Is Acid Painful or not?

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Is acid really painful? For patients who suffer with arthritis, fibromyalgia, myofascial pain, lumbar radiculopathy, etc., the answer is definitely YES [1-6]. Pain associated with tissue acidosis occurs where there is/are tissue injury, inflammation, ischemia, fatiguing exercise, or tumors [7-14]. So, what is the scientific evidence to show that acid does evoke pain? In 1996, Issberner and colleagues demonstrated an infusion of phosphate buffer (pH 5.2) into the forearm muscles caused immense muscle pain in human [15]. More recently, Frey Law and colleagues showed the infusion of acidic phosphate buffer (pH 5.2) to human leg muscles triggered a primary mechanical hyperalgesia in the local infusion site (indicating a local pain), and a second hyperalgesia in a distal part like ankle (indicating a referred pain) [16]. The mechanism which underlying the acid-induced muscle pain has been thoroughly investigated in a rodent model of acid-induced chronic widespread pain developed by Sluka’s group [17-20].

Accumulating evidence has shown that acid-sensing ion channel 3 (ASIC3) and transient receptor potential cation channel V1 (TRPV1) are the main acid sensors involved in the development of acid-induced muscle pain [18, 20]. However, this concept may be over simplified the main function of acid signaling in muscle pain. Chen and colleagues revealed that around 50% of small-to-medium sized (20-40 μm in diameter) muscle afferent DRG neurons expressed acid-induced inward currents independent of ASIC3 and TRPV1, suggesting the non-ASIC3, non-TRPV1 acid signaling may also contribute to the pain modulation in the muscle afferent neurons [20,21]. To test whether the non-ASIC3, non-TRPV1 acid signaling plays a role in pain modulation in muscle nociceptors, pharmacological blockage and genetic ablation approach were used in the Sluka’s model of acid-induced chronic widespread pain [22]. In this pain model, mice would develop referred and mirror-image chronic hyperalgesia after 2 injections (separated 1–5 days) of pH4.0 acid saline to the same side of the gastrocnemius muscle [18]. The first acid injection not only produces transient hyperalgesia that diminishes...
in 24 h, but also triggers a priming effect on ASIC3- and/or TRPV1-positive muscle nociceptors \cite{20}. The priming effect of muscle nociceptors allows the mice to develop a long-lasting hyperalgesia, which would last for more than 4 weeks when a second acid insult injected to the same muscle 1 to 5 days later. In the Chen & Chen’s paper (2014), we reported that, during the first acid injection accompanied by the blockage of ASIC3 and TRPV1 channels abolished the acid-induced transient hyperalgesia and subsequently impede the formation of chronic hyperalgesia by the second acid challenge 5 days later. As the ASIC3- and TRPV1-mediated signaling was pharmacologically blocked during the first acid injection, the second acid challenge given 5 days later evoked only transient hyperalgesia. Intriguingly, the second acid injection totally failed to induce any hyperalgesic effect if given in 2 days, suggesting that the non-ASIC3,
non-TRPV1 acid signaling would mediate a prolonged antinociceptive effect that lasts at least for 2 days (Fig. 2).

What is the molecular mediator underlying the acid-induced antinociception in muscle? Chen & Chen also reported the acid-induced antinociceptive signaling must require the release of SP from non-ASIC3, non-TRPV1 muscle afferent neurons \[^{22}\]. In 2012, Lin and colleagues discovered that SP evoked antinociceptive effects in ASIC3-expressing muscle nociceptors, whereby SP enhances Kv7-mediated potassium current to counteract the activation of ASIC3 \[^{19}\]. In muscle, acid (increased proton concentration due to tissue acidosis) not only depolarizes ASIC3-expressing muscle nociceptors, but also simultaneously stimulates SP release in local nerves. SP acts on the NK1 receptors of muscle nociceptors, in which NK1 receptor activation is coupled with tyrosine kinase and Kv7 potassium channels, but not the conventional G-protein signaling. In mice lacking SP signaling, either genetic ablation or pharmacological inhibition, a single intramuscular acid injection is sufficient to induce a long-lasting hyperalgesia \[^{19}\]. Likewise, the non-ASIC3, non-TRPV1 acid signaling-mediated prolonged antinociception is abolished in SP knockout mice \[^{22}\], indicating SP may be the key mediator involved in the acid-induced antinociception in muscle. However, the mechanism of how SP release is triggered in non-ASIC3, non-TRPV1 expressing neurons to modulate muscle pain is still unknown.

SP is a neuropeptide released from nociceptors and is well known to modulate pain signals in both spinal dorsal horn and primary afferent neurons \[^{23-27}\]. In the CNS, SP plays a pivotal role in leading to central sensitization by the activation of glutamate-dependent excitatory postsynaptic potential \[^{28}\]. In the PNS, the endogenous release of SP in cutaneous sensory nerves causes neurogenic inflammation \[^{23, 29}\]. Although SP is expressed in muscle nociceptors, intramuscular SP injection does not elicit neurogenic inflammation response and pain sensation \[^{2, 30}\], suggesting the differential function of SP modulates pain transmission in the skin and muscle nociceptors.

To probe the possible ways that can trigger the enhancement of endogenous SP release in muscle, we adopted pharmacological approach to block the ASIC3 and TRPV1 signaling in the mouse model of acid-induced chronic widespread pain. We clearly demonstrated that SP
analgesia was induced via the non-ASIC3, non-TRPV1 acid signaling in wild type mice but not in SP null mutants. To further support this finding, we used NK1-selective agonist SM-SP to mimic the SP effect, which lead to NK1 receptor activation. Pretreatment with NK1-selective agonist 1 day before the first acid injection diminished acid-induced transient hyperalgesia and thus replicated the prolonged antinociceptive phenomena of the non-ASIC3, non-TRPV1 acid signaling. These results clearly suggest that SP is the main key player to have acid-mediated prolonged antinociceptive effect on muscle nociceptors in a non-ASIC3, non-TRPV1 signaling pathway. To show the working duration of SP effect, we repeated the experiment and pretreatment with NK1-selective agonist 5 day before the acid injection. The result demonstrated an evoked acid-induced transient hyperalgesia at 5 days, suggesting the SP antinociception only works between 1 to 5 days. However, more experiments are needed to justify the specific duration of SP analgesic effect between these periods of time.

Taken together, the Chen & Chen’s study show acid mediates a prolonged antinociceptive pathway, in which acid may act on neither ASIC3- nor TRPV1-positive muscle afferent neurons to cause the release of SP [22]. These non-ASIC3 or non-TRPV1 muscle afferent neurons may express other ASIC subtypes (e.g. ASIC1a, ASIC1b, and ASIC2a) or a group of proton-sensing G protein-couple receptors (e.g. G2A, GPR4, OGR1, and TDAG8) involved in the SP release, but yet to be determined [31,32]. Moreover, how SP inactivates the muscle nociceptors from further firing in 2 days after the first acid insult still remains unknown. Nonetheless, these findings give us an opportunity to expand our knowledge further of how acid not only can cause muscle pain but also act as a break to prevent nociception or limit the hyperalgesia to a transient phase via the SP antinociceptive signaling (Fig. 1).

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