Acid-Sensing Ion Channels (ASICs) as extracellular pH sensors in the central and peripheral nervous system.

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Acid-sensing ion channels (ASICs) are neuronal homo- or hetero-multimeric voltage-insensitive cationic channels. They are activated by extracellular acidification, which can trigger membrane depolarization in response to local acidosis. They are mostly Na^+ selective and belong to the epithelial amiloride-sensitive Na^+ channel and degenerin (ENaC/DEG) family of ion channels. Six isoforms have been identified so far in mammals. ASIC1b and ASIC3 are specific of sensory neurons whereas ASIC1a, -2a and -2b are found in both the peripheral and the central nervous system (CNS). ASICs desensitize rapidly and the properties of most of them, and especially those expressed in the CNS, make these channels sensitive to dynamic extracellular pH fluctuations. However, ASIC3-containing channels carry in addition to the fast and rapidly inactivating response characteristic of ASIC currents, a sustained component that does not inactivate while the medium remains acidic and that modulates sensory neuron excitability. ASIC1 has been implicated in long-term potentiation of synaptic transmission, fear-related behavior and ischemic brain injury. We and others have also associated ASICs to a number of different sensory processes such as nociception, visual transduction, sour taste perception, hearing functions, and mechanoperception.

In the recent years, we have mainly focused on the regulatory mechanisms controlling the activity of these channels. We have found that neuropeptides as well as zinc and protein kinase C (PKC) are able to modulate their activity, which may be important in inflammatory conditions where ASIC expression is increased. We have developed novel pharmacological tools, like toxin blockers specific for ASIC1a and ASIC3, to study their function. We have more recently identified several ASIC associated proteins such as CIPP (Channel-Interacting PDZ domain Protein) and NHERF-1 (Na^+/H^+ Exchanger Regulatory Factor-1) that play a key role in ASIC3 activity, including plasma membrane expression and association with the cytoskeleton. We have also shown that PICK-1 (protein interacting with C-kinase-1) is necessary for the PKC up-regulation of both ASIC2a and ASIC3. All these modulators are essential contributors to the role of ASICs in nociception both in central (spinal) neurons and in sensory neurons, where these channels have been proposed to sense painful tissue acidosis that occurs in ischemic, damaged or inflamed tissue.

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