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Acidosis, Acid-Sensing Ion Channels, and Neuronal Cell Death

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Abstract Acidosis is a common feature of many neuronal diseases and often accompanied with adverse consequences such as pain and neuronal injury. Before the discovery of acid-sensing ion channels (ASICs), protons were usually considered as a modulator of other ion channels, such as voltage-gated calcium channels, *N*-methyl-D-aspartate, and γ-amino butyric acid(A) receptor channels. Accordingly, the functional effects of acidosis were considered as consequences of modulations of these channels. Since the first cloning of ASICs in 1997, the conventional view on acidosis-mediated pain and cell injury has been dramatically changed. To date, ASICs, which are directly activated by extracellular protons, are shown to mediate most of the acidosis-associated physiological and pathological functions. For example, ASIC1a channels are reported to mediate acidosis-induced ischemic neuronal death. In this article, we will review the possible mechanisms that underlie ASIC1a channel-mediated neuronal death and discuss ASIC1a channel modulators involved in this process.

Keywords Acidosis · ASIC1a · Neuronal cell death · Spermine · Ischemic stroke

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Introduction

Protons are the smallest of molecules but contribute to many important physiological functions. In the nervous system, protons modulate synaptic transmission, neuronal plasticity, and membrane excitability [1]. It has been shown that the pH level inside synaptic vesicles is ~1.5 pH units lower than that in the cytosol [2]. Protons are co-released with neurotransmitters during synaptic transmission leading to the extracellular acidification of the synaptic cleft and modulation of synaptic activity (Fig. 1a) [2, 3]. In the presynaptic terminal, protons reduce neurotransmitter release by feedback inhibition of voltage-gated Ca^{2+} channels (VGCC) [4, 5]. Postsynaptically, protons greatly suppress the activity of *N*-methyl-D-aspartate (NMDA) [6, 7] and γ-amino butyric acid (GABA(A)) receptors [8, 9] (but see [10]). Moreover, in *Caenorhabditis elegans*, protons act as a neuronal transmitter to mediate muscle contraction [11]. On the other hand, protons over-accumulate due to disturbance of acid–base balance in diseases such as traumatic brain injury, ischemic stroke, and epileptic seizure [12–18]. This pathologically excessive acidification is termed acidosis, which often leads to defects in brain function, and even worse, severe neuronal injury.

Fourteen years ago, acid-sensing ion channels (ASICs) were first cloned and shown to be widely distributed in the nervous system [19]. This discovery greatly changed the view on tissue acidification and its consequences. Since then, ASICs have been extensively studied as key targets in many different aspects of acidosis [20]. Although ASICs are not the only player of proton-induced cellular functions, they mediate many important proton-regulated processes, among which acidosis-induced neuronal death, such as that occurring in diseases like ischemic stroke, is mediated by ASIC1a channels [21, 22]. Both blockade of ASIC1a

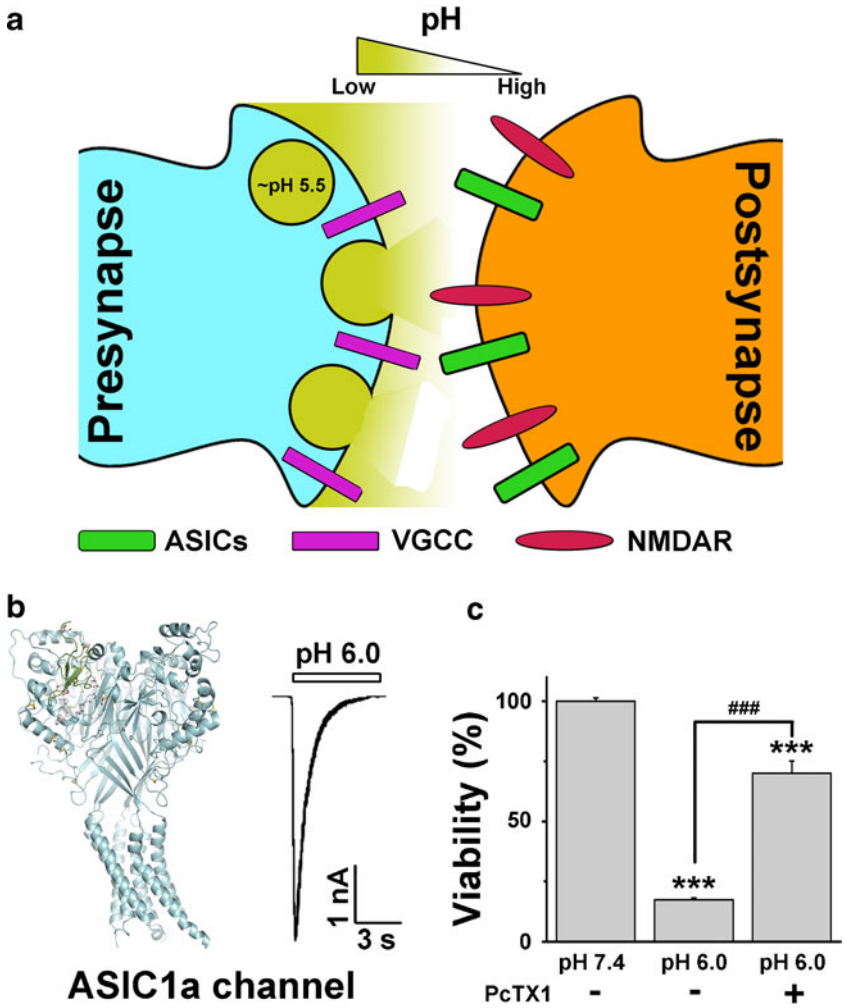

Fig. 1 Synaptic cleft acidification and ASIC1a channel activation. **a** Protons are co-released with neurotransmitters from acidic vesicles during neurotransmission and modulate both presynaptic and postsynaptic ion channels, such as VGCC, NMDA receptors (*NMDAR*), and ASICs. **b** Stereo view of the three-dimensional structural model of human ASIC1a channels. This figure is made using PyMol. *Right panel*: Acid-induced whole cell current from Chinese hamster ovary cells expressing human ASIC1a. **c** Neuronal cell death following ASIC1a activation and neuroprotection by blocking ASIC1a channel using specific ASIC1a inhibitor, PcTX1 (unpublished data. $n=5$; ***$p<0.001$, unpaired t test, pH 6.0-treated group vs. pH 7.4-treated group. ###$p<0.001$, unpaired t test, pH 6.0-treated group vs. pH 6.0 plus PcTX1-treated group)

channels and deletion of the *ASIC1* gene rescued neurons from ischemic cell death (Figs. 1c and 3a). Although protons are the only known agonists of ASIC1a channels, a variety of endogenous molecules can modulate the activities of these channels and have a profound influence on ASIC1a channel-mediated neuronal death [23]. These findings suggest that ASIC1a is a potential new drug target for clinical therapy of acidosis-associated diseases. In this mini-review, we summarized the up-to-date knowledge of mechanisms and modulators of ASIC1a channel-mediated neuronal death, hoping to call for future researches on acidosis-associated diseases.

Acidosis and ASICs

Acidosis

Acidosis is a pathological condition in which acid–base balance is disturbed in the direction of excess acidity in the body fluid. There are two major types of acidosis, respiratory acidosis and metabolic acidosis. Respiratory acidosis is due to a build-up of carbon dioxide caused by hypoventilation [24]. Metabolic acidosis mainly results from the increased accumulation of nonvolatile acids (usually lactic acid) or due to the loss of bicarbonate resulting from impaired mitochondrial function and abnormal energy metabolism [16]. Additionally, in the nervous system, extracellular acidosis also can result from excessive release of acidic vesicles due to aberrantly high neuronal activity (Fig. 1a) [15], such as seizures [17, 18].

Acidosis is a common phenomenon in many central nervous system (CNS) diseases. In ischemic brain, pH falls to 6.0 due to the accumulation of lactic acid the by-product of glycolysis and as a consequence of protons produced by ATP hydrolysis [12, 25, 26]. Similarly, the pH in the spinal cord is about 6.6 in mice with experimental autoimmune encephalomyelitis (EAE) [27]. Also, during seizure brain pH is reduced from ~7.35 to 6.8 [17, 18]. Furthermore, metabolic acidosis often occurs in neurodegenerative diseases. For example, cerebral acidosis (~pH 6.6) [28] and lactate accumulation in Alzheimer's disease (AD) may be due to impaired oxidative

energy metabolism and inflammation [29]. It was reported that acidosis increased the expression level of cellular Aβ in cultured rat hippocampal neurons [30]. Later in a rodent model of Alzheimer's disease, it was shown that acidosis contributed to the aggregation of Aβ [31, 32]. These studies suggested that acidosis may contribute to the dysregulation of Aβ and plague deposition, which may cause neuronal dysfunction in AD [33]. Lactic acidosis was also observed both in Parkinson's disease (PD) patients [34] and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mouse models [35] due to impairment of mitochondrial function. Acidosis may also contribute to the degeneration of substantia nigra (SNc) neurons induced by MPTP [36]. In addition, lactic acidosis also occurs in brains of Huntington's disease (HD) patients as well as in animal models of this disease. Acidosis in these conditions may result from aberrant energy metabolism that plays a role in the process of polyQ aggregation and the pathogenesis of HD [37–40].

It is generally conceded that there are adverse consequences of acidosis [16, 21, 22, 27, 31, 36, 40, 41], although there are reports that acidic preconditioning provided protection in ischemic injury [42] and acidosis may contribute to seizure termination [43]. It is reasonable to suggest that restoration of acid–base balance and blockade of the down-stream pathways of acidosis provide two promising approaches to eliminating the adverse consequences of acidosis such as neuronal death. However, considering the complexity of acid–base homeostasis mechanisms in the nervous system, the later approach would appear to be an easier and more operable option. In this respect, ASICs are becoming recognized as prime candidates as new therapeutic targets in acidosis-related diseases.

ASICs

ASICs represent a subgroup of proton-gated degenerin/epithelial Na^+ channels, with seven isoforms reported to date [19, 44]. Their distribution is widespread in the nervous system, but only 1a, 2a, and 2b subtypes are expressed in neurons of the CNS [20]. Homomeric ASIC1a channels are Na^+ and Ca^{2+} permeable, whereas other combinations are only permeable to Na^+ (Fig. 1b) [19, 21, 45]. In CNS neurons, ASIC1a-containing channels (referred to ASIC1a channels) respond to extracellular pH reduction ranging from 6.9 to 5.0 to generate rapid depolarizing currents [19], and activation of these channels enhances the probability of action potential initiation [46].

The pathological acidosis associated with CNS diseases is in a range of pH values (ischemia, ~pH 6.5–6.0; seizure, ~pH 6.8; AD, ~pH 6.6) that are sufficient to activate ASIC1a channels. Indeed, many studies showed that ASICs, especially ASIC1a channels, play an important role in these diseases [21, 22, 27, 36, 40, 43, 47, 48]. With the use of specific inhibitors and in animals where the channels have been genetically deleted, ASIC1a channels were shown to mediate delayed ischemic neuronal death in the mouse middle cerebral artery occultation (MCAO) ischemic model, which led to the hypothesis that elevated intracellular Ca^{2+} resulting from entry via ASIC1a channels induces neuronal toxicity [21, 22]. In addition, in the EAE model, *ASIC1* gene deletion mice had both reduced axonal degeneration and reduced clinic deficits compared with wild-type ones, which suggests that ASIC1a channels contribute to the damage in neuro-inflammatory diseases like multiple sclerosis [27]. However, ASIC1a channels exhibited not only these adverse aspects, but also some beneficial ones. For example, activation of ASIC1a channels expressed in inhibitory interneurons, which are activated by the acidosis, protected the brain by terminating seizures [43]. Furthermore, ASIC1a channels were also reported to be involved in neurodegenerative diseases. Inhibition of ASIC1a channels protected SNc neurons from MPTP-induced degeneration in a PD model and decreased the aggregation of htt-polyQ in an HD model [36, 40]. As discussed above, lactic acidosis was also observed in the brains of AD patients and animal of these disease models [28, 29], and it was shown to induce Aβ dysregulation and aggregation, which may contribute to neuronal degeneration [30, 31, 33]. Thus, it is quite possible that ASIC1a channels contribute to the neuronal damage in neurodegenerative diseases.

Strictly speaking, ASICs inhibitors, which are prone to have side effects due to potential actions on other target molecules, are overused in previous studies to identify the role of ASICs on PD and HD models. For example, amiloride, an extensively used ASICs inhibitor, is also an effective inhibitor of Na^+/H^+ exchanger, which is activated by acidosis [49]. Thus, caution should be taken when evaluating the contributions of ASICs in diseases using pharmacological tools. Rodent genetic models such as *ASIC* gene deletion mice and molecular manipulations such as RNA interference of ASIC subunits should be sought to obtain supporting evidence to confirm pharmacological findings. Among all diseases that have been suggested to involve ASIC channels, there is sufficient and credible evidence to support the main and critical pathological function of ASIC1a channels in mediating ischemic neuronal death.

ASIC1a Channels and Neuronal Cell Death

Possible Mechanisms of ASIC1a Channel-Mediated Cell Death

Although it is now well accepted that ASIC1a channels mediate ischemic neuronal death [21, 22], the mechanism (s) for this effect remains unclear. It was found in in vitro

studies that reducing extracellular Ca^{2+} concentration inhibited acidosis-induced, ASIC1a-mediated neuronal death, which suggested that Ca^{2+} entry and consequent intracellular Ca^{2+} rises may be involved [21, 45]. According to the amount and source, elevations in intracellular Ca^{2+} levels may activate a variety of signaling pathways, leading to necrosis as well as apoptosis [50–52]. Compared with some glutamate receptors (e.g., NMDA receptors), activation of ASIC1a channels leads to a much weaker intracellular Ca^{2+} elevation (Fig. 2b) [19, 21, 45, 53]. As such, ASIC1a-mediated neuronal toxicity represents a new death mechanism different from excitotoxicity, which is always accompanied with a massive uncontrolled intracellular Ca^{2+} elevation [54]. Additionally, it has been reported that *C. elegans* MEC-4 Na^+ channels, which also belong to the degenerin/epithelial Na^+ channel superfamily, initiated neuronal necrosis in a calpain-dependent way [55]. Ca^{2+} influx through MEC-4 channels activated Ca^{2+}-induced Ca^{2+} release from the endoplasmic reticulum to promote neuronal death [55]. A similar mechanism may be at play for the ASIC1a-mediated ischemic neuronal death.

A recent report has revealed some new insights into ASIC1a channel-mediated neuronal death in vitro [56]. It was found that the ASICs inhibitors, psalmotoxin1 (PcTX1) and amiloride, both of which had been shown to inhibit ASIC1a channel-mediated neuronal death, also reduced reactive oxygen species (ROS) production. It was thus suggested that ASIC1a channel activation led to ROS generation, which in turn contributed to the delayed neuronal death. However, there is no direct evidence to show that antioxidants inhibit ASIC1a channel-mediated neuronal death. On the contrary, an earlier paper had demonstrated that two antioxidants, L-NAME and trolox, failed to rescue acidosis-induced (pH 6.0, 1 h) and ASIC1a channel-mediated death [21], suggesting that ROS might be a by-product of ASIC activation rather than the direct cause for the death. Besides causing damage directly, ROS are important modulators of many proteins. It was reported that ROS reduced the peak amplitude of ASIC1a channel currents through decreasing membrane trafficking due to inter-subunit disulfide bond formation [57, 58], indicating that ROS may provide neuroprotection against acidosis-induced injury [58]. Actually, the amount of ROS is greatly increased in the ischemic brain through many different pathways [59]. Although ROS may decrease surface expression of ASIC1a channels, too much ROS can still lead to severe neuronal death through different pathways [59]. Moreover, it is very interesting that acidosis was reported to potentiate oxidative neuronal death [60]. Thus, the time and amount of ROS generation are very critical for ischemic neuronal death. For example, if the ROS was generated before ischemia, it would decrease the surface of ASIC1a channels and therefore reduce the subsequent neuronal death. On the other hand, if too much ROS was generated during ischemia, it would lead to severe neuronal death, which is potentiated by acidosis.

The integrity and function of mitochondria are critical for most types of cell death, due to generation of ROS and release of pro-death proteins from mitochondrial intermembrane space [61]. It has been shown that mitochondrion plays a critical role in acidosis-induced injury in cardiac myocytes [62]. In this case, hypoxia–acidosis led to cell death by the opening of mitochondrial permeability transition pore (miPTP) because of accumulation of Bcl-2 family member Bcl-2/adenovirus E1B 19 kDa interacting protein 3 (BNIP3), and this could be rescued by the miPTP inhibitor cyclosporine A [62]. The same mechanism was also reported in kidney epithelial cells,

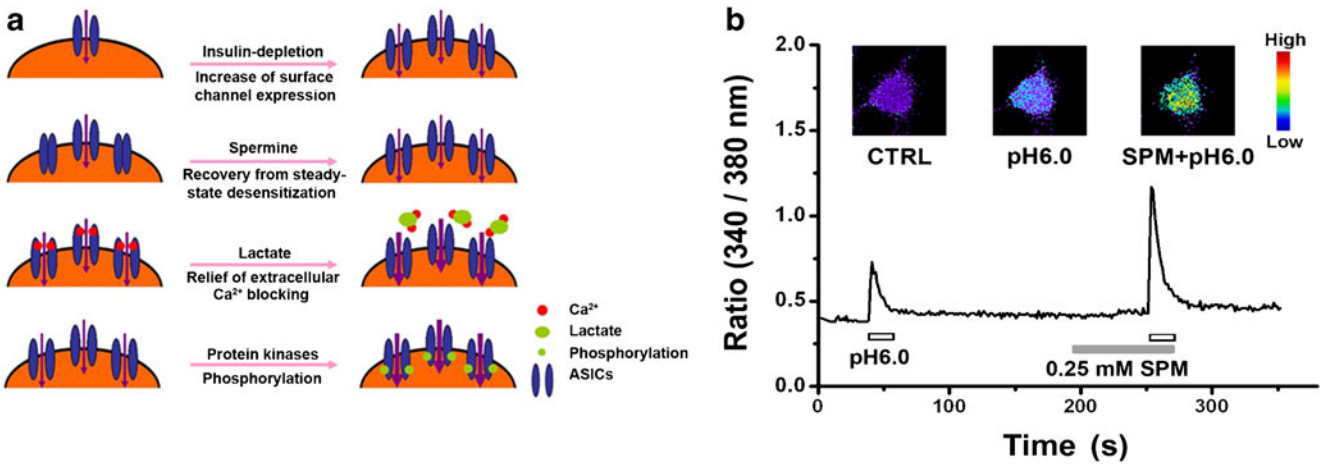

Fig. 2 Sensitization of ASIC1a channel and acid-induced intracellular Ca^{2+} elevation by spermine (*SPM*). **a** Four known mechanisms underlying ASIC1a sensitization. From *top* to *bottom*, increase of surface channel expression; recovery from steady-state desensitization; relief of extracellular Ca^{2+} blocking; phosphorylation. See text for detail. **b** Representative plot of 340/380 ratio changes (corresponding to intracellular Ca^{2+} levels) induced by pH decrease in the absence or presence of 0.25 mM SPM. Example ratio images before (CTRL) and during pH drop in the absence (pH 6.0) and presence of SPM (SPM+pH 6.0) are shown on the top. Reprinted from Duan et al. [66]

and the mitochondrial activity inhibitor, such as rotenone, rescued the death [63]. Unsolved questions are what the role of mitochondria is in ASIC1a channel-mediated neuronal death, whether miPTP also opens in acidosis-treated neurons (induced by elevated intracellular Ca^{2+} or other BNIP3-like molecules?) and, if so, how ASIC1a channels contribute to these events. As discussed above, activation of ASIC1a channels leads to elevation of intracellular ROS, which is indicative of mitochondrial contribution. Except for this, very little is known about the relationship between ASIC1a channels and mitochondria at the current stage. To fully understand the mechanism(s) of ASIC1a channel-mediated neuronal death and provide effective treatments, the contribution of mitochondria should be studied thoroughly.

Endogenous Modulators of ASIC1a-Mediated Cell Death

Compared with NMDA receptors, ASIC1a channels exhibit a much lower Ca^{2+} permeability. In addition, the rapid peak current only lasts for seconds (Fig. 1b) [19] because ASIC1a channels completely desensitize after a few seconds of continued exposure to an acidic extracellular solution [64], suggesting that the total amount of Ca^{2+} that can pass through ASIC1a channels is limited (Fig. 2b). Therefore, it is logical to think that there exist some modulators to enhance the function of ASIC1a channels in order to allow them to act as death initiators. As expected, many endogenous substances have been found to amplify the functions of ASIC1a channels under pathological conditions [23]. According to their modulatory functions, these substances have been divided into four classes (Fig. 2a). First, a recent paper showed that insulin is a key component to maintain a low level of ASIC1a channels on neuronal surface, and insulin (or serum) depletion promoted trafficking of intracellularly localized ASIC1a channels to plasma membrane, which may contribute to cell death [48, 65]. The precise signaling pathways of insulin (or serum depletion)-induced cell surface expression of ASIC1a proteins remain unknown. It is possible that there are multiple factors involved in this process considering the complex components of serum. Second, we recently showed that spermine, one of the endogenous polyamines, facilitated ASIC1a channels from steady-state desensitization and greatly enhanced ASIC1a channel-mediated ischemic damage (Figs. 2b and 3) [66]. A similar modulatory effect on ASIC1a channels has also been reported for the dynorphin opioid peptides. However, dynorphins have been shown to have neuroprotective effects during cerebral injury and ischemia. The paradoxical effects

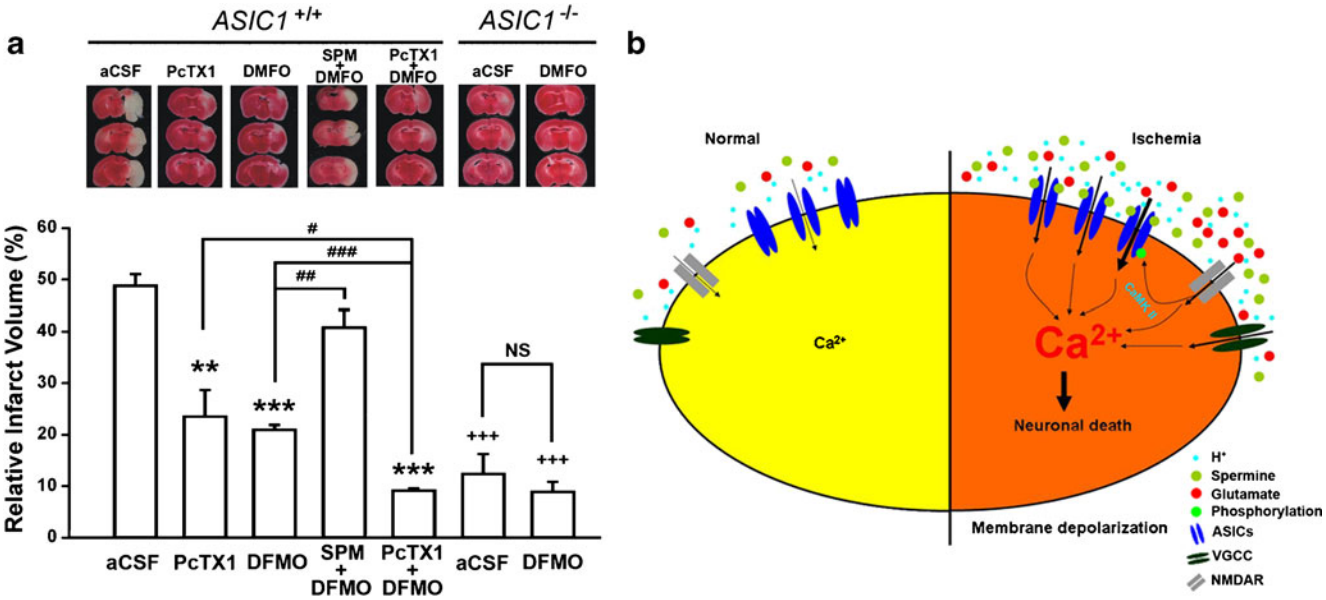

Fig. 3 SPM exacerbated ASIC1a-mediated ischemic neuronal damage. **a** In an ischemia model (60 min MCAO), PcTX1 (1 μM) and DFMO (75 μg/μl) injection reduced the infarct volume in brains from WT mice in an additive manner (n=4–6; **p<0.01, ***p<0.001, unpaired t test, compared with aCSF group from WT mice. #p<0.05, ###p<0.001, unpaired t test, compared with PcTX1 plus DFMO group). Co-injection of SPM (2.5 mM) with DFMO reversed the neuroprotective effect of DFMO (##p<0.01, unpaired t test, compared with DFMO alone). *ASIC1* deletion also reduced the infarct volume but DFMO was ineffective in ASIC1 null mice (n=6; +++p<0.001, unpaired t test, compared with aCSF group from WT mice). *Images on the top* show examples of 2, 3, 5-triphenyltetrazolium hydrochloride-stained brain sections and infarct areas for the corresponding treatment groups. Reprinted from Duan et al. [66]. **b** Schematic representation showing ASIC1a sensitization by spermine and CaMKII under ischemic conditions. In ischemic brain, ASIC1a channel-mediated current and $[Ca^{2+}]_i$ elevation are enhanced by elevated extracellular spermine and NR2B-dependent CaMKII phosphorylation of ASIC1a. Depolarization caused by both ASIC1a channels and NMDA receptors contribute to the opening of VGCC. Thus, $[Ca^{2+}]_i$ elevation due to ASIC1a channels, NMDA receptors, and VGCC leads to ischemic neuronal death

are likely due to their ability to activate neuroprotective G-protein-coupled receptors, overwhelming their ability to enhance neuronal death through modulation of ASIC1a channels [67]. Third, as discussed above, in many diseases, metabolic acidosis is always the result of accumulated lactic acid, which is considered as a waste product of glycolysis due to hypoxia and a critical factor for acidosis-induced tissue damage [16, 24]. Lactate has been shown to be one of the most important modulators of ASICs [68]. For ASIC1a channels, lactate enhances ASIC1a currents by relieving extracellular Ca^{2+} block [68]. Although this modulation is usually considered as a form of heterosensitization in pain [68], it is also possible that lactate enhances ASIC1a channel function and causes more prominent intracellular Ca^{2+} elevations, which in turn leads to neuronal cell death [20, 68]. Fourth, ASIC1a channels can also be regulated by other channels, such as NMDA receptors. We have previously shown that activation of NR2B-containing NMDA receptors during ischemia enhances ASIC1a channel currents through phosphorylation at Ser478 and Ser479 of ASIC1a by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), leading to exacerbated neuronal death [22].

All modulations discussed above are reported to enhance ASIC1a channel currents. However, as ion channels, the localization (e.g., synaptic or somatic) and expression patterns (e.g., clustering or not) are also very important for their functions [69]. It was reported that synaptic scaffolding protein interacting with C kinase 1 (PICK1) binds to ASIC1a [70]. This, together with other evidence [71–73], indicates a postsynaptic localization of ASIC1a channels. Given that activation of ASIC1a channels facilitates the opening of NMDA receptors by relieving Mg^{2+} blockade [71], the above findings suggest that ASIC1a channels may also regulate other important postsynaptic receptors such as NMDA receptors and thereby contribute to nerve injury mediated through these channels [74]. Additionally, clustering is an important property of synaptic ion channels. By increasing local density of ion channels, clustered ones are more effective for signaling transmission than dispersed ones [69, 75, 76]. It was reported that protein kinase A-dependent phosphorylation of Ser479 in ASIC1a C terminus attenuated the channel clustering by interfering their binding with synaptic scaffolding protein PICK1 [70], which suggests a regulation mechanism of synaptic distribution of ASIC1a channels and ASIC1a channel-mediated neuronal death.

Generally, there is still a lack of sufficient study on the physiological/pathological significance of most reported ASIC1a modulations by endogenous substances. The exploration of how these modulations contribute to ASIC1a channel-mediated neuronal death will shed new light on clinic therapies of ASIC1a channel-associated diseases, such as ischemic stroke.

ASIC1 and Spermine: A New Mechanism of Ischemic Neuronal Death

Spermine is one of endogenous polyamines, the levels of which are elevated in the ischemic brain [77, 78]. We recently found that extracellular spermine at physiologically relevant concentrations can enhance ASIC1a channel function via prolongation of channel activity and acceleration of channel recovery from steady-state desensitization [66], allowing efficient channel reactivation in response to repetitive pH fluctuations [79]. Ca^{2+} imaging and cell toxicity assays indicate important biological consequences of such modulation of ASIC desensitization. Thus, spermine causes more severe neuronal depolarization and cytoplasmic Ca^{2+} overload (Fig. 2b), which might lead to mitochondria-related injury and neuronal damage [80]. All of these were greatly diminished after pharmacological blockade of ASIC1a channels or deletion of the *ASIC1* gene. Similarly, in in vivo focal ischemia models, spermine-induced ischemic brain injury was dramatically reduced by ASIC1a channel blockade or *ASIC1* gene deletion. Most importantly, blockade of endogenous spermine biosynthesis by ornithine decarboxylase inhibitor α-difluromethylornithine (DFMO) significantly attenuated ASIC1a channel-mediated ischemic neuronal damage both in vitro and in vivo (Fig. 3a). Taken together, our findings clearly indicate that spermine contributes critically to ASIC1a channel-mediated ischemic injury of neurons (Fig. 3b).

The mechanistic details of spermine modulation of ASIC1a channels and its consequences on channel activity during acidosis associated with ischemic brain injury are intriguing. At the molecular level, spermine causes a rightward shift of the steady-state desensitization curve of ASIC1a channels towards increasing acidity and decreasing pH. This allows for channel to recover more easily from desensitization under more moderate alkalinization, a natural process that occurs in many brain regions as a result of synaptic activities, which are mainly attributed to activation of ionotropic glutamate and GABA receptors [81–83]. The transient extracellular alkalinization is due to two mechanisms: first, a GABA(A) receptor-mediated process, most likely associated with efflux of bicarbonate ions across GABA(A) anion channels; and second, a bicarbonate-independent process associated with excitatory synaptic transmission [84, 85]. The synaptic activities can bring about as much as 0.2 pH unit of alkalinization, which lasts for several seconds and is often followed by a period of acidification of ~ 0.1 to 0.2 pH unit for a few minutes. Because ASIC1a channels undergo complete steady-state desensitization at pH<7.0, the moderate alkalinization caused by synaptic activities during acidosis (~pH 6.8) may not bring sufficient channel recovery in the absence of spermine. However, in the presence of spermine, the steady-

state desensitization at pH 6.8 to 7.0 is less complete than in its absence, allowing significant channel recovery even with a small (~0.2 unit) pH increase, such as those that occur due to synaptic activities. Therefore, the presence of spermine facilitates ASIC1a channel reactivation in response to subsequent acidification. This suggests that spermine plays a critical role in the recovery of the ASIC1a channels and contributes significantly to repeated channel activation during pH fluctuations under acidosis conditions. The actual range of pH changes during ischemia may be larger than discussed above and should differ in space and time because of all other changes associated with ischemic penumbra, including recurrent spreading depressions and elevation in the levels of extracellular K^+ and glutamate [79], all of which affect extracellular pH.

ASICs or NMDA Receptors: The Choice in Clinic Therapy

Acidotoxicity and excitotoxicity are two major cell death mechanisms in ischemic brain. Therefore, the potential therapeutic targets are among ASIC1a channels and glutamate receptors such as NMDA receptors. However, antagonists of NMDA receptors have been shown to be unsuccessful in human clinic trials of stroke [54, 86, 87]. One important reason is that they are effective only during a very narrow time window of about 1 h post stroke [54, 86]. More importantly, NMDA receptors undertake many important neuronal functions; their blockade would lead to many undesirable side effects. It has been reported that NMDA receptor blockers induce a psychotic state resembling schizophrenia [54, 88]. These concerns have limited the application of NMDA agonists and/or antagonists in human patients. On the contrary, it needs several hours that the acidosis and the activation of ASIC1a channels proceed from the ischemic core into the ischemic penumbral regions. Thus, the protection window of ASIC1a channel blockade is 5 h post stroke [89, 90], much longer than that of NMDA receptors. In addition, *ASIC1*$^{-/-}$ animals exhibit no obvious defect in physiological functions [20, 71], suggestive of less side effects in clinical therapy. Therefore, ASIC1a channels appear to be more superior drug targets than NMDA receptors.

On the other hand, this is not to say that all cell deaths are adverse events. In some situations, such as virus infection, "endogenous adjuvant" released from dead cells recruits inflammatory reactions to eliminate the virus-infected cells [91]. As we know, inflammation is always accompanied with acidosis (~pH 7–5.5) [92, 93]. In this context, it was recently reported that ASIC1a channels are expressed in dendritic cells and they contribute to dendritic cell function [94]. In addition, many endogenous inflammatory mediators, such as arachidonic acid, have been reported as enhancers of ASICs [95]. Therefore, it is possible that ASIC1a channels also contribute to the cell death during inflammation, which may be beneficial to the organism. Thus, much broader and deeper insights into the physiological and pathological functions of ASIC1a channels and their involvement in mediating cell death are required before establishing the therapeutic interventions based on these channels.

Conclusion

Acidosis, which is one of the common features of neuronal diseases, has been extensively studied in many aspects. ASIC1a channels, as important targets of acidosis, mediate the damages caused by acidosis. With the accumulation of new knowledge about ASIC1a channel-mediated neuronal death, including the mechanisms of channel regulation and the discovery of endogenous channel modulators, ASIC1a channels have demonstrated the potential advantages as new therapeutic targets for a wide range of acidosis-associated neuronal diseases.

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