Editorial

Reactive aldehydes: a new player in inflammatory pain

Erika L. Galer, Peter M. Grace

Department of Psychology and Neuroscience and the Center for Neuroscience, University of Colorado Boulder, Boulder, Co 80309, USA
Correspondence to: Peter M. Grace, PhD. Campus Box 345, University of Colorado Boulder, Boulder, Co 80309, USA.
Email: peter.grace@colorado.edu.

Submitted Jan 30, 2015. Accepted for publication Feb 03, 2015.
doi: 10.3978/j.issn.2305-5839.2015.03.27
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.03.27

Pain is a costly problem worldwide. USA expenditures on pain are higher than those for cancer, heart disease, and diabetes combined, at approximately $560 billion annually (1). As noted recently (2), pain therapeutics are dominated by well-established drug classes that are focused on symptom reduction, and are plagued by limited efficacy and/or significant adverse effects. NSAID's are used to treat acute pain and are accompanied by risk of cardiovascular damage, liver damage, kidney damage, and delayed bone healing (3). COX-2 inhibitors have limited efficacy and can cause cardiovascular problems (4,5). Mechanism-based treatments that are individualized to patients with particular underlying pathophysiology have long remained the goal for preclinical and clinical researchers alike (6,7). In a recent article, Zambelli *et al.* (8) document their discovery of a new mechanism of inflammatory pain that may lead us closer to a mechanism-based therapeutic approach.

Zambelli *et al.* investigated the role of a variant of the gene ALDH2 (ALDH2*2) in inflammatory pain. ALDH2 is a gene that encodes for the cytosolic and mitochondrial enzyme aldehyde dehydrogenase that is responsible for aldehyde metabolism. The enzyme is known for its role in alcohol metabolism. The product of ALDH2*2 is an non-functional form of aldehyde dehydrogenase that leads to cellular accumulation of acetaldehyde. Following an intraplantar carrageenan injection, Zambelli *et al.* found that ALDH2*2 knock-in mice were more allodynic than the wild type mice. There were no baseline differences in nociception between the genetic variants, suggesting that the gene does not contribute to basal nociception. Zambelli *et al.* then assessed the analgesic efficacy of Alda-1, a small molecule chaperone that binds to both the functional and non-functional forms of acetaldehyde dehydrogenase. Systemic Alda-1 treatment reversed carrageenan-induced allodynia to baseline levels in both the ALDH2*2 knock-in mice and wildtype mice.

Zambelli *et al.* hypothesized aldehydes to cause allodynia of rats after an intraplantar carrageenan injection. Following intraplantar carrageenan, rats were systemically treated with Alda-1. Alda-1 significantly attenuated thermal hyperalgesia and mechanical allodynia compared to vehicle-treated rats. Furthermore, hindpaw levels of the reactive aldehydes, 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA) were elevated following intraplantar carrageenan compared to saline. 4-HNE and MDA levels were decreased by Alda-1 treatment. Hence, the nociceptive behavior is correlated with aldehyde load induced by inflammation. To assess sufficiency of aldehyde load to induce nociceptive behavior, Zambelli *et al.* examined the direct effect of acetaldehydes on nociceptive behavior. Acetaldehyde injection induces nociceptive behaviors in both variant and wild-type mice, but these were more robust in the ALDH2*2 mice. Zambelli *et al.* did not test whether Alda-1 attenuates acetaldehyde-induced nociceptive behaviors in order to demonstrate a direct effect on acetaldehyde metabolism. Nor did they examine whether 4-HNE and MDA were the metabolites responsible for nociceptive behavior. Nonetheless, increased aldehyde load has been linked to inflammatory pain for the first time, suggesting a new therapeutic approach.

Zambelli *et al.* have introduced us to a novel role for acetaldehyde metabolism in inflammatory pain, opening up many new avenues for investigation. The first is a mechanism by which reactive aldehydes contribute to pain sensitivity following an inflammatory insult. Reactive aldehydes are a common by-product in cellular processes. In response to oxidative stress, polyunsaturated fatty acids become peroxidized into different aldehydes (9). One of

the most studied reactive aldehydes is 4-HNE. 4-HNE has been shown to cause cytotoxic effects, inhibition of DNA, RNA, and protein synthesis, and inflammatory cell migration (9). These effects can be observed in the surrounding tissue as well as distal tissue, since reactive aldehydes are migratory (9). 4-HNE activates both TRPV1 and TRPA1 receptors, inducing nociceptive hypersensitivity and release of substance P and calcitonin gene related peptide (CGRP) in the spinal cord (10,11). TRPV1 and TRPA1 are part of the transient receptor potential (TRP) family of ion channels that are expressed on C fibers of afferent somatosensory neurons. TRP channels have a well-established role in inflammatory and neuropathic pain (12). The pathway(s) by which aldehyde load is increased during inflammatory pain, and whether TRP channels mediate nociceptive hypersensitivity due to dysfunctional aldehyde metabolism requires elucidation.

The second line of investigation is the new small molecule chaperone, Alda-1. Perez-Miller *et al.* (13) found the small molecule Alda-1 to be an agonist for mitochondrial aldehyde dehydrogenase. Alda-1 bound both the functional and non-functional forms of acetaldehyde dehydrogenase to activate the enzyme. The Alda-1 molecule is new and should be further explored for the treatment of pain. A necessary step is to investigate how ubiquitous increased aldehyde load is among different pre-clinical models of inflammatory pain and even neuropathic pain, and whether these models are sensitive to Alda-1 treatment. Given that current anti-inflammatories have limited efficacy and serious side effects, new approaches are desperately needed.

A potential way to clinically validate the mechanism described in this study is to determine the association of ALDH2*2 with pain. Strikingly, the ALDH2*2 variant is carried by 35-45% of the East Asian population (14). Comparative studies show that Asian populations are more responsive to painful stimuli than other ethnicities (15-17). This is at odds with the finding of the present study, in which there were no basal nociceptive differences between variant carriers or wild-type mice. Nonetheless, while the results of this study would predict an increased burden of inflammatory pain among ALDH2*2 carriers, such gene association studies have not yet been performed.

Zambelli *et al.* has shown that the ALDH2*2 variant decreases the metabolism of reactive aldehydes 4-HNE and MDA after an inflammatory challenge, which coincides with decreased pain thresholds in rodents. Further investigation into the mechanisms by which reactive aldehydes affect pain thresholds would be of interest since reactive aldehydes are a common biological product. It would also be of interest to investigate how prevalent this mechanism is among preclinical inflammatory and neuropathic pain models. Moreover, the potential for Alda-1 as a mechanistically targeted pain therapeutic is an important outcome of this study.

Acknowledgements

Peter M. Grace is an NHMRC CJ Martin Fellow (ID: 1054091).
Disclosure: The authors declare no conflict of interest.

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Cite this article as: Galer EL, Grace PM. Reactive aldehydes: a new player in inflammatory pain. Ann Transl Med 2015;3(S1):S23. doi: 10.3978/j.issn.2305-5839.2015.03.27

