Currying Favor With Central Inhibitory Circuits. Focus on: “Effects of TRPA1 Agonists Mustard Oil and Cinnamaldehyde on Lumbar Wide-Dynamic Range Neuronal Responses to Innocuous and Noxious Cutaneous Stimuli in Rats”

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Injury to skin decreases pain thresholds and increases the pain produced by subsequent noxious stimuli. The nature of these changes, termed allodynia and hyperalgesia respectively, depends on a number of factors and has historically been studied by examining the physiological subtype of primary afferent fibers involved (see Treede et al. 1992). Now that the identification of the transient receptor potential (TRP) superfamily of proteins has ushered in a new era in pain research, scientists can address mechanistic questions to understand the plastic changes resulting from skin injury. Members of TRP subfamilies, such as TRPV1, TRPM8, and TRPA1 (to name a few), are expressed in different subpopulations of primary afferents, each of which have different termination patterns in the spinal cord. Moreover, TRPs are activated by both distinct and overlapping stimuli. For example, TRPV1 and TRPM8, respectively, can be activated by both thermal (heat and cold) and chemical (capsaicin and menthol) stimuli; whereas, TRPA1 is unique among TRP family members in that it can be activated by noxious cold as well as a variety of pungent substances found in mustard oil, cinnamon oil (cinnamaldehyde), and garlic. The arrival of specific TRP agonists puts us in a position to revisit results generated previously using nonspecific chemical stimuli and to design experiments to specifically address longstanding questions on the mechanisms that underlie peripheral sensitization, central sensitization, and the potential interplay between the two.

In a recent article, Merrill and colleagues (2008) characterized the effects of two TRPA1 agonists, mustard oil (allyl isochocyanate, AITC) and cinnamaldehyde (CA) on wide-dynamic range (WDR) neurons in the rat spinal cord in vivo. WDR neurons, which are primarily located in lamina V, possess several key features that make them essential for understanding nociceptive transmission and modulation. First, they respond to mechanical, thermal, and chemical stimuli over a range of stimulus intensities. Second, they are positioned to receive, and integrate, polysynaptic input from primary afferent neurons (A- and C-fibers) by way of the substantia gelatinosa (SG) in the superficial dorsal horn and to relay this information to sites within the brain. Third, WDR neurons exhibit a phenomenon known as “wind-up” in which repetitive electrical stimulation yields progressive increases in C-fiber-evoked responses centrally.

Activation of TRPA1 produces acute pain, neurogenic inflammation, and hypersensitivity to thermal and mechanical stimuli in several species including mouse, rat, and man. For each TRPA1 agonist, the authors examined the direct effect of the compound on the activity of WDR neurons and the subsequent responses to exogenous stimuli. They first show that AITC directly activates approximately half of the WDR neurons tested. By contrast, CA fails to directly excite WDR neurons. Nonetheless, both AITC and CA enhanced the responses to noxious thermal, but not mechanical, stimuli. These results are consistent with the notion that AITC sensitizes peripheral heat nociceptors as was previously demonstrated by Reeh and colleagues (1986), who studied the effect of AITC on C-fiber afferents. These investigators found that topical application of AITC to the receptive fields of polymodal nociceptors enhanced responses to subsequent thermal, but not mechanical, stimuli and that low-threshold mechanosensitive C-fibers, which were unresponsive to thermal stimuli ≤52°C, could be excited by AITC and made responsive to heat stimuli. Interestingly, AITC-induced ongoing discharges in these fibers were abolished by application of ice (cooling to 12°C). TRPA1 is present in a subset of nociceptive peptidergic primary afferent neurons that express TRPV1, but it is not coexpressed with TRPM8. Numerous studies have raised the possibility of cross-sensitization and modulation of primary afferent activity by neurons that express TRPV1, TRPM1, and TRPM8. The present study reinforces this notion in that activation of TRPA1 by AITC can sensitize subsequent responses to heat mediated by TRPV1. CA did not affect responses to cooling, but the role of TRPA1 in cooling responses remains an open question as the effect of AITC on cooling was not tested.

That topically applied AITC enhances the activity of WDR neurons via activation of primary afferent nociceptors and promotes peripheral sensitization could be predicted from the existing literature. However, a surprising, and potentially important, finding from this paper was that the wind-up response of WDR neurons was reduced, even when AITC induced peripheral sensitization. CA, like AITC, induced peripheral sensitization but did not activate WDR neurons and failed to reduce wind-up. Therefore inhibition of the wind-up response after TRPA1 activation requires afferent drive sufficient to engage spinal inhibitory circuits. Consistent with this idea, Lu and Perl (2003) showed that unmyelinated fibers modulate C-fiber afferent activity in SG neurons. Furthermore, earlier this year Kosugi et al. (2007) showed that in spinal cord slices TRPA1 agonists enhance inhibitory as well as excitatory postsynaptic currents in all neurons studied. By contrast, capsaicin does not affect inhibitory synaptic transmission, which suggests that TRPA1 and TRPV1 do not fully overlap at central terminals of primary afferent fibers. What accounts for this inhibitory effect of AITC on wind-up? Can a similar
phenomenon be observed with endogenous activation of TRPA1 and/or under other pronociceptive conditions? Recent results implicate 4-hydroxynonenal (HNE) as an endogenous aldehyde that can produce pain and neurogenic inflammation by activating TRPA1 (Trevisani et al. 2007). Using scavengers of reactive oxygen species and peripheral injection of capsaicin, data from Lee and colleagues (2007) suggest that oxidative stress in the spinal cord contributes to behavioral hyperalgesia and the associated heightened responses of WDR neurons. Thus activation of TRPV1 in the periphery could, in principle, increase levels of reactive oxygen species in the spinal cord and activate presynaptic TRPA1. To translate this effect into a reduced wind-up response, one would need to consider the possibility for bimodal actions of putative endogenous ligand(s) on TRPA1, as has been demonstrated with menthol (Karashima et al. 2007) and/or a shift in the balance of excitatory and inhibitory transmission evoked by peripheral application of AITC.

Merrill et al. provide evidence that TRPA1 participates in a polysynaptic inhibitory pathway within the dorsal horn. Considered with several other groundbreaking papers on TRPA1 published in 2007, this work lays the foundation for identifying endogenous activators of TRPA1 within the spinal cord and raises several intriguing possibilities. Under what circumstances could activation of TRPA1 potentiate inhibitory synaptic transmission in the superficial dorsal horn? Rather than considering analgesia in the context of blocking peripheral activation of primary afferent nociceptors, does TRPA1 provide an opportunity for directly and/or selectively activating central inhibitory pathways? TRPA1 could serve as a cornerstone on which we build our understanding of central control of nociception at the level of the spinal cord.

REFERENCES


