra-femoral tumor inoculation, raising the possibility that impaired walking may reflect avoidance behavior due to sensitization of afferents in the skin or muscle distal to the tumor bearing femur. While not tested in the current study, several strategies are being developed to silence subsets of primary afferents including $A\beta^7$, $A\delta^8$ and non-peptidergic C fibers in rodents which may help answer this question. It is important to note that the relative distribution of TRPV1 on subsets of afferents is species and strain dependent with greater expression of TRPV1 in non-peptidergic C fibers in rats and some strains of mice. Additionally, the severity of bone cancer pain does not always correlate with the extent of osteolysis. Patients with metastatic prostate cancer often develop painful osteosclerotic lesions due to aberrant bone formation. Bone cancer pain from different types of cancer may not be dependent on increased TRPV1 activation. There is likely considerable heterogeneity in mechanisms responsible for bone cancer pain and future preclinical studies using multiple bone cancer models and evolving targeting strategies are needed to provide a more complete picture of the contribution of sensory neuron subsets to ongoing and movement evoked bone cancer pain.

Clinically, systemic delivery of QX-314 may be advantageous providing widespread analgesia to cancer patients with multiple metastases; however a significant concern that would delay clinical introduction is the potential for toxicity which was not examined in the current study. Systemic QX-314 causes central nervous system (CNS) and cardiac toxicity in mice⁹, with a higher potency than systemic lidocaine which is frequently administered clinically in a variety of pain syndromes. Severe irritation and death has been reported in mice with spinal administration of QX-314 at relatively low concentrations (5.8 mM)¹⁰. Additionally, repeat perineural administration of QX-314 with co-administration of a TRPV1 agonist (dilute 0.05% capsaicin) causes delayed mechanical hypersensitivity and signs of nerve degeneration in rats¹¹. It is not clear if a similar risk of toxicity exists with continuous systemic delivery of QX-314 in conditions where TRPV1 is persistently activated as in the current study. Appropriate toxicity screening in rodents and humans would be required before QX-314 could be considered a viable clinical therapy.

Overall, the current study supports an important role for TRPV1 activation in driving ongoing bone cancer pain and the authors propose an intriguing approach to block aspects of this pain state, however additional research is needed to identify a safe and effective strategy for targeting this mechanism to provide clinical relief for metastatic bone pain.

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