



Transient receptor potential vanilloid 1 (TRPV1) as a new target for osteoarthritis-related pain: a commentary on “Sensitization of TRPV1 by protein kinase C in rats with mono-iodoacetate-induced joint pain”

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Comment on: Koda K, Hyakkoku K, Ogawa K, *et al.* Sensitization of TRPV1 by protein kinase C in rats with mono-iodoacetate-induced joint pain. *Osteoarthritis Cartilage* 2016;24:1254-62.

Received: 03 October 2016; Accepted: 28 October 2016; Published: 04 November 2016.

doi: 10.21037/aoj.2016.10.03

View this article at: <http://dx.doi.org/10.21037/aoj.2016.10.03>

Transient receptor potential vanilloid 1 (TRPV1) is a 6-transmembrane ionotropic receptor expressed in peripheral sensory dorsal root ganglion neurons and the dorsal horn of the spinal cord. This receptor was first described in 1997 as responsive to capsaicin and is known to play important roles in noxious stimuli (capsaicin, heat, acid, and endogenous ligands) and allodynia in inflammatory pain. Sensitization of TRPV1 is provoked by phosphorylation of its two Ser residues (Ser502 and Ser800), which occurs secondary to phosphorylation of protein kinase C (PKC) by extracellular inflammatory mediators, including ATP and bradykinin, released from surrounding inflamed tissues. Especially, PKC ϵ plays a key role through its predominant involvement in primary afferent nociceptors (1).

Osteoarthritis (OA)-related chronic pain is a principal cause of impaired activity of daily living. Recent studies have demonstrated a role for TRPV1 in OA pain. Therefore, understanding the functional mechanism of TRPV1 may provide novel targets for the treatment of OA-related chronic pain. Several TRPV1 antagonists have been developed and shown to reduce pain in animal models. However, clinical applications using TRPV1 antagonists were hampered by side effects (hyperthermia and accidental burn) (2). A recent study using local intra-articular administration of the TRPV1 antagonist, JNJ-17203201, demonstrated attenuation of the sensitization

of joint afferent neurons and the pain response without systemic side effects (3). These results indicated that the local injection of TRPV1 antagonists may be a practical method for pain reduction and further progress with this approach is expected.

In the study by Koda *et al.* using a mono-iodoacetate (MIA)-induced joint pain model in rats, the function of TRPV1 was demonstrated to be enhanced through its phosphorylation by PKC ϵ in knee joints and dorsal root ganglion neurons that innervate the knee joints. They also used an enzyme-linked immunosorbent assay to demonstrate that phosphorylation of TRPV1 at Ser800, but not Ser502, was related to capsaicin-induced pain in this model. Phosphorylation at Ser800 was induced by phosphorylation of PKC ϵ as confirmed by the administration of a PKC inhibitor and activator in the knee. Since the MIA rat model is similar to inflammatory pain rather than neuropathic pain, these findings confirmed the importance of sensitization of TRPV1 in OA pain and suggested the potential for the development of PKC inhibitors (especially PKC ϵ), as well as TRPV1 antagonists, to treat this pain, though PKC ϵ inhibitors are not expected to be effective for neuropathic pain. However, the function of PKC ϵ in many organs, such as myocardial protection and the prevention of hypertrophic changes in chondrocytes, should be considered and investigated before the clinical application of such therapy (4,5). Despite these hurdles,

the findings made by Koda *et al.* have great significance and may pave the way for novel therapies utilizing local administration of TRPV1 antagonists or PKC inhibitors to attenuate activation and sensitization of TRPV1 in the nervous system.

The therapy of pain, especially chronic pain, is changing from the control of local inflammation to the attenuation of functional activation of the nervous system. The mechanism of pain modulation is multifactorial and the targets for intervention are diverse, depending on the modes of pain. The development of new drugs with specific and local effects that work through the TRPV1 mechanism, and identification of additional therapeutic targets, will provide substantial benefits to OA patients and possibly other types of chronic pain.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Executive Editor-in-Chief, Dongquan Shi, MD, PhD (Department of Sports Medicine and Adult Reconstruction, Drum Tower Hospital, Medical School, Nanjing University, Nanjing, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/aoj.2016.10.03>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/aoj.2016.10.03

Cite this article as: Ishiguro H, Kaito T. Transient receptor potential vanilloid 1 (TRPV1) as a new target for osteoarthritis-related pain: a commentary on “Sensitization of TRPV1 by protein kinase C in rats with mono-iodoacetate-induced joint pain”. *Ann Joint* 2016;1:21.