

Chapter 2

The Molecular Mechanism of Cellular Sensing of Acidity

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Introduction

Acidic conditions often accompany a variety of pathologic conditions such as inflammation and ischemia. They may be caused by defective pH stabilization mechanism that is usually the result of tissue injury, increased metabolism, hypoxia, hypercapnia, and increased activity. Inability to maintain pH during stroke, for example, leads to worse prognosis [66, 67]. On the other hand, acidosis activates sensory neurons in the case of myocardial infarct and tissue inflammation. Examples have been shown where animals have even utilized toxins, to enhance or protect against acidic conditions [10, 21, 25, 50]. Cellular sensing and appropriate response to acid by ion channels and receptors to extracellular pH (pH_o) or intracellular pH (pH_i) is necessary for organ systems to maintain proper physiologic conditions.

Various microenvironments such as ones found in brain are particularly sensitive to pH changes which may exert pathologic downstream consequences. Likewise, cells in nonneuronal microenvironments also maintain physiologic proton gradients that vary between the extracellular milieu and the cytosol. pH_o varies in each anatomical compartment with normal pH_o typically between 7.3 and 7.4; both non-neuronal and neuronal cells alike have the capacity to maintain intracellular pH between ~ 7.3 and ~ 7.0 [66]. However, in pathologic conditions like ischemic brain, pH_o may fall to 6.5–6.0 [66].

Change in pH_o or pH_i directly affects various membrane receptors and transporters where activation or inhibition of these molecules may be initiated by pH alterations. Acid-sensing ion channels (ASICs), identified as a subfamily of the epithelial sodium channel/degenerin family (DEG/ENaC), are directly activated by an increase in extracellular proton concentration [59]. Found in the central nervous system (CNS) and peripheral nervous system (PNS), sensing pH_o changes by ASICs contributes to CNS neuronal function and higher-order processes like learning and memory, synaptic plasticity, anxiety, depression, and seizure termination. ASICs

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participate in sensory transduction, mechanosensation, pain, retinal function and other roles have also been described [1, 38, 52, 63]. ASICs have been the subject of increasing interest due to their direct relationship with acidosis-related neuronal injury and have provided a promising new target for therapeutic intervention of stroke. In contrast to ASICs, several voltage-gated and ligand-gated channels are inhibited during acidic conditions. For example, N-methyl-D-aspartate (NMDA) channels are ligand-gated channels that are inhibited by a decrease in pH_o [27]. Similar to ASICs, some members of the transient receptor potential (TRP) family of channels have also been shown to have pH_o sensitivity where a decrease in pH_o causes channel activation [33]. The TRP superfamily was originally identified in *Drosophila* and is responsible for sensory transduction of the retina [20]. The TRP family is found in excitable and nonexcitable cells and is responsible for a wide variety of pathological conditions [30]. Specific receptors and transporters can also be influenced by changes in pH_i . ASIC activation and inactivation, for example, can be modulated by pH_i ; such changes can be caused by drugs or endogenous mechanisms [60].

This chapter focuses on the cellular and molecular mechanisms of sensing acidity of ASICs primarily in the nervous system. However, nonneuronal mechanisms and other ion channels/receptors to sense acidic conditions are also addressed.

Biochemistry of Acid-Sensing Ions Channels (ASICs) and Other Acid-Sensing Molecules

ASICs are voltage-independent, amiloride-sensitive, cation-selective ion channels which belong to the DEG/ENaC family of channels [52]. There are four genes (ASIC 1–4) in mammals that encode six distinct subunits ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3, and ASIC4 [67]. The sub-distinction designation of “a” or “b” corresponds to the differences between the NH_2 termini and location of the alternate splice site for ASIC1 and ASIC2. Recently resolved crystal structure from chicken, *Gallus gallus*, shows that ASIC subunits assemble as trimers to form functional channels which can be homomeric, consisting of identical subunits, or heteromeric, consisting of different subunits [31, 35]. Caveats to homomeric formation, ASIC2b and ASIC4 do not form functional channels but may associate with other subunits to form functional heteromeric channels. The formation of heteromers along with subunit combination and stoichiometry dictate channel properties such as gating, permeability, and activation. While ASIC1a homomers, which are ubiquitously expressed in the nervous system, respond to low pH_o by mediating a fast and transient inward current with a threshold pH of 7.0 and the pH for half maximal activation ($\text{pH}_{0.5}$) at 6.2 [67], homomeric ASIC3 channels, mostly found in the PNS, respond to pH_o drops by a biphasic response with a fast desensitizing current followed by a sustained component and a high sensitivity to protons with a $\text{pH}_{0.5}$ of 6.7 [63].

Each ASIC subunit consists of two transmembrane domains, TM1 and TM2, and a large cysteine-rich extracellular loop. Both NH_2 and COOH termini of ASICs lie within the intracellular space [52]. The extracellular domain (ED) of ASIC1a consists of 318 of 528 total residues with many crevices and intersubunit contact sites which have a role in gating or binding of other modulators of channel activity such as zinc [18]. Heteromeric and homomeric ASIC1b is one example where Zn^{2+} regulates channel activity by acting on cysteine149 located in the ED [36]. Other metals such as Cu^{2+} inhibits the ASICs and reduces acid-mediated membrane depolarization [61]. Reduction in extracellular $[\text{Ca}^{2+}]$ is known to regulate the activities of ASIC1a, ASIC1b, and ASIC3 channels as well as subfamily member of TRP channels, e.g., TRPM7 [20, 47].

ASIC Structure and Function

ASICs are closed when extracellular protons have not reached the channels' respective threshold concentration. When bound by protons, channels rapidly activate and then desensitize [57]. ASICs reside in at least three conformational states, the first is a nonconducting resting state where the channel can be activated in response to decrease in pH, a second conducting or open state where ions are transported through the pore and lastly, a desensitized or nonconducting state where $[\text{pH}_o]$ is not able to cause further activation [46]. The ED of ASIC1a protrudes from the plane of the membrane outward and is organized into discrete regions. Using the analogy of a hand, ASIC regions have been named “palm, knuckle, β -ball, finger, and thumb” domains based on their biochemical arrangement [35, 49, 72]. Residues within TM2 constitute the pore while TM1 also contributes a segment in the extracellular vestibule of the pore [31, 52]. The pore of ASIC1a forms an hourglass configuration in the desensitized state with contribution from TM2 which holds the residues in place [35, 57]. In addition, TM2 helices are tilted at a 50° angle from the membrane and the intersection with TM1 residues from the outer vestibule are speculated to form a desensitization gate [13, 31, 57]. A cluster of negatively charged residues have been suggested to form the tentative proton sensor in the cleft between the “thumb” and “finger” domains of ASIC1, in which carboxyl–carboxylate interaction pairs may play a role in channel gating [35]. Two carboxyl–carboxylate pairs E230 through D358 and E212 through D414 and a carboxyl–hydroxyl interaction pair E23 through S354 contribute to the underlying structure [51]. The aforementioned region can be referred to as the acidic pocket and contributes to a highly negative potential serving as binding sites for Ca^{2+} , Na^{2+} and H^+ [51]. The binding of either of the cations affects H^+ binding and vice versa [51]. Recently, a series of publications have elucidated the intimate structure/function relationship [5, 7, 39]. X-ray crystallography has determined that the TM2 can be divided into two distinct regions, TM2a and TM2b, and that the break in the helical structure is approximately parallel to the membrane [5]. Interestingly, the TM2b element interacts with the TM1 region of the neighboring

subunit generating a continuous TM2b helical segment [6]. This geometry allows the area between the two TM segments, termed the "GAS" (glycine, alanine, serine) selectivity filter, to effectively form a GAS belt [5]. From this arrangement, the GAS filter helps to form a component of the ion channel pore [6]. The entire structure of the pore consists of a gate and several integrated vestibules in a similar fashion to P2x receptors [7].

ASIC3 characteristically has a biphasic current in response to acidosis with a rapidly inactivating peak current and sustained plateau phase that persists as long as there is acid stimulation [23]. This is in contrast to the ASIC1a current profile which displays a rapidly inactivating transient current that deactivates in the presence of acid. As member of the Na^+ family of channels, ASICs have a reversal potential near +60 mV, so that when activated at typical resting potentials causes membrane depolarization. Data from several studies suggest that this depolarization is tied to Ca^{2+} influx causing neuronal injury [60, 68, 73].

Functional expression of ASIC channels relies on several factors including the trafficking of the molecule to the cell surface. Donier et al. reported that annexin light chain p11, a member of the S100 small phospholipid and Ca^{2+} -binding protein family, utilizes the intracellular N-terminus of ASIC1a in a heterologous system to traffic the protein to the membrane [26]. ASIC trafficking also requires PICK1, protein interacting with C-kinase-1, which regulates membrane incorporation and function of ASIC1a in a lipid binding-dependent manner [37].

Gating, Permeability, and Proton Interactions

ASIC1a homomeric channels have clear permeability to Ca^{2+} , establishing them as another vanguard of Ca^{2+} -mediated ischemic brain injury [41, 67, 73]. Despite the ability to conduct Ca^{2+} ions, there are data suggesting that external increased $[\text{Ca}^{2+}]$ can reduce the conductance of ASIC1a and 2a [22]. Notably, the hallmark of ASICs is the characteristic permeability to Na^+ ions. Compared to other Na^+ , ASICs are less permeable to K^+ , Li^+ , and H^+ ions; additionally, subunit composition greatly affects the permeability of heterologous systems like ASIC1a+ASIC2. Interestingly, ASICs are inhibited by heavy metals Gd^{3+} , Pb^{2+} , Ni^{2+} , Cd^{2+} , Cu^{2+} , and Mg^{2+} . Zn^{2+} conversely has a dual effect, potentiating at micromolar concentrations and inhibiting at nanomolar concentrations [18]. Interestingly, openings of chloride channels (CIC), for example, by γ -aminobutyric acid (GABA) or glycine, modulate the ASIC activity in neurons [17].

There is a wealth of information supporting that activation of ASICs requires protonation of multiple residues [31, 42, 46, 57]. The pre-TM2 region is essential for gating and ion permeability and changes in gating are speculated to be done through the reorganization of the palm domain in the extracellular region. For example, interplay between ASIC1a subunits requires that the opening of the conductive pathway for ion flow involves the coordinated rotation of TM2 [46, 72]. ASIC1 proton sensitivity is conferred by amino acid substitutions Q77L and

T85L of the external segment of TM1 [32]. The arrangement between TM1 and TM2 is such that TM1 forms the exterior of the TM complexes mostly in contact with the lipid bilayer while TM2 forms the pore complex [31]. Four vestibules organize the passage of ions through the ASIC protein complex. Fenestrations before the extracellular vestibule are located just prior to the pore and proximal to the wrist region. Symmetrically related carboxyl moieties contribute to pore occlusion and concentration of cations leads to increased channel conductance [31, 57]. Located halfway between the lipid bilayer, the pore forms the desensitization gate by a constriction of the TM2 complexes and several key residues conferring physical blockage of the passage after extending activation by H^+ [31]. However, to undergo the physical blockade, only a small conformational change is required by the selectivity filter and the spatially distinct ion channel gate [5].

The interface between the binding and pore domains plays a critical role in the gating of Cys loop ligand-activated receptors [13]. Protons bind just before TM1 and tryptophan (Trp) regions under the thumb where they enact proton-mediated conformational changes in the pre-TM2 region allowing cation flux through the pore [35]. A critical region of the thumb associates with chloride ions suggesting that there is an interaction or relationship between ASICs and ligand-gated CIC [17]. Another region of proton binding is adjacent to the extracellular vestibule. In all, three binding sites may be necessary in the open, conducting state of the channel [31]. Proton binding sites and conformational changes in the TM domains imply that the trigonal antiprism coordination is the optimal arrangement of proton binding. Structurally, the N-terminal of the TM1 region may stabilize the channel in the open state [13].

It has been suggested that ASICs can be activated by nonproton ligands as well, and the structure of the ED may contribute functionally to the protein [42]. 2-guanidine-4-methylquinazoline (GMQ) is a guanidinium heterocyclic ring and an example of a nonproton ligand for ASIC3 which interacts with the subunit at ED E79 and E423 [74]. Later, the same group was able to elucidate the binding mode and architecture of the nonproton binding domains of GMQ required for ASIC3 activation [75]. Screening approaches for alternative ASIC channel ligands also identified Phe-Met-Arg-Phe (FMRF) amide and neuropeptide FF, found in humans, in modifying channel properties by potentiating or inducing a sustained component but not activation of ASICs [2]. Other FMRF-like peptides, dynorphin A and big dynorphin, reduce steady-state inactivation of the ASIC1a channels [19]. Mentioned previously, animal toxins and venoms like MitTx, isolated from the venom of the Texas coral snake *Micrurus tener tener*, cause pain by activation of ASIC1a and/or ASIC1b [10]. Psalmotoxin (PcTx1), isolated from the venom of the South American tarantula *Psalmopoeus cambridgei*, however inhibits ASIC1a channels by shifting the channels into the desensitized state [16]. Furthermore, other peptides and small molecules inhibit ASIC1, ASIC2, and ASIC3 currents such as mambalgins-1, isolated from the venom of the black mamba snake, *Dendroaspis polylepis polyepis*, A-317567, amiloride, and Sevanol, isolated from a plant *Thymus armeniacus* [76]. Pharmacological use of these compounds is being explored to exploit their therapeutic benefit for pain, stroke, and other neurologic diseases.

Other Acid-Sensing Molecules

Of the acid-sensing molecules, ASICs and TRPV1 are the most intensively studied. However, other acid-sensing members include potassium channels such as members of the two-pore-domain K^+ channels are differentially regulated by small deviations of extra- or intracellular pH from physiological levels [33, 33]. Other members of the TRP superfamily, TRPV4, TRPC4, TRPC5, TRPP2, along with ionotropic purinoceptors (P2X), inward rectifier K^+ channels, voltage-activated K^+ channels, L-type Ca^{2+} channels, hyperpolarization-activated cyclic nucleotide-gated channels, gap junction channels, and Cl^- channels display some acid sensitivity [33].

The superfamily of voltage-gated Cl^- is ubiquitously expressed in many tissues such as the brain, muscle, and kidney. Cl^- are activated, inhibited, or gated by pH changes [4]. Pharmacologic agents 4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid (DIDS) and diphenylamine-2-carboxylic (DPC) acid inhibit activity. One such microenvironment within the testes is acidified by fluid secreted from Sertoli cells. The change in pH is then sensed by extracellular acidic pH-activated Cl^- (also named as acid-sensing Cl^- channel, ASCC). ASCCs elicits an outwardly rectifying current in Sertoli cells [4], human umbilical cord vein endothelial cells [43], lung epithelial cells [9], myocytes [71], and monocyte/macrophage [53]. Still, details of channel function and therapeutic potential have yet to be identified for this recent, yet little investigated ion channel.

Previously mentioned, members of the TRP family can be modulated and/or activated by acidic pH. An example in detection of noxious stimuli is the transient receptor potential vanilloid 1 (TRPV1) channel, or capsaicin receptor. Also found in neuronal and nonneuronal tissues [30, 77], TRPV1 is implicated in the development of diseases such as inflammatory heat hyperalgesia, visceral hyperreflexia, and airway inflammation among others [3]. The channel consists of six TM spanning segments with the pore located between TM5 and TM6 [20, 33]. Additionally, four subunits are assembled as tetramers to form a functional channel. Most TRPs behave as nonselective cation channels, with Ca^{2+} permeability which is a salient feature of TRPV1 conductance [33]. Likewise, transient receptor protein melastatin-7 (TRPM7) also conducts Ca^{2+} [58] and Zn^{2+} [34]. During ischemic conditions, intracellular $[Ca^{2+}]$ increases leading to Ca^{2+} overload and cell toxicity [33, 34, 58]. In conditions such as diabetes where acidic conditions are associated with inflammation, Ca^{2+} influx via TRP channels can cause activation of monocytes [65], thus modulating the immune response.

Potassium channels such as ATP-sensitive K^+ channels (K_{ATP}) have also been shown to be sensitive to acid. Potassium inward rectifier 6.2 ($K_{ir,6.2}$) subunits in combination with SUR1 in oocytes display a graded response to pH_o in both the presence or absence of CO_2 , the response is modulated by pH_i manipulation [69].

Systems Biology

The Eye

The distribution of the ASICs is concentrated in the CNS/PNS. Sensory organs like the eye, where cells in the microenvironment of the retina express ASICs, are sensitive to pH fluctuation during ocular diseases [56]. Loss of retinal ganglion cells of the eye during ischemia contributes to poor vision and may eventually lead to blindness. Data have shown that in hypoxic conditions, Ca^{2+} -permeable ASIC1a channels enact cytotoxic injury through Ca^{2+} -mediated mechanisms leading to neuron death. So far, at least three studies have investigated ASIC expression and functionality in the eye [11, 44, 56].

Chemosensation

Other sensory modalities, like the tongue, have chemosensory neuronal innervations to convey taste information. ASICs have been implicated in taste sensation [54] and the superfamily of DEG/ENaC channels, in general, have been implicated in chemosensation transduction pathways involved in salt and sour taste [8, 14].

Synaptic Transmission

It is known that ASICs participate in synaptic transmission [62]. The hippocampus is an essential part of the brain that contributes to learning and memory. ASICs expressed in neurons found in the hippocampus and located at the postsynaptic membrane may be stimulated by ejection of protons from synaptic vesicles [62]. Mentioned earlier, ASICs are found in many brain regions. The hippocampus and cortex are principal areas being researched, where neurons can be isolated for culture and their characteristics pertaining to ASICs can be studied. At the cellular level, ASICs localize to the soma, the dendrites, and most importantly the synapse. The composition of ASIC expression along the neuron no doubt varies in the CNS, and neurons are most likely to express ASIC1a across all areas of the membrane. Loss of ASIC1a directly contributes to loss or impairment of spatial learning, fear and anxiety, eye blink conditioning, and other behaviors [62]. In a seminal paper, Wemmie et al. concluded that ASICs are expressed in synaptosomes and that the disruption of ASIC expression results in impaired hippocampal long-term potentiation (LTP)[62]. They also suggest that NMDA channels, also involved in learning and memory, and synaptic plasticity, are impacted by activation of ASIC channels at the postsynaptic membrane [62].

Cardiovascular/Respiratory

Physiologic mechanisms to detect and respond to pH changes are distributed widely. Examples of critical organs such as the central and peripheral chemoreceptors, aortic, and carotid bodies use pH sensing to maintain tissue homeostasis. Focusing on the centralized components, cardiovascular and respiratory centers are located in the brain within the pneumotaxic center, the dorsal respiratory group, and lastly the ventral respiratory group [45]. CO_2 rests in equilibrium with carbonic acid and when dissociated, separates into bicarbonate and H^+ ; the greater the amount of CO_2 , the lower the pH. Increases in CO_2 are subsequently sensed as acid in the peripheral chemoreceptors and triggers afferent neuron excitation [45]. In turn, this signal is relayed to central receptors and areas of the brain that regulate breathing. Could ASICs or other mechanisms be involved in this process? More work is needed to clearly define how chemoreceptors process information on pH_o . In guinea pig, acidosis decreases the basal tone of tracheal rings. This acid-induced airway relaxation seems to be independent of sensory nerves, suggesting a regulation of airway basal tone mediated by smooth muscle ASICs [28].

The detection of ischemia-related cardiac acidosis is sensed by cellular mechanisms such as ASIC1a, ASIC3, TRPV-1, and outwardly rectifying Cl^- channels ($I_{\text{Cl acid}}$). Mentioned earlier, tissue acidosis is a major stimulus for afferent neuron signaling initiated via peripherally located ASICs. Found in mouse and guinea pig, atrial and ventricular cardiomyocytes, $I_{\text{Cl acid}}$ are stimulated by a decrease in pH_o causing an outward flux of anions [71]. This response is in line with tissue acidosis resultant of lactate but the physiological significance of this discovery has yet to be determined. More supporting in vitro evidence for acid sensing in cardiac dorsal root ganglion show that ASIC3-mediated current most clearly mimics in vivo physiology. A characteristic of ASIC3-mediated current is the sustained component which may contribute to the long-lasting sensation of angina [70]. However, ASIC current, also dependent on subunit composition, is modulated by anions affecting the pH dependence of activation and desensitization kinetics [40]. This might lay a possible link between anion flux by $I_{\text{Cl acid}}$, a possible extracellular fluid composition sensing mechanism of ASICs, along with pH_o sensing. Highlighting this proposed extracellular fluid sampling paradigm, in metabolic diseases such as diabetes mellitus, ASIC3's exquisite sensitivity to H^+ plays a role in insulin resistance by yet unresolved mechanisms [64]. The aforementioned ligand-gated CIC may play a role in regulating ASIC inhibition by concurrent opening of GABA receptors [17].

Pathologies Associated with Dysregulation of pH Sensing

CNS: Acidosis-Mediated, Glutamate-Independent Neuronal Injury

ASICs are largely responsible for acidosis-mediated, glutamate-independent neuronal injury in ischemic brain [48, 66, 68]. Injury is at least partially caused by

a flux of Ca^{2+} that cannot be overcome by endoplasmic reticulum buffering. In addition, Ca^{2+} calmodulin-dependent protein kinase II (CaMKII) is also coupled with ASIC1a activation, promoting acidosis-mediated ischemic damage [29]. Trafficking and scaffold protein PICK1 also plays a role in ASIC1a-mediated neuronal injury by increasing surface expression of the ion channel possibly during acidic conditions [37].

Recently discovered mambalgin-1 attenuates pain in the PNS by limiting activation of ASIC1a, ASIC1b, ASIC1a+ASIC2b, and ASIC1a+ASIC2a homomers and heteromers, respectively [25]. Perhaps this newly derived peptide might protect against ASIC-mediated stroke pathologies primarily because ASIC1a+ASIC2a heteromers are highly expressed in the brain. Currently, protection from stroke using the nonspecific ASIC antagonist amiloride has proven successful in animal models but lacks the specificity of mambalgin-1 and PcTX1 [68]. Therapeutic cocktails of ASIC inhibitors may be prepared and tested, in combination, for additive or synergistic effect. Additionally, protection can be effected through gene knock-out in experimental animals or directly by intracerebroventricular administration of NaHCO_3^- [48].

PNS: Pain, Acidosis

In the PNS, sensory transduction is carried by neurons containing various ASIC subunits, some of which are homomeric and others form heteromultimeric channels. In addition to ASIC1a, ASIC2 splice variants 2a and 2b are expressed in the dorsal root ganglion [24] and colocalize with ASIC3 [1]. Alvarez de la Rosa speculates that the ASIC2+ASIC3 pairing may serve as a mechanism for mechanotransduction activated by stretch, swelling, or suction applied to the cell membrane as found in *Caenorhabditis elegans* which contains an orthologous ASIC2 mechanosensation mechanism [1, 24]. Additionally, ASIC1 and ASIC3 homomers were identified in dorsal root ganglia (DRG) where ASIC3 contributes to pain transduction [1, 24, 55]. Inflammation may cause tissue acidosis leading to depolarization and sensation of pain. Conversely, experimental ASIC3 silencing has led to reduced pain sensitization in mice [23]. In humans, aberrant expression of ASIC3 could elicit pain from slight deviation in pH [23].

PNS transduction of pain is relayed from sensory nerve endings that are stimulated by heat, cold, mechanical deformation, inflammation, tissue damage, and chemical stimuli. ASIC1a and ASIC3 subunits are both expressed in the PNS and are the subject of intense investigation to find alternative therapeutic remedies for analgesia. ASIC3^{-/-} knockout animals display a variety of physiological characteristics modulating pain perspective, especially at moderate and high-intensity pain [15]. Perhaps there is an indirect link between the activity of ASIC1a- and ASIC3-mediated pain during periods where high or chronic stress may prevail? Nevertheless, a complex interplay exists between ASIC subunits as exemplified by ASIC3/ASIC2b pairing while prevalent paradigms have suggested that ASIC3 homomers are the sole mediator of pain [24]. The interrelated

nature of ASICs interaction has set forth a new postulate that a triple gene knock-out of ASIC1a, 2 and 3 would have an effect on mechanosensation and pain. Interestingly, a total knockout of ASICs in mice (excluding ASIC4) did not decrease sensation of pain or decrease nerve firing; but, increased cutaneous mechanosensation [38]. Compensatory up- or downregulation of other ion channels might be involved in mechanosensation and detection of noxious stimuli like that of localized tissue acidosis.

Still further, other mechanisms may mediate pain due to acidosis. Recently, an interesting phenomenon was reported by Qiu et al. that serotonin (5-HT₂) enhanced ASIC current in DRG neurons via intracellular mechanisms, although the specific subunit composition is yet to be determined [49].

Degenerative diseases such as osteoarthritis have pain mediated by ASIC3 which can be attenuated by ASIC3 selective blocker APETx2. Interestingly, ASIC3 polymorphisms are involved in human insulin resistance which is related to glucose metabolism [64]. Although seemingly unrelated, ASIC3 expression in peripheral sensory neurons may include metaboreceptive capabilities corresponding to tissue acidosis.

Summary and Conclusion

Key points:

- Acid activates ASICs from a constitutively closed configuration to an active conducting state and finally a desensitized state where the molecule is insensitive to protons [12].
- Multiple sites on the ED of ASIC1a contribute to acid sensing.
- Pore opening requires the coordinated rotation of TM2 domains.
- Other ligands such as FMRF amide and neuropeptide FF are able to modulate ASICs. Perhaps other endogenous ligands can activate this ion channel.
- ASICs are largely responsible for acidosis-mediated, glutamate-independent neuronal injury in the ischemic brain through the flux of Ca²⁺.
- Other ion channels and receptors are involved in acid sensing: TRPs, N-methyl-D-aspartate receptors, outwardly rectifying Cl⁻ channels and ATP-sensitive K⁺ channels.

Current evidence supports the role of ASICs and other receptors in acid sensing, acid-induced pain, acid-induced injury, and acid-induced feedback of homeostatic mechanisms. Characteristically expressed in neurons of the CNS and PNS, acid-sensing molecules are distributed throughout the body in a variety of tissues. The structure of each acid-sensing molecule is unique and is intimately related to the function of the channel. Each acid-sensing molecule has a specialized function and contributes to the overall balance of pH sensing and pH regulation. As a channel directly activated by extracellular protons, ASIC research should be considered to be at the forefront of disease where acidic conditions are generated.

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