Reactive aldehydes: an initial path to develop precision medicine for pain control

Vanessa O. Zambelli[1], Che-Hong Chen[2], Eric R. Gross[3]

[1]Laboratory of Pain and Signaling, Butantan Institute, São Paulo 05503-900, Brazil; [2]Department of Chemical and Systems Biology, [3]Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA

Correspondence to: Dr. Eric R. Gross. Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA. Email: ergross@stanford.edu.

Abstract: With the risks of opioid addiction, abuse, and overdose, there is a need to identify new molecular targets contributing to pain sensation in order to develop directed treatments for pain. One mechanism to treat pain is to target reactive aldehydes either by limiting production or by increasing metabolism. In response to a recent editorial in the *Annals of Translational Medicine* (*ATM*), we discuss how reactive aldehyde production can trigger pain and how the enzyme mitochondrial aldehyde dehydrogenase 2 (ALDH2) regulates inflammatory pain by reactive aldehyde metabolism. We also comment about the possible clinical impact caused by the inefficiency of reactive aldehyde metabolism for the ~540 million people with an ALDH2*2 variant. Further, we discuss how developing therapeutics specifically targeting ALDH2 may lead to the development of a pathway to potentially create precision medicine for pain control.

Keywords: Reactive aldehydes; aldehyde dehydrogenase 2 (ALDH2); ALDH2*2; precision health; pain

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We would like to thank Galer and Grace for their well written editorial regarding our recent manuscript (1,2). We also would like to thank *Annals of Translational Medicine* (*ATM*) for the opportunity to respond to the editorial and further share our expertise in this field. Ultimately, studying reactive aldehyde production and metabolism may provide more personalized approaches for pain control and allow for novel treatment strategies to assist people suffering from pain without the undesired risks of drug addiction, abuse and overdose.

Several questions remain in regards to how aldehyde production can trigger pain. Reactive aldehyde production occurs by lipid peroxidation of mitochondrial and plasma membranes from reactive oxygen species (ROS). Our results suggest a noxious insult is required to produce painful levels of reactive aldehydes (2). We agree with the authors of the editorial that deciphering more of the signaling pathway which is triggered after reactive aldehyde production is needed both at the level of cell-to-cell interactions and the molecular signaling which occurs within a cell. For example, leukocyte migration during inflammatory disease is the main source of ROS (3). In carrageenan- or formalin-induced inflammation models, leukocytes may be responsible for generating 4-HNE, malondialdehyde and acetaldehyde at sources of injury. Further, acetaldehyde and 4-HNE directly activate transient receptor potential (TRP) channels (4,5). Both cell-to-cell interactions and the connection between reactive aldehydes and TRP channel activation indeed need further study. Regardless of the signaling pathways activated, designing therapeutics limiting reactive aldehyde production may provide treatments particularly helpful as a pre-treatment when pain is expected, such as during surgeries.

After reactive aldehydes are produced by a noxious insult, targeting aldehyde metabolism (or detoxification) would be beneficial. Small molecules, such as Alda-1, which improve aldehyde metabolism, will be important to clear reactive aldehydes quickly which may cause pain. The Mochly-Rosen laboratory also recently described an alternative strategy to metabolize reactive aldehydes

by borrowing other ALDH enzymes to do the work of aldehyde dehydrogenase 2 (ALDH2) (6). This may be another strategy to treat patients who have a decreased ability to metabolize reactive aldehydes, such as those with an ALDH2*2 genetic variant.

Generally, in order for effective translation of these findings, research is needed to understand how reactive aldehydes are involved in the pain signaling pathway for different types of pain. It is critical to decipher and distinguish the contribution of reactive aldehydes for pain of different duration (acute or chronic), type (inflammatory, neuropathic) and location (head, chest, abdomen, testicular, cervical and peripheral). Most likely specific types of pain will be more responsive to strategies targeting aldehyde metabolism compared to others.

For the ~540 million people in the world who carry the ALDH2*2 variant (which severely limits reactive aldehyde metabolism by over 60% compared to the wild type ALDH2), more studies are needed to elucidate how the ALDH2*2 variant effects pain and pain control in humans. It is also important to recognize that two subgroups of the ALDH2*2 population will require further study; heterozygotes for the ALDH2*2 variant and homozygotes for the ALDH2*2 variant (since homozygotes have a more severe decreased ability to metabolize reactive aldehydes). As suggested by our study, when ALDH2*1/*2 rodents are subjected to noxious insults, the response to a noxious stimulus (such as formaldehyde) is increased in intensity and duration (2). In humans, people with an ALDH2*2 variant perhaps are more susceptible to developing diabetic- and alcohol-induced neuropathy (7,8). Further, specific drug selection to treating pain may need to be considered since acetaminophen blocks ALDH2 activity by ~14-28% (9). This reduction in enzymatic activity may be negligible for those with a wild type ALDH2 variant. However, for those with an ALDH2*2 variant, acetaminophen may not be as effective for pain control for this patient population since it may limit further reactive aldehyde metabolism.

The ALDH2*2 variant itself is also clearly linked to additional pathophysiology including an increased susceptibility for heart disease, osteoporosis and esophageal cancer (10). Due to these considerations, with the generous support of President Yen and Taipei Medical University, an inaugural symposium was held in Taiwan that brought together over 25 research groups studying the pathophysiology caused by the inefficiency of reactive aldehyde metabolism and provided a basis to form a consortium. With more combined research efforts from laboratories with their scientific expertise, we may continue to discover more ways to tailor medicine specifically for those with an ALDH2*2 variant to ultimately provide them the best medical care available. Providing treatments tailored to people with reduced aldehyde metabolism may be a first step of delivering precision medicine for those with an ALDH2*2 variant while understanding how pain is regulated for all patient populations.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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