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Review Article

Acid-sensing ion channels and their role in controlling pain in the post-operative stage

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Abstract: Acid-sensing ion channels (ASICs) are proton-gated cation channels that are widely expressed throughout the nervous system and play a central role in sensory processing, particularly in nociception. Due to their involvement in key physiological processes, ASICs have emerged as promising targets for the modulation of pain perception. Postoperative pain management is primarily dependent on pharmacological agents, such as opioids and non-steroidal anti-inflammatory drugs (NSAIDs), to alleviate discomfort and facilitate recovery. However, the long-term use of these analgesics is associated with significant risks, including opioid dependence, tolerance, and other adverse effects. As such, the development of non-pharmacological alternatives for pain management is critically needed. Modulating ASIC activity offers a compelling approach to attenuate pain perception, providing an opportunity to reduce reliance on traditional pharmacological agents and their associated side effects. This highlights the importance of further research into ASICs as therapeutic targets for pain management, which could revolutionize postoperative care by offering safer and more effective pain relief strategies.

Keywords: Acid-sensing ion channels, pain, post-operative pain management, pain modulation, surgery

Introduction

Acid-sensing ion channels (ASICs) are proton-gated cation channels expressed in both the central and peripheral nervous systems [1], where they play a critical role in detecting extracellular pH fluctuations [1, 2]. The structure of ASIC subunits consists of two hydrophobic transmembrane domains, short intracellular N- and C-termini, and a large cysteine-rich extracellular loop [2]. ASIC channels are primarily activated by protons and are permeable to Na^+; however, certain subunits, such as ASIC1a, exhibit additional permeability to Ca^{2+} [3]. Functional ASIC channels are formed by the assembly of homomeric or heteromeric subunitsor identical anddistinct subunits, respectively [4-6]. Each subunit has a distinct name such as ASIC1, ASIC2, ASIC3, which can then be subdivided into ASIC1a, ASIC2b, etc. ASIC2b and ASIC4 cannot form functional channels by themselves, but they can form a heteromeric complex with other ASIC subunits [7, 8]. For example, ASIC4 can associate with ASIC1a or ASIC3 to form heteromeric channels and modulate the activity of ASIC1a and ASIC3 [9, 10]. ASICs contribute to various physiological processes, and are regulated by specific activators and blockers [11-17], allowing them to modulate distinct physiological responses, including drug-seeking behavior [18, 19] and nociception [20-22].

Certain ASIC subtypes, such as ASIC1a, are predominantly expressed in the central nervous system (CNS), while others, such as ASIC3, are found in the peripheral nervous system (PNS) [12, 35, 49]. ASICs are sensitive to changes in extracellular pH [23, 24], enabling them to detect pathological conditions associated with altered pH levels [20, 22, 25-32]. Lactic acidosis, commonly associated with injury or inflammation, often occurs due to inadequate oxygen supply at the tissue level [51, 52], or as a consequence of conditions like diabetic ketoacidosis [53], sepsis [54], and myocardial ischemia [55]. Upon activation, ASICs in muscle nociceptors and non-neuronal cells generate a large, rapidly desensitizing inward ion current [24]. Notably, the desensitization rates of ASICs vary

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depending on the subunit composition; for instance, ASIC1a, ASIC1b, and ASIC2a exhibit more strong pH-dependent desensitization [33], whereas ASIC3 demonstrates less pH-dependent desensitization [3, 34, 35]. In addition to pH decreases, ASICs can be activated by other factors such as non-proton ligands (e.g. glutamate, calcium, and zinc) [36-42] and mechanical stimuli [3, 43, 44]. Modulation of ASIC function can influence the sensitivity of sensory pathways and regulate physiological responses, including parasympathetic control of circulation and subsequently blood pressure [45-48].

In the United States, approximately 40-50 million surgeries are performed annually, with around 80% of patients reporting postoperative pain [56, 57]. Although various analgesics are employed to manage postoperative pain, they often come with undesirable side effects. Opioids, once widely prescribed for pain relief, have become a major concern due to their potential for misuse and addiction. Studies indicate that the prescription of opioids is associated with an increased risk of chronic opioid use, with a 44% higher likelihood of long-term opioid dependence following surgery [58]. These findings underscore the need to reduce opioid use in clinical practice and highlight the importance of developing alternative therapeutic strategies, particularly those targeting ASIC channels, for improved pain management.

Role of ASICs in pain

ASIC1a, ASIC1b, ASIC2b, and ASIC3 are highly expressed in small and medium nociceptive neurons across both the central and peripheral nervous systems and are particularly associated with high-threshold unmyelinated C fibers and myelinated Aδ fibers, both of which are integral to pain transduction and nociception [3]. Pain can be directly induced through the application of protons to the skin, with inhibition of proton influx via ASICs resulting in reduced pain perception [59]. Moreover, mild acidosis can inhibit various potassium channels, leading to the depolarization of ASICs and a subsequent increase in pain sensation [60]. This acidosis further impairs glutamatergic and GABAergic neurotransmission, thereby exacerbating nociceptive signaling and contributing to heightened pain [61].

Localized inhibition of ASICs has been explored as a strategy for targeting pain in specific regions of the body. In the heart, ASIC3 is the predominant isoform, with an increase in channels seen particularly following events of cardiac damage such as myocardial ischemia [62]. During ischemia, the accumulation of lactic acid increases which promotes the expression of ASICs, leading to a heightened proton influx through these channels and an amplification of pain signals. Similarly, ASIC3 is also the primary isoform in the gastrointestinal tract, and ischemic conditions, such as mesenteric ischemia, results in an upregulation of ASIC3 channels in the affected tissues [63-65]. Given the distinct localization of different ASIC subtypes throughout the body, specific activators and inhibitors of these channels can be utilized to achieve targeted, localized pain management.

Materials/methods

We conducted a comprehensive literature search using PubMed. The search was limited to English-language articles published between 1991 to 2024, and included the terms acid-sensing, ASIC, ion channels, and pain control. Additional relevant studies were identified by manually reviewing the reference lists of the selected articles.

Two reviewers independently screened the 80 titles and abstracts of the retrieved articles for relevance. Studies meeting the inclusion criteria were selected for full-text review. Any disagreements were resolved through discussion and consensus.

Inclusion criteria were: (1) original and review articles; (2) published in English; (3) published from 1991 to 2024; (4) and discussing the topic of acid sensing ion channels, particularly its role in pain. Articles such as commentary pieces, letters to the editor, and case reports were excluded.

Results

Current regimen for postoperative pain management

The standard approach for managing postoperative pain typically involves a combination of opioids, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs). Effective man-

agement of postoperative pain is essential for promoting patient recovery and facilitating a smooth transition back to baseline functional status [71]. However, the use of opioids as first-line analgesics has been increasingly reduced due to concerns surrounding opioid misuse, addiction, and overdose-related fatalities [72, 73]. Additionally, prolonged opioid use can lead to the development of tolerance, necessitating higher doses to achieve the same level of pain relief, which in turn increases the risk of adverse effects [74]. Currently, there is a pressing need to identify alternative pharmacological agents for pain management that minimize the risk of physical dependence while maintaining therapeutic efficacy. To optimize pain control, it is essential to understand the underlying nature of the pain, as it can manifest in distinct forms such as inflammatory, neuropathic, or nociceptive pain [75]. Each type of pain involves different nerve fibers and mechanisms, which necessitate tailored treatment strategies for optimal management.

The role of ASICs in postoperative pain management

In investigating the role of ASICs in modulating pain, it is clear that ASIC1 and ASIC3 channels, which are co-expressed on innate immune cells, play a critical role in pain mechanisms. Primary hyperalgesia, which is defined as pain originating directly from tissue injury, and secondary hyperalgesia, which refers to pain in areas distant from the injury site [35], are both significantly influenced by these channels. Studies done on animal models with deficiencies in ASIC1 and ASIC3 have demonstrated that both primary and secondary hyperalgesia fail to develop upon exposure to noxious stimuli [35]. Moreover, complete blockade of ASIC3 channels in mice, even in the presence of muscle inflammation, effectively inhibited both types of hyperalgesia [35].

Further research on ASIC3 channels has revealed that their absence can increase the sensitivity of rapidly adapting mechanoreceptors in the skin, while simultaneously decreasing the mechanosensitivity of Aδ- and C-fiber nociceptors [50]. Clinically, this results in heightened sensitivity to mechanical stimuli but a diminished perception of pain. A similar effect has been observed in animal models deficient in ASIC1a and ASIC2 channels [50].

Neuropathic pain, caused by damage to the somatosensory nervous system, is characterized by the release of inflammatory mediators such as interleukin-1α, interleukin-1β, and tumor necrosis factor-α, which activate nearby immune cells and sensitize nociceptors, contributing to pain [76]. In rodent models with neuropathic pain, the manipulation of ASIC channels, specifically the deletion of ASIC3, has been shown to reduce the duration of mechanical pain and attenuate thermal hyperalgesia, supporting the hypothesis that modulation of these channels can mitigate pain and inflammation [76].

Muscle pain, typically resulting from inflammation, structural changes, or biomechanical dysfunction, is often associated with a decrease in tissue pH. ASIC3 channels play a central role in detecting the pH drop and triggering a desensitizing inward current, which promotes the expression of inflammatory mediators and subsequently, increases the number of ASIC channels present at the site of injury [35]. In animal models of muscle inflammation, the absence of ASIC1 prevented the development of primary hyperalgesia, while the absence of ASIC3 inhibited the onset of secondary hyperalgesia [35]. These findings suggest that ASIC1 is primarily involved in primary hyperalgesia, while ASIC3 is crucial for secondary hyperalgesia. Furthermore, injection of an acidic solution in animal models induced primary hyperalgesia in those with functional ASIC1b channels but did not provoke this response in models lacking ASIC1b channels [35].

ASICs have been shown to play a role in the modulation of emotions as well [81, 82]. Areas of the brain responsible for emotional regulation, the amygdala and hippocampus, have high concentrations of ASICs and thus can be affected by ASIC inhibitors and activators [79]. Similar to the development of pain during inflammation, emotional stress is another acidic condition which activates ASICs to permit sodium ion influx and thus neural activity within the brain. Both physical injury and emotional distress act upon ASICs thus causing similar effects in terms of the perception of harm [79]. ASIC1a and ASIC2 have been identified as two key channels in the amygdala with studies reporting that mice depleted of ASIC1a channels faced a reduction in the emotion of fear [79].

When considering the utility of ASIC modulation and its effects in pregnant women, research is limited. One study has identified the role of ASIC2a in seizures to demonstrate that pregnant mice with reduced expression of ASIC2a have an increased sensitivity to seizures [80]. Seizures in pregnancy can not only harm the mother, but they are also associated with eclampsia, a serious condition where seizures occur due to high blood pressure, thus causing severe damage to fetal blood flow and development [80]. Little research has been done on the use of ASIC manipulation as a method for pain control in pregnant women. Some medications that are used after delivery for pain control include ibuprofen, acetaminophen, and opioid medications, which may be effective but also present the risk of pharmaceutical dependence which can affect the mother and baby much later down the line. Future research to understand the utility of ASICs in pregnant women, especially in terms of pain control post-delivery, will not only aid in the development of non-pharmaceutical treatments for these mothers but also decrease the risk of potential dependence.

Discussion

Compounds known to modulate ASIC activity

Several compounds have been identified as modulators of ASIC activity, showing potential in pain management. Notably, peptides such as APETx2, derived from the *Anthopleura elegantissima* sea anemone, and PcTx1 from South American tarantulas, have been shown to effectively block ASIC channels, thereby providing pain relief [24, 66]. APETx2 specifically inhibits ASIC3 channels, while PcTx1 selectively inhibits ASIC1a homomultimers [24]. In rodent models, APETx2 has demonstrated efficacy in reducing postoperative pain 24 hours following surgery and in managing muscular pain [67, 68]. These findings suggest that APETx2 may be particularly useful for alleviating muscular discomfort. Additionally, peptides π-AnmTX Hcr 1b, -2, -3, and -4, which share sequence similarities with APETx2, inhibit ASIC1a, thereby broadening the scope of potential pain management options compared to the selective inhibition of ASIC3 by APETx2 [69].

NS383 is a small molecule known to inhibit ASIC1a and ASIC3, with partial inhibition observed when ASIC1a and ASIC3 are co-expressed with ASIC2a subunits [70]. In clinical trials, NS383 demonstrated potency 10 to 30 times greater than amiloride, a well-known diuretic and ASIC inhibitor, though it had minimal effects on homomeric ASIC2a channels [3, 70]. Unlike amiloride, which exhibits consistent inhibitory effects across a pH range of 5 to 6.5, the efficacy of NS383 decreased as pH levels dropped [70]. The pain modulation effects of both compounds were evaluated in animal models induced with complete Freund's adjuvant (CFA), which leads to persistent inflammatory hyperalgesia and increased ASIC subunit expression in pain pathways [70]. Significant changes in weight-bearing behavior were observed 24 hours after CFA injection, indicating spontaneous pain, which was alleviated by NS383, amiloride, and acetaminophen, confirming their role in mitigating inflammation-induced pain [70]. However, only amiloride and acetaminophen affected the tail flick response in CFA-treated rats, suggesting broader analgesic properties, while NS383 was effective solely in alleviating pathophysiological pain, highlighting its targeted action [70].

Investigations have also explored the potential for pain modulation through ASIC1a activation using the MIT-toxin from the Texas Coral Snake. This toxin induces pain by promoting tissue acidification, which triggers the release of neuropeptide CGRP, a vasodilator, and Substance P, which also enhances vascular permeability [61]. Additionally, 2-guanidine-4-methylquinazoline (GMP) and its metabolite AGM have been shown to activate ASIC channels, promoting the release of inflammatory mediators and contributing to hyperalgesia [71]. These findings suggest that inhibition of these metabolites could reduce pain by counteracting their inflammatory effects.

Interestingly, the depletion of ASIC1a may also confer neuroprotective benefits by preventing neuronal cell death. Under normal conditions, insulin increases the expression of ASIC1a on the cell membrane, and its depletion can safeguard cells from damage [71]. Spermine, an endogenous molecule in the CNS [71], can exacerbate ischemic damage through ASIC1a activation. Therefore, inhibiting spermine may offer a protective strategy against ischemic neuronal injury [71].

Glutamate, a neurotransmitter with a specific binding site on ASIC1, has been implicated in neuronal injury and research has been focused on compounds that can block this interaction. One such compound, CGS19755 (selfotel), can penetrate the blood-brain barrier and exhibits a higher binding affinity for ASIC1a than glutamate, acting as a competitive antagonist and offering potential as a treatment for brain injury [36]. Additionally, LK-1 and LK-2, derivatives of selfotel, also function as competitive inhibitors at the glutamate-binding site, providing neuroprotection in this process [36].

Common analgesics such as morphine, NSAIDs, and lidocaine exert their effects by interacting with ASIC channels, although with varying degrees of efficacy. Morphine influences all ASIC subunits, particularly in dorsal root ganglia, whereas lidocaine primarily targets ASIC1a, ASIC2a, and ASIC3 by inhibiting proton flux through these channels [61]. NSAIDs selectively inhibit ASIC1a and ASIC3 channels, reducing the overexpression of their mRNA and thereby decreasing channel activity, which may alleviate pain signaling [61]. NSAIDs are particularly effective in inflammatory conditions where there is an increased expression of ASIC channels, resulting in a more pronounced inhibitory effect [61].

Mambalgin-1, a compound that acts as an inhibitor of ASIC1b, produces an anesthetic-like effect when blocking ASIC subunit activity [61]. In rodent models of non-inflammatory muscle pain, animals lacking ASIC3 did not experience pain, even after repeated administration of acidic solutions, indicating that ASIC3 is the primary subunit responsible for non-inflammatory muscle pain [77, 78]. Similarly, in models of inflammatory muscle pain, the administration of an ASIC3 inhibitor resulted in a significant reduction in pain [77, 78]. These findings suggest that ASIC3 inhibitors, such as Mambalgin-1, could be promising candidates for novel analgesic and anesthetic therapies.

Obstacles to the use of ASICs as pain modulators

Despite significant advances in understanding the role of ASICs in postoperative pain modulation, several challenges remain in translating these findings into practical clinical applications. One major obstacle is the selective action of ASIC inhibitors such as PcTx-1, which targets ASIC1a channels predominantly in the CNS [24]. While PcTx-1 is effective in regions such as the spinal cord and brainstem, which are not fully protected by the blood-brain barrier (BBB), its systemic administration can lead to unwanted side effects due to off-target effects in other areas of the CNS [24]. Additionally, systemic administration of PcTx-1 may not adequately penetrate the BBB to exert its analgesic effects in other critical regions of the brain, limiting its therapeutic potential. However, intra-arterial injection of such molecules has been proposed as a potential strategy to enhance their effectiveness by bypassing the BBB, thus potentially extending the scope of pain management options for patients [24]. This approach could improve the efficacy of compounds that are otherwise ineffective due to their inability to cross the BBB, thereby broadening the therapeutic window for pain relief.

Intranasal administration of ASIC inhibitors, such as PcTx-1, has also demonstrated some success, particularly regarding its neuroprotective effects. Intranasal delivery allows direct access to the CNS, bypassing the BBB and facilitating faster and more targeted action [24]. However, the clinical success of such treatments has not been universally replicated with intravenous administration, as systemic delivery often results in suboptimal concentrations in the brain, further complicating the therapeutic use of these compounds. Thus, while alternative routes of administration, such as intranasal or intra-arterial delivery, offer potential advantages, significant challenges remain in optimizing their delivery and ensuring the sustained efficacy and safety of ASIC modulators. Therefore, the development of more effective compounds, alongside tailored drug delivery systems, will be necessary to overcome these obstacles and fully utilize the potential of ASICs as modulators of pain.

Conclusion

ASICs play an integral role in the regulation and transmission of various physiological signals, including those associated with pain perception. In the context of postoperative pain management, current treatment regimens heavily rely on opioids and other potent analgesics, which, while effective in the short term, often

present significant adverse effects and the potential for long-term dependency. Given the widespread expression of ASICs throughout the nervous system, including in tissues relevant to pain pathways, modulation of these channels presents a promising therapeutic approach to attenuate pain perception. This is of particular importance in postoperative care, where minimizing reliance on traditional pharmacological agents is crucial for enhancing patient recovery and reducing the risk of opioid misuse.

While current research has provided valuable insights into the role of ASICs and their inhibitors in pain modulation, a comprehensive understanding of their full therapeutic potential, particularly in the context of postoperative pain relief, remains incomplete. The existing literature points to the need for more extensive and targeted studies to elucidate the mechanisms through which ASIC modulation can effectively alleviate pain without the need for conventional analgesics. Furthermore, as research into non-pharmacological substances that modulate ASIC activity progresses, there is substantial hope that novel, safer, and more effective alternatives to traditional pain management strategies can be developed. Consequently, further investigations into ASICs and their modulators are essential to advance our understanding and optimize the application of these channels in the clinical management of postoperative pain.

Disclosure of conflict of interest

None.

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