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Acid-Sensing Ion Channels in Neurodegenerative Diseases: Potential Therapeutic Target

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1. Introduction

Under pathological conditions such as tissue inflammation, ischemic stroke, traumatic brain injury, and epileptic seizure, accumulations of lactic acid due to enhanced anaerobic glucose metabolism and the release of proton from ATP hydrolysis result in significant reduction of tissue pH, a condition termed acidosis. Acidosis can activate a distinct family of ion channels: acid-sensing ion channels (ASICs) (Waldmann et al., 1997b), which are heavily expressed in the peripheral sensory and central neurons (Waldmann & Lazdunski, 1998; Krishtal, 2003; Wemmie et al., 2006; Lingueglia, 2007; Xiong et al., 2006, 2007, 2008; Sluka et al., 2009). ASICs belong to the amiloride-sensitive degenerin/epithelial Na^+ channel (DEG/ENaC) superfamily (Kellenberger & Schild, 2002). Four genes (*ACCN1 - 4*) encoding at least six ASIC subunits have been cloned. Each subunit has two transmembrane domains with a large extracellular loop and short intracellular N- and C-termini (Waldmann et al., 1997b). Functional ASICs are trimeric complexes of these subunits (Jasti et al., 2007; Gonzales et al., 2009) and most of these subunits can form homomeric and/or heteromeric channels (Benson et al., 2002; Baron et al., 2002, 2008; Wemmie et al., 2002, 2003; Askwith et al., 2004; Chu et al., 2004, 2006; Xiong et al., 2004; Zha et al., 2006; Sherwood et al., 2011). ASICs are enriched in brain neurons (Alvarez de la Rosa et al., 2003; Wemmie et al., 2003; Xiong et al., 2004; Sherwood et al., 2011), where at least three (ASIC1a, ASIC2a and ASIC2b) of the seven subunits can be found. ASIC1a is the dominant subunit in brain and homomeric ASIC1a and heteromeric ASIC1a/2b channels are permeable to both Na^+ and Ca^{2+} ions (Waldmann et al., 1997b; Yermolaieva et al., 2004; Zha et al., 2006; Sherwood et al., 2011). ASICs are inhibited by the diuretic amiloride, a non-specific ASIC blocker (Waldmann et al., 1997b). The tarantula toxin psalmotoxin 1 (PcTX1) blocks the homomeric ASIC1a (Escoubas et al., 2000) and heteromeric ASIC1a/2b (Sherwood et al., 2011) channels. The roles of ASICs in a variety of neurologic conditions are still under active investigation. ASIC1a channels localize at synapse and contribute to synaptic plasticity, learning/memory, and fear conditioning (Wemmie et al., 2002, 2003, 2004). Activation of Ca^{2+}-permeable homomeric ASIC1a and heteromeric ASIC1a/2b channels is involved in acidosis-mediated ischemic

brain injury (Xiong et al., 2004; Pignataro et al., 2007; Sherwood et al., 2011). Moreover, ASIC1a channels play critical roles in neurodegenerative diseases such as multiple sclerosis (Friese et al., 2007; Vergo et al., 2011), Parkinson's (Arias et al., 2008) and Huntington's (Wong et al., 2008) disease and in seizures (Chang et al., 2007; Ziemann et al., 2008) and depression (Coryell et al., 2009). Thus, controlling their activation might ameliorate acidosis-mediated CNS disorders (Xiong et al., 2008). This chapter provides an overview of recent advance in electrophysiological properties as well as pharmacological profiles of ASICs, and their roles in neurodegenerative disorders.

2. Electrophysiological and pharmacological properties of ASICs

2.1 Electrophysiological properties of ASICs

The electrophysiological properties and pharmacological profiles of ASICs have been extensively explored in heterologous expression systems (Chu et al., 2004; Hesselager et al., 2004) and in neurons from different brain regions, such as cortex (Varming, 1998; Xiong et al., 2004; Chu et al., 2004, 2006), hippocampus (Baron et al., 2002; Askwith et al., 2004), striatum (Jiang et al., 2009), cerebellum (Allen & Attwell, 2002), retinal ganglion (Lilley et al., 2004), and spinal cord (Wu et al., 2004; Baron et al., 2008). Fig. 1 shows typical ASIC current mediated by homomeric ASIC1a, 1b, 2a, or 3 channels expressed in CHO cells.

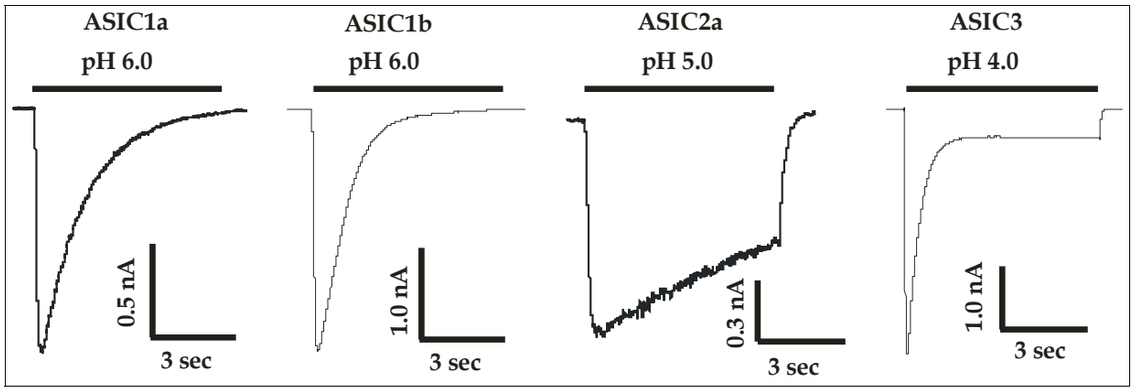

Fig. 1. Acid-triggered inward currents in CHO cells expressing indicated ASIC subunits

Homomeric ASIC1a channels have a pH for half-maximal activation (pH_{50}) between 6.2 and 6.8 (Babini et al., 2002; Benson et al., 2002; Chu et al., 2002; Jiang et al., 2009). Although the precise configuration of ASICs in native neurons is not clear, homomeric ASIC1a and heteromeric ASIC1a/2 channels are the major components in brain neurons (Wemmie et al., 2002; Askwith et al., 2004; Xiong et al., 2004; Jiang et al., 2009; Sherwood et al., 2011). For example, our recent studies have shown that rapid drops in extracellular pH from 7.4 to lower levels (e.g., 6.5, 6.0, 5.0 and 4.0) induced transient inward currents in cultured medium spiny neurons (MSNs) of the mouse striatum (Fig. 2A) (Jiang et al., 2009). The dose-response curve for activation of ASICs revealed a pH_{50} value of 6.25 (Fig. 2B). This pH_{50} value of ASICs in MSNs is comparable to that of homomeric ASIC1a channels (Walmann et al., 1997). The ASIC currents in MSNs had a linear I-V relationship with a reversal potential close to +60 mV (Fig. 2C, D), indicating that ASICs in MSNs are Na^+-selective.

In contrast to homomeric ASIC1a channels, the following properties distinguish rodent ASIC1b from ASIC1a: (1), although the amino acid sequence of approximately 2/3 of the

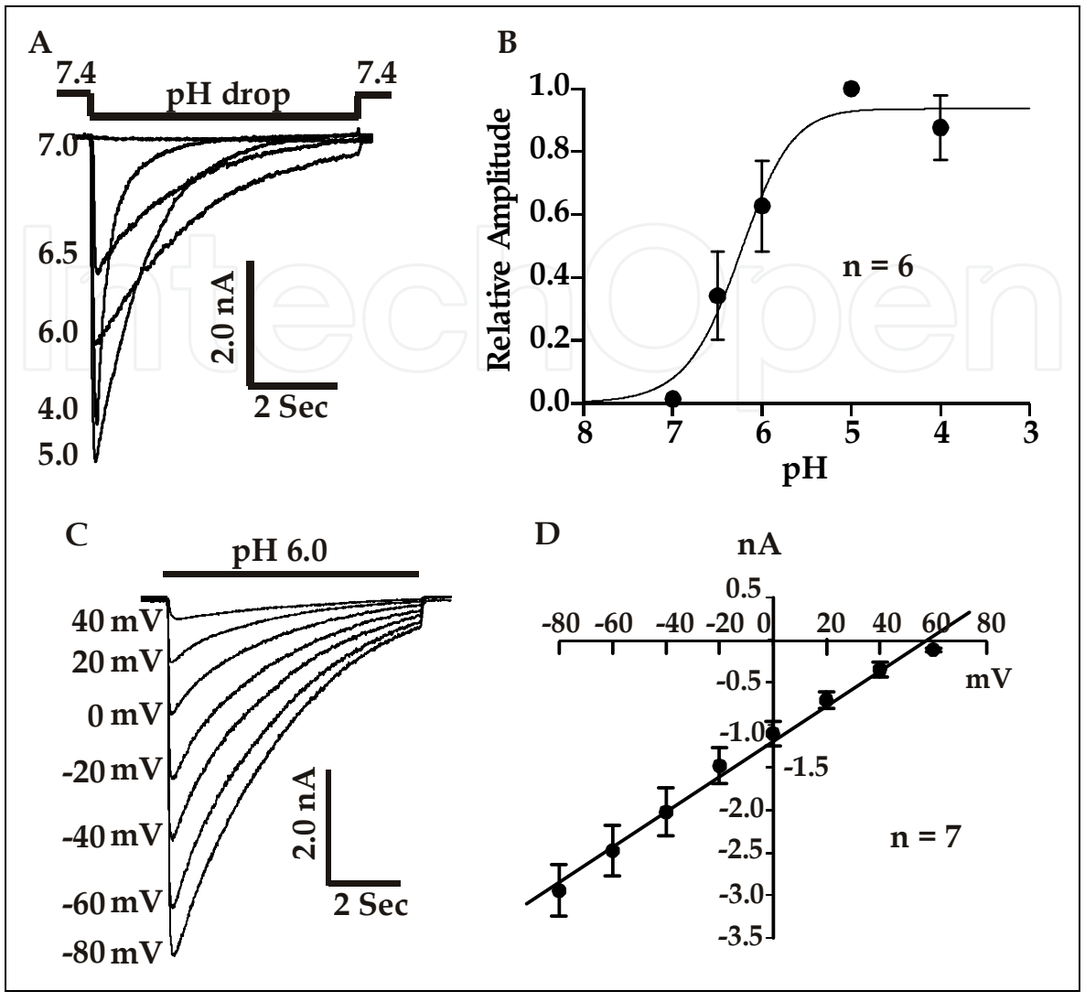

Fig. 2. Electrophysiological properties of ASICs in cultured mouse MSNs. (A) pH-dependent activation of ASIC currentsin in MSNs. (B) Dose-response curve for activation of the currents by pH drops. The pH_{50} value is 6.25 and the Hill coeficient is 0.94. (C) The I-V relationship of acid-activated currents with different holding levels by decreasing the pH from 7.4 to 6.0 in MSNs. (D) The I-V curve. The extrapolated reversal potential is close to 60 mV, which is close to the sodium equilibrium potential

ASIC1a and ASIC1b proteins are identical, there are significant differences in the sequence for the first one third (about 172 amino acids) of the protein beginning at the N terminal; this sequence includes the intracellular N-terminus, the first transmembrane domain, and the proximal part of the ectodomain (Chen et al., 1998; Bassler et al., 2001); (2), the expression of ASIC1b in the nervous system is limited to peripheral sensory neurons, while ASIC1a is also expressed in the CNS; (3), rodent ASIC1b is impermeable to Ca^{2+} while ASIC1a channels have significant Ca^{2+} permeability; Interestingly, a recent study has shown that human ASIC1b channels are permeable to Ca^{2+} (Hoagland et al., 2010); (4), the threshold for activation of ASIC1b current is lower than ASIC1a (~6.5 for ASIC1b and ~7.0 for ASIC1a) and it has lower pH_{50} (5.9); (5), ASIC1b is potentiated by PcTx1(Chen et al., 2006), which is a specific inhibitor of ASIC1a.

Homomeric ASIC2a channels are relatively insensitive to proton, with a pH_{50} of 4.4 (Price et al., 1996; Waldmann et al., 1996; Lingueglia et al., 1997). However, ASIC2a subunits can associate with ASIC1a to form heteromeric channels in brain (Askwith et al., 2004; Chu et al., 2004, 2006; Xiong et al., 2004; Jiang et al., 2009). Different from homomeric ASIC2a subunits, homomeric ASIC2b subunits do not form functional channels by themselves, but can associate with other ASIC subunits to form heteromultimeric channels (Lingueglia et al., 1997; Hesselager et al., 2004; Sherwood et al., 2011). For example, ASIC2b can be associated with ASIC1a to form functional channels and contribute to acidosis-induced neuronal injury (Sherwood et al., 2011).

ASIC3, like ASIC1b (Chen et al., 1998), is expressed primarily in peripheral sensory neurons (Waldmann et al., 1997a; Babinski et al., 1999; Wu et al., 2004; Lingueglia, 2007; Lin et al., 2008). In contrast to other subunits of ASICs, homomeric ASIC3 channels can respond to a large drop of extracellular pH with a transient inactivating current followed by a sustained component (Waldmann et al., 1997a; Sanilas et al., 2009) (Fig. 1). The transient currents are highly sensitive to protons, with a pH_{50} of around 6.5 (Waldmann et al., 1997a; Hesselager et al., 2004). Electrophysiological studies have shown that ASIC3 subunits function as homomeric or heteromeric channels in sensory neurons (Sutherland et al., 2001; Benson et al., 2002; Deval et al., 2004, 2008; Lin et al., 2008; Hattori et al., 2009). They can sense extracellular acidification occurring in physiological and/or pathological processes, such as cutaneous touch, pain perception, inflammation and ischemia (Benson et al., 1999; Immke & McCleskey, 2001; Price et al., 2001; Sutherland et al., 2001; Mamet et al., 2003; Molliver et al., 2005; Sluka et al., 2007; Ikeuchi et al., 2009). For example, ASIC3 channels expressed in cardiac sensory neurons can respond to myocardial ischemia (Benson et al., 1999; Sutherland et al., 2001; Yagi et al., 2006). Further, cutaneous sensory neurons from rats display large ASIC3-like currents when stimulated by moderate acidosis (Deval et al., 2008). Consequently, it is generally accepted that ASIC3 is a sensor of moderate acidosis during ischemia and inflammatory pain in sensory neurons (Lingueglia, 2007).

ASIC4 subunits are expressed in pituitary gland. Similar to ASIC2b, they do not seem to form functional homomeric channels (Aropian et al., 2000; Grunder et al., 2000).

2.2 Pharmacological profiles of ASICs

2.2.1 Amiloride

Amiloride, the potassium-sparing diuretic agent, is a commonly used nonspecific blocker for ASICs. It inhibits the ASIC current and acid-induced increase in intracellular Ca^{2+} ($[Ca^{2+}]_i$) with an IC_{50} of 10–60 μM (Waldmann et al., 1997b; de Weille et al., 1998; Chen et al., 1998; Benson et al., 1999; Chu et al., 2002; Wu et al., 2004; Xiong et al., 2004; Yermolaieva et al., 2004; Jiang et al., 2009). For example, our recent study has shown that amiloride dose-dependently inhibited the ASIC currents in MSNs with an IC_{50} of 13.6 μM (Fig. 3) (Jiang et al., 2009). Unlike the currents mediated by other homomeric ASICs, however, the sustained current mediated by homomeric ASIC3 channels is insensitive to amiloride (Waldmann et al., 1997b; Benson et al., 1999; Yagi et al., 2006). Based on the studies of ENaC, it is believed that amiloride inhibits ASICs by a direct blockade of the channel (Schild et al., 1997; Adams et al., 1999). The pre-TM II region of the channel is critical for the effect of amiloride. Mutation of Gly-430 in this region, for example, dramatically changed the sensitivity of ASIC2a current to amiloride (Champigny et al., 1998). Consistent with its inhibition on the ASIC current, amiloride has been shown to suppress acid-induced pain in peripheral

sensory system (Ugawa et al., 2002; Sluka et al., 2003; Jones et al., 2004; Dube et al., 2005), and acidosis-mediated injury of CNS neurons (Xiong et al., 2004; Yermolaieva et al., 2004). However, because of its nonspecificity for other ion channels (e.g., ENaC and T-type Ca^{2+} channels) and ion exchange systems (e.g., Na^+/H^+ and Na^+/Ca^{2+} exchanger), it is less likely that amiloride will be used as a future neuroprotective agent in human subjects. It is worth mentioning that the normal activity of Na^+/Ca^{2+} exchanger, for example, is critical for maintaining the cellular Ca^{2+} homeostasis and the survival of neurons against delayed calcium deregulation caused by glutamate receptor activation (Bano et al., 2005). Inhibition of Na^+/Ca^{2+} exchange by amiloride may therefore compromise normal neuronal Ca^{2+} handling, thus potentiating the glutamate toxicity (Bano et al., 2005).

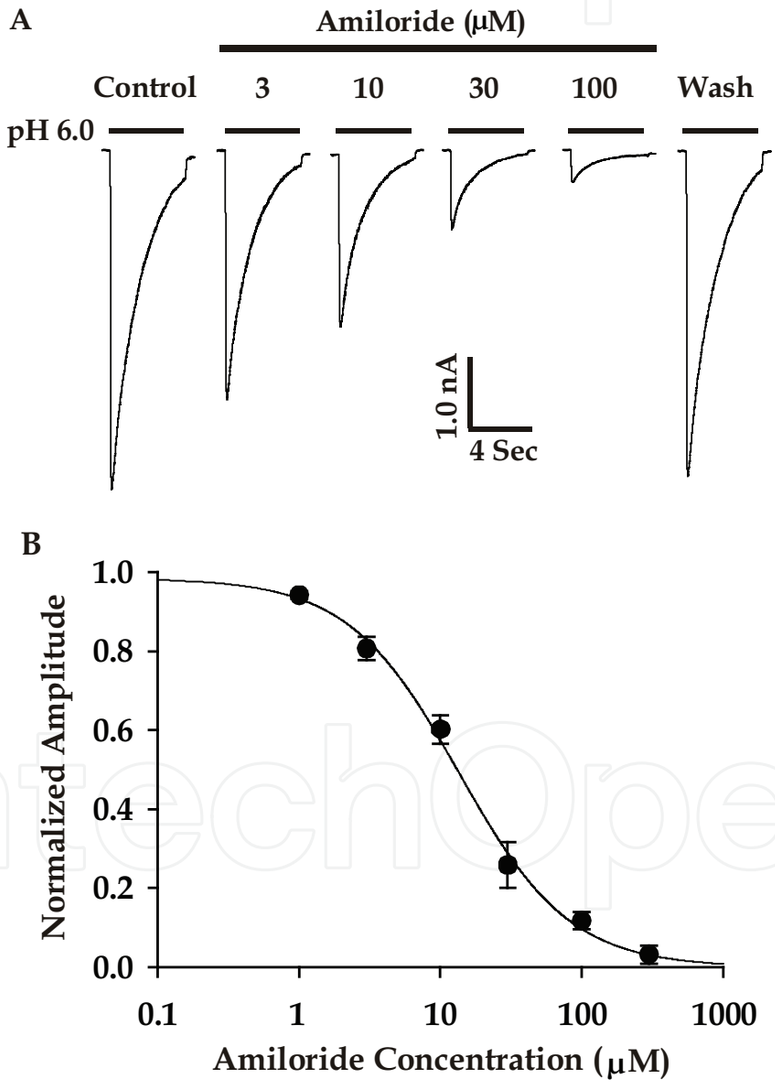

Fig. 3. Dose-dependent blockade of ASIC currents in cultured MSNs by amiloride, a non-specific ASIC blocker. (A) Amiloride dose-dependently inhibits the ASIC currents activated by pH 6.0. (B) Dose-inhibition curve of the acid-induced currents by amiloride. The IC_{50} of amiloride is 13.6 μM

2.2.2 A-317567

A-317567, a small molecule structurally unrelated to amiloride, is another nonselective ASIC blocker (Dube et al., 2005). It inhibits the ASIC1a, ASIC2a, and ASIC3-like currents with an IC_{50} of 2–30 μM. Unlike amiloride, which has no effect on the slow component of the ASIC3 current, A-317567 blocks both the fast and the sustained ASIC3 currents. Also different from amiloride, A-317567 does not show diuresis or natriuresis activity (Dube et al., 2005), suggesting that it is more specific for ASICs than amiloride. Its inhibition of sustained ASIC3 current suggests that it might be potent in reducing acidosis-mediated chronic pain. Indeed, A-317567 has been shown to be effective in suppressing the pain in a rat model of thermal hyperalgesia at a dose tenfold lower than amiloride (Dube et al., 2005).

2.2.3 PcTX1

Being a peptide toxin isolated from venom of the South American tarantula *Psalmopoeus cambridgei*, PcTX1 is a potent and specific inhibitor for homomeric ASIC1a channels (Escoubas et al., 2000). This toxin contains 40 amino acids cross-linked by three disulfide bridges. In heterologous expression systems, PcTX1 specifically inhibits the acid-activated current mediated by homomeric ASIC1a subunits with an IC_{50} of 1 nM (Escoubas et al., 2000). At concentrations that effectively inhibit the ASIC1a current, it has no effect on the currents mediated by other configurations of ASICs (Escoubas et al., 2000), or known voltage-gated Na^+, K^+, Ca^{2+} channels as well as several ligand-gated ion channels (Xiong et al., 2004). Unlike amiloride, which directly blocks the ASICs, PcTX1 acts as a gating modifier. It shifts the channel from its resting state toward the inactivated state by increasing its apparent affinity for protons (Chen et al., 2005). Recently, PcTX1 has also been shown to suppress heteromeric ASIC1a/2b channels (Sherwood et al., 2011).

2.2.4 APETx2

Being a peptide toxin isolated from sea anemone *Anthopleura elegantissima*, APETx2 is a potent and selective inhibitor for homomeric ASIC3 and ASIC3 containing channels (Diochot et al., 2004). The toxin contains 42 amino acids, also cross-linked by three disulfide bridges. It reduces transient peak acid-evoked currents mediated by homomeric ASIC3 channels (Diochot et al., 2004). In contrast to the peak ASIC3 current, the sustained component of the ASIC3 current is insensitive to APETx2. In addition to homomeric ASIC3 channels (IC_{50} = 63 nM for rat and 175 nM for human), APETx2 inhibits heteromeric ASIC3/1a (IC_{50} = 2 μM), ASIC3/1b (IC_{50} = 900 nM), and ASIC3/2b (IC_{50} = 117 nM). Homomeric ASIC1a, ASIC1b, ASIC2a, and heteromeric ASIC3/2a channels, on the other hand, are not sensitive to APETx2 (Diochot et al., 2004).

2.2.5 Nonsteroid anti-inflammatory drugs (NSAIDs)

NSAIDs are the most commonly used anti-inflammatory and analgesic agents. They inhibit the synthesis of prostaglandins (PGs), a main tissue inflammatory substance. A recent study demonstrated that NSAIDs also inhibit the activity of ASICs at their therapeutic doses for analgesic effects (Voilley et al., 2001). Ibuprofen and flurbiprofen, for example, inhibit ASIC1a containing channels with an IC_{50} of 350 μM. Aspirin and salicylate inhibit ASIC3 containing channels with an IC_{50} of 260 μM, whereas diclofenac inhibits the same channels with an IC_{50} of 92 μM. In addition to a direct inhibition of the ASIC activity, NSAIDs also prevent inflammation-induced increase of ASIC expression in sensory neurons (Voilley et al., 2001).

2.2.6 Aminoglycosides (AGs)

AGs (streptomycin, neomycin and gentamicin) are a group of antibiotics that have been shown to block Ca^{2+} channels (Zhou and Zhao, 2002), excitatory amino acid receptors (Pérez et al., 1991), and transient-receptor-potential V1 channels (Raisinghani and Premkumar, 2005). Recently, Garza et al determined the effect of AGs on proton-gated ionic currents in DRG neurons of the rat, and in human embryonic kidney (HEK)-293 cells (Garza et al., 2010). In DRG neurons, streptomycin and neomycin produced a significant, reversible reduction in the amplitude of proton-gated currents in a concentration-dependent manner. In addition, they slowed desensitization rates of ASIC currents. Gentamicin also showed a significant reversible action on the ASIC currents. In HEK-293 cells, streptomycin produced a significant reduction in the amplitude of the proton-gated current, whereas neomycin and gentamicin had no significant effect. These results indicate that ASICs are molecular targets for AGs, which may explain, in part, their effects on excitable cells. Moreover, AGs might potentially represent a novel class of molecules with high affinity, specificity, and selectivity for different ASIC subunits.

2.2.7 Diarylamidines

Diarylamidines have been widely used for the treatment of protozoan diseases such as trypanosomiasis and leishmaniasis since 1930s (Baraldi et al., 2004; Mishra et al., 2007). Recently, Chen and colleges found that four members of the diarylamidines, 4', 6-diamidino-2-phenylindole, diminazene, hydroxystilbamidine and pentamidine strongly inhibit ASIC currents in hippocampal neurons with IC_{50} of 2.8, 0.3, 1.5 and 38 μM, respectively. The inhibitory concentration is much lower than amiloride. Sub-maximal concentrations of diminazene also potently accelerate desensitization of ASIC currents in hippocampal neurons. Diminazene blocks ASIC1a, -1b, -2a, and -3 currents expressed in CHO cells with a rank order of potency 1b > 3 > 2a > or = 1a. This study indicates that diarylamidines represent a novel class of non-amiloride ASIC blockers and suggests that diarylamidines as small molecules may be developed as therapeutic agents in the treatment of ASIC-involved diseases (Chen et al., 2010).

3. Activation of ASICs induces membrane depolarization and increases intracellular Ca^{2+} in brain neurons

Since all ASICs are Na^+-selective channels which have a reversal potential near Na^+ equilibrium potential (+60 mV), activation of ASICs at normal resting potentials produces exclusively inward currents which result in membrane depolarization and the excitation of neurons (Baron et al., 2002; Wu et al., 2004; Jiang et al., 2009). For example, our recent study has shown that a minor drop in extracellular pH from 7.4 to 6.8 induces significant membrane depolarization, which accompanies trains of action potentials (Fig. 4) (Jiang et al., 2009). This acid-induced membrane depolarization is significantly attenuated by either amiloride or PcTX1 (Fig. 4). Tetrodotoxin, a voltage-gated Na^+ channel blocker, has little effect on the membrane depolarization but completely diminished the action potentials triggered by a drop in pH from 7.4 to 6.8. For homomeric ASIC1a channels, acid activation induces Ca^{2+} entry directly through these channels (Walmann et al., 1997b; Chu et al., 2002; Xiong et al., 2004; Yermolaieva et al., 2004). In addition, the ASIC-mediated membrane depolarization may facilitate the activation of voltage-gated Ca^{2+} channels and NMDA receptor-gated channels (Wemmie et al., 2002; Zha et al., 2006), further promoting neuronal

excitation and $[Ca^{2+}]_i$ accumulation. The Ca^{2+}-permeability of ASICs in CNS neurons has been characterized using fluorescent Ca^{2+} imaging and ion-substitution protocols (Xiong et al., 2004; Yermolaieva et al., 2004). In mouse cortical, striatal and hippocampal neurons, activation of ASICs by decreasing in extracellular pH induces increases in $[Ca^{2+}]_i$. This acid-induced increase in $[Ca^{2+}]_i$ could be recorded in the presence of a cocktail blocking other voltage-gated and ligand-gated Ca^{2+} channels (Xiong et al., 2004; Jiang et al., 2009), indicating Ca^{2+} entry directly through ASICs. The acid-induced increase in $[Ca^{2+}]_i$ is eliminated by specific and non-specific ASIC1a blockade, or by ASIC1 gene knockout (Xiong et al., 2004; Yermolaieva et al., 2004; Jiang et al., 2009). Consistent with the finding of fluorescent imaging, acid-activated inward current is activated when extracellular solution contains Ca^{2+} as the only conducting cation (Xiong et al., 2004). Thus, homomeric ASIC1a channels constitute an additional and important Ca^{2+} entry pathway for neurons.

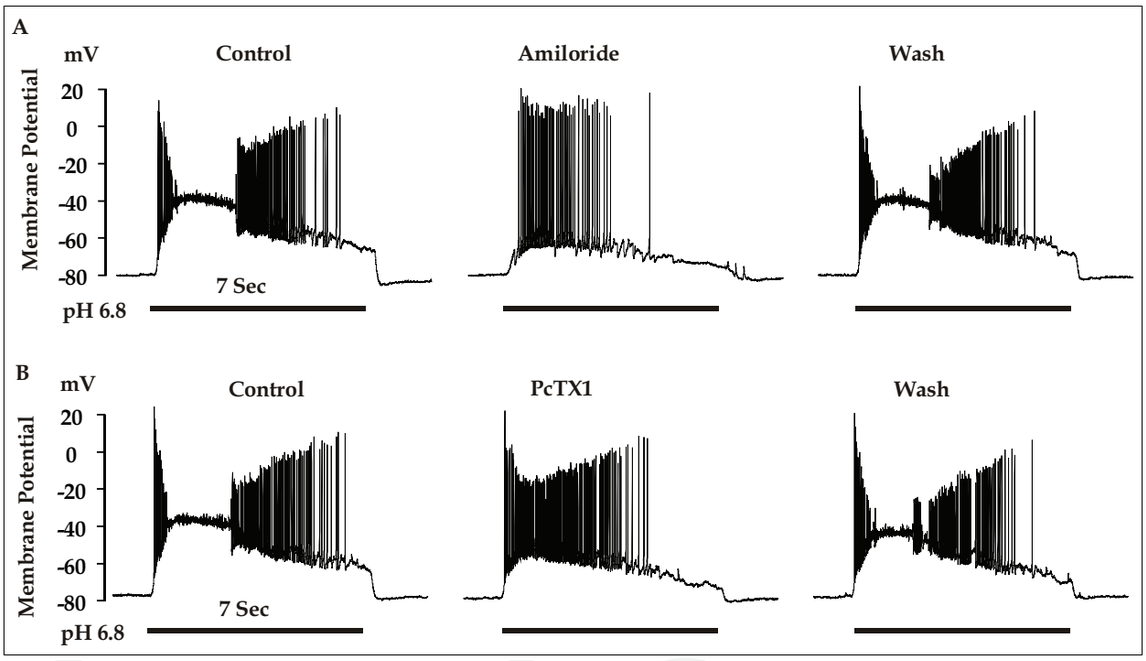

Fig. 4. pH drop triggered membrane depolarization and action potentials by activation of ASICs in cultured MSNs. Membrane depolarization by a drop in pH from 7.4 to 6.8 subsequently triggered trains of action potentials. The membrane depolarization was inhibited by amiloride (A) and PcTX1 (B)

4. Physiological implications of ASICs in the CNS

4.1 ASIC1a channels in synaptic plasticity, learning and memory

A change in pH at the synaptic cleft following synaptic release may render ASICs the opportunity to regulate synaptic transmission. The findings that ASICs are present at synaptic sites and can interact with postsynaptic density protein 95 as well as C kinase 1-interacting proteins (Hruska-Hageman et al., 2002; Wemmie et al., 2002; Zha et al., 2006, 2009) support this notion. Indeed, studies by Wemmie and coworkers have demonstrated that ASIC1a activation is involved in synaptic plasticity, learning and memory (Wemmie et al., 2002). They demonstrated that high frequency stimulation produces long-lasting

potentiation of excitatory postsynaptic potentials (EPSP) in hippocampal slices from wild-type mice. However, the potentiation of EPSP decays rapidly to the baseline in slices from ASIC1a null mice. Further studies showed that the NMDA receptor antagonist D-2-Amino-5-phosphonovalerate inhibits EPSP summation in slices from wild-type but not ASIC1a-knockout mice, suggesting that the loss of ASIC1a impaired NMDA-receptor function. ASIC1a disruption does not impair presynaptic vesicle release, as evidenced by normal single evoked EPSPs and paired-pulse facilitation. Interestingly, a later study by Cho and Askwith demonstrated that the presynaptic release probability is increased in cultured hippocampal neurons from the ASIC1 knockout mice (Cho & Askwith, 2008). Although localizations of ASICs at neuronal cell body and postsynaptic sites have been clearly demonstrated (Wemmie et al., 2002; Zha et al., 2006), it remains to be determined whether ASICs are also expressed at presynaptic sites.

4.2 ASIC1a channels in fear-related behavior

ASIC1a is enriched in key structures of fear circuit (e.g. amygdala) (Wemmie et al., 2003). Thus, ASIC1a may influence fear responses. Indeed, Wemmie and colleagues demonstrated that ASIC1-null mice display significant deficits in cue and context fear conditioning (Wemmie et al., 2003). The loss of ASIC1a also reduces unconditioned fear in the open field test, during acoustic startle, and in response to predator odor (Coryell et al., 2007). Overexpressing ASIC1a, on the other hand, increases fear conditioning (Wemmie et al., 2004), but not unconditioned fear responses (Coryell et al., 2008).

Further studies by Wemmie's group suggest that activation of ASIC1a in brain chemosensors contributes to CO_2 induced fear-related behavior (Ziemann et al., 2009). It has long been known that breathing CO_2 triggers panic attacks in patients with panic disorder, and that these patients show an increased sensitivity to CO_2 inhalation (Papp et al., 1993). In addition, patients with increasing hypercarbia due to respiratory failure become extremely anxious. How can CO_2 inhalation contribute to fear behavior and related panic disorders? Wemmie and colleagues have provided evidence that ASIC1a channels are involved (Ziemann et al., 2009). They showed that inhaled CO_2 triggers a drop in brain pH and induces fear behavior in mice. Eliminating or inhibiting ASIC1a significantly limits this activity. Overexpressing ASIC1a in the amygdala rescues the CO_2-induced fear deficit in ASIC1a null mice. Buffering brain pH, on the other hand, attenuates fear behavior, whereas lowering pH in the amygdale reproduces the effect of CO_2. These studies provide a novel molecular mechanism underlying CO_2-induced intense fear and related anxiety/panic disorders and define the amygdala as an important chemosensor that detects hypercarbia/acidosis and initiates behavioral responses (Ziemann et al., 2009).

4.3 ASICs and retinal integrity

pH variations in the retina are involved in the fine-tuning of visual perception. Expression of ASICs in the retina suggests that they might play a role (Lilley et al., 2004). One study by Ettaiche suggested that ASIC2 is important for retinal function and likely protects against light-induced retinal degeneration. They showed that both photoreceptors and neurons of the mouse retina express ASIC2a and ASIC2b. Inactivation of the ASIC2 gene in mice leads to an increased rod electroretinogram of a- and b-waves, indicating an enhanced gain of visual transduction. ASIC2 knockout mice also show more sensitivity to light-induced retinal degeneration. Thus, ASIC2 is likely a negative modulator of rod phototransduction,

and that functional ASIC2 channels are beneficial for the maintenance of retinal integrity (Ettaiche et al., 2004). However, since homomeric ASIC2a channels have an extremely low-sensitivity to protons (i.e. pH_{50} of 4.4), it is not clear whether active channel activity is required for this role.

Further studies by Ettaiche and colleagues also suggested an involvement of ASIC1a in retinal physiology (Ettaiche et al., 2006). In situ hybridization and immunohistochemistry detected the expression of ASIC1a in the outer and inner nuclear layers (cone photoreceptors, horizontal cells, some amacrine and bipolar cells) and in the ganglion cell layer. ASIC1a knockdown by antisense oligonucleotides and ASIC1a blockade by relatively specific inhibitor PcTX1 decreased the photopic a- and b-waves and oscillatory potentials. This finding suggests that ASIC1a is involved in normal retinal activity. Interestingly, a recent study by Render and colleagues did not detect any remarkable morphological changes in cone photoreceptors in ASIC1a-/- mice, at least at 5 or 22-27 weeks of age (Render et al., 2010). Thus, the exact role of this subunit in retinal integrity and/or function remains to be determined.

In addition to ASIC1a and ASIC2, a potential role of ASIC3 in retinal function and survival has been reported (Ettaiche et al., 2009). Ettaiche and colleagues demonstrated the presence of ASIC3 in the rod inner segment of photoreceptors, in horizontal and some amacrine cells. ASIC3 is also detected in retinal ganglion cells (RGCs) but contributes little to ASIC currents recorded in cultured RGCs. At 2 - 3 months, knockout mice experienced a moderate enhancement of scotopic electroretinogram a-wave amplitude and a concomitant increase of b-wave amplitude without alteration of retinal structure. Older (8-month-old) mice had large reductions in scotopic a- and b-waves, respectively, and reductions in oscillatory potential amplitudes associated with complete disorganization of the retina and degenerating rod inner segments. At 8 and 12 months of age, GFAP and TUNEL staining revealed an up-regulation of GFAP expression in Müller cells and the presence of apoptotic cells in the inner and outer retina (Ettaiche et al., 2009). Thus, ASIC3 also appears to be required for the maintenance of retina integrity.

5. ASICs in neurodegenerative diseases

5.1 ASIC1 channels and multiple sclerosis

Multiple sclerosis is a neuroinflammatory disease associated with axonal degeneration. Although inflammation and demyelination are the primary features of CNS lesions, axonal degeneration correlates best with clinical deficits in individuals with this disease. It has been suggested that the inflammatory insult leads to axonal degeneration by causing neuronal mitochondrial dysfunction, energy failure and alteration of ion exchange mechanisms (Waxman, 2006). Since excessive accumulation of Na^+ and Ca^{2+} ions is associated with axonal degeneration (Stys & LoPachin, 1998), Friese et al determined whether ASIC1a activation, which is known to cause accumulation of Na^+ and Ca^{2+} ions, contributes to such process in inflammatory lesions of the CNS (Friese et al., 2007). They showed that in an experimental model of autoimmune encephalomyelitis (EAE), ASIC1 null mice exhibit a significantly reduced clinical deficit and axonal degeneration as compared to wild-type mice. Further, pH measurements in the spinal cord of EAE mice display tissue acidosis sufficient to open ASIC1. The ASIC1 gene disruption also shows protective effect in nerve explants in vitro. ASIC blockade by amiloride is equally neuroprotective in nerve explants and in EAE. Thus, ASIC1a may be a potential target for axon degeneration associated with multiple sclerosis.

More recently, Vergo et al., from the same group studied acute and chronic EAE and multiple sclerosis spinal cord and optic nerve tissues to examine the distribution of ASIC1 and its relationship with neuronal and glial damage (Vergo et al., 2011). They found that ASIC1 was upregulated in axons and oligodendrocytes within lesions from mice with acute EAE and from patients with active multiple sclerosis. The expression of ASIC1 was associated with axonal damage as indicated by co-localization with the axonal injury marker beta amyloid precursor protein. Moreover, blocking ASIC1 with amiloride protected both myelin and neurons from damage in the acute model, and when given either at disease onset or, more clinically relevant, at first relapse, ameliorated disability in mice with chronic-relapsing EAE. Together these findings suggest that blockade of ASIC1 has the potential to provide both neuro- and myelo-protective benefits in multiple sclerosis (Vergo et al., 2011).

5.2 ASICs and Parkinson's disease (PD)

PD is characterized by motor impairments and a loss of dopaminergic neurons in the substantia nigra (SNc) (Dauer & Przedborski, 2003). However, the mechanism of neuronal injury is not entirely clear. Previous studies have shown that the vulnerable neurons in this region also express ASIC1a (Wemmie et al., 2003; Pidoplichko & Dani, 2006). Given that PD, like ischemia, is associated with cerebral lactic acidosis, Arias et al tested the effect of ASIC blockade in a mouse model of PD induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment (Arias et al., 2008). As expected, amiloride was found to protect SNc neurons from MPTP-induced degeneration, and to preserve dopaminergic cell bodies in the SNc. Administration of PcTX venom resulted in a modest effect, attenuating the deficits in striatal DAT binding and dopamine. These findings suggest a potential role for ASICs in the pathogenesis of Parkinson's disease.

5.3 ASICs and Huntington's disease (HD)

HD is a fatal neurodegenerative disorder. Energy metabolism deficit and acidosis have been observed in both *in vitro* and *in vivo* models of HD as well as in the brains of HD patients (Wong et al., 2008). To examine the potential involvement of ASICs in the pathology of HD, Wong et al tested effect of amiloride derivative benzamil both *in vitro* and *in vivo* (Wong et al., 2008). They showed that benzamil markedly reduced the huntingtin-polyglutamine (htt-polyQ) aggregation in an inducible cellular system. In addition, the effect of benzamil was recapitulated in the R6/2 animal model of HD. Further experimentation showed that benzamil alleviated the inhibition of ubiquitin-proteasome system (UPS) activity, resulting in enhanced degradation of soluble htt-polyQ specifically in its pathological range. Blocking the expression of ASIC1a with siRNA also enhanced UPS activity, resulting in decreased htt-polyQ aggregation in the striatum of R6/2 mice. Thus, targeting ASIC1a might be an alternative approach to combat HD and other polyQ-related disorders.

5.4 ASIC1a and Alzheimer's disease (AD)

Based on ASIC1a channels in synaptic plasticity and learning/memory, a recent preliminary study has suggested that a reduced function of ASIC1a channels may contribute to the learning and memory deficit associated with AD (Maysami et al., 2009). In this study, Maysami et al showed that acid-activated currents in mouse cortical neurons and in CHO cells expressing ASIC1a are inhibited by nanomolar concentrations of amyloid beta peptide,

a critical player for the pathology of AD. In addition to a reduction of current amplitude, amyloid beta peptide also slows down the activation of the channels. Thus, restoring the activity of ASIC1a channels could be a new intervention for AD.

5.5 ASICs in depression-related behavior

Depression disorders are a highly prevalent condition among adults in general population but the molecular pathways underlying depression are poorly understood. Recent studies by Coryell and colleagues have linked ASIC function to depression-related behavior (Coryell et al., 2009). They demonstrated that genetically disrupting ASIC1a in mice produced antidepressant-like effects in the forced swim test, the tail suspension test, and following unpredictable mild stress. Pharmacologically inhibiting ASIC1a also had antidepressant-like effects. The effects of ASIC1a disruption in the forced swim test were independent and additive to those of several commonly used antidepressants. Restoring ASIC1a to the amygdale of ASIC1a null mice reversed the forced swim test effects. The mechanism underlying the involvement of ASIC1a in depression-related behavior is not clear. It is likely that brain-derived neurotrophic factor (BDNF) is involved since both ASIC1a disruption and inhibition interfere with the ability of stress to reduce BDNF in the hippocampus. Thus, antagonists of ASIC1a channels may have potential for combating human depression.

5.6 ASICs and anxiety disorders

Anxiety disorders are debilitating neuropsychiatric disorders. Current treatments for anxiety disorders include pharmacological agents such as benzodiazepines and selective serotonin reuptake inhibitors. These agents, while effective in many patients, can induce a variety of side effects. Thus, it is necessary to develop a new generation of effective and better-tolerated anxiolytic agents. In this regard, Dwyer et al have shown that ASIC1a inhibitors have an effect in preclinical rodent models of autonomic and behavioral parameters of anxiety (Dwyer et al., 2009). In the stress-induced hyperthermia model, acute administration of ASIC inhibitors PcTX1, A-317567, and amiloride prevented stress-induced elevations in core body temperature. In the four-plate test, acute treatment with PcTX1 and A-317567 produced dose-dependent increases in the number of punished crossings. Further experiment showed that infusion of A-317567 into the amygdala significantly elevated the extracellular levels of GABA, but not glutamate, in this brain region. These findings suggest that ASIC inhibition has anxiolytic-like effects in some behavioral models and that GABAergic mechanisms are involved in the effects.

A recent study also suggests an involvement of ASIC3 in anxiety-like behavior (Wu et al., 2010). Although it is widely accepted that ASIC3 is predominately distributed in the peripheral nervous system, its expression has been found in rat hypothalamus (Meng et al., 2009). Study by Wu and colleagues also reported the expression of ASIC3 in the sensory mesencephalic trigeminal nucleus of mouse brain (Wu et al., 2010). However, whether ASIC3 plays any functional role in the brain was unclear. Wu et al showed that, in anxiety behavior tasks, ASIC3 null mice spent more time in the open arms of an elevated plus maze than did their wild-type littermates. ASIC3 null mice also displayed less aggressiveness toward intruders but more stereotypic repetitive behaviors during resident-intruder testing than did wild-type littermates. Therefore, loss of ASIC3 produces behavioral changes in anxiety and aggression in mice, which suggests that ASIC3-dependent sensory activities might be related to the central process of emotion modulation (Wu et al., 2010).

Although the studies from ASIC1a and ASIC3 knockout mice indicated that ASICs contribute to neuropsychiatric disorders such as depression and anxiety, whether these neurological conditions are associated with significant change in local or global pH in the CNS remains to be determined.

5.7 ASICs in acidosis-mediated ischemic neuronal injury

During neurological conditions such as brain ischemia, increased anaerobic glycolysis due to reduced oxygen supply leads to lactic acid accumulation (Rehncrona, 1985). Accumulation of lactic acid, alone with increased H^+ release from ATP hydrolysis, causes a decrease in pH, resulting in brain acidosis. During brain ischemia, for example, extracellular pH falls to 6.5 or lowers (Rehncrona, 1985; Nedergaard et al., 1991).

Acidosis has long been known to play an important role in ischemic brain injury (Tombaugh & Sapolsky, 1993; Siesjo, et al., 1996), and a direct correlation of brain acidosis with infarct size has been described (Siesjo, 1988). However, the exact mechanism underlying acidosis-mediated neuronal injury remained uncertain. Severe acidosis may cause non-selective denaturation of proteins and nucleic acids (Kalimo et al., 1981); trigger cell swelling through stimulation of Na^+/H^+ and $Cl^-/HCO3^-$ exchangers, which leads to cellular edema and osmolysis (Kimelberg et al., 1990); hinder postischemic metabolic recovery by inhibiting mitochondrial energy metabolism and impairing postischemic blood flow via vascular edema (Hillered et al., 1985). The stimulation of pathologic free radical formation by acidosis has also been described (Rehncrona et al., 1989). At the neurotransmitter level, profound acidosis inhibits astrocytic glutamate uptake, which may contribute to excitatory neuronal injury (Swanson et al., 1995). Marked acidosis, with tissue pH<5.5, may influence neuronal vulnerability indirectly by damaging glial cells (Giffard et al., 1990).

The widespread expression of ASIC1a in the brain, its activation by pH drops to the level commonly seen during ischemia, and its demonstrated role in intracellular Ca^{2+} accumulation suggested a potential involvement of these channels in the pathology of brain injury. Indeed, a number of recent studies have demonstrated an important role for ASIC1a activation in acidosis-mediated neuronal injury (Xiong et al., 2004; Yermolaieva et al., 2004; Gao et al., 2005; Pignataro nt al., 2007; Sherwood et al., 2009, 2011; Gu et al., 2010; Jetti et al., 2010; Li et al., 2010; Mari et al., 2010). In cultured mouse and human cortical neurons, for example, activation of ASICs by acid incubation induced glutamate receptor-independent neuronal injury inhibited by specific ASIC1a blockade, and/or by ASIC1 gene knockout (Xiong et al., 2004; Li et al., 2010). In rodent models of brain ischemia, intracerebroventricular injection of ASIC1a blocker/inhibitor reduced the infarct volume from transient or permanent focal ischemia by up to 60%(Xiong et al., 2004; Pignataro et al., 2007). Similarly, ASIC1 gene knockout produced significant neuroprotection in mice (Xiong et al., 2004). The protection by ASIC1a blockade had a time window of efficacy of up to 5 hours, and the protection persists for at least 7 days (Pignataro nt al., 2007).

More recently, Sherwood et al., found that ASIC2b subunit can form functional channels with ASIC1a in cultured hippocampal neurons, and that the heteromeric ASIC1a/2b channels are calcium-permeable (Sherwood et al., 2011). Further, activation of heteromeric ASIC1a/2b channels contributes to acidosis-induced neuronal death. These data indicate that ASIC2, like ASIC1a, plays a role in acidosis-induced neuronal death and implicate the ASIC1a/2b subtype as a novel pharmacological target to prevent neuronal injury after stroke (Sherwood et al., 2011).

Since activation of NMDA receptors and subsequent Ca^{2+} toxicity have been known to play an important role in ischemic brain injury, the outcome of co-application of both antagonists has also been investigated. Compared to ASIC1a or NMDA blockade alone, co-application of NMDA and ASIC antagonists produced additional neuroprotection, and the presence of ASIC1a blockade prolonged the time window of effectiveness of NMDA blockade (Pignataro nt al., 2007). Thus, ASIC1a represents a novel pharmacological target for ischemic brain injury.

In contrast to ASIC1a, a study by Johnson and colleagues suggests that an increased ASIC2a expression could provide protection against ischemic injury (Johnson et al., 2001). They showed an increased ASIC2a expression in neurons that survived global ischemia. This may be explained by the possibility that increased ASIC2a expression favors the formation of heteromeric ASIC1a/ASIC2a channels with reduced acid-sensitivity and no Ca^{2+} permeability.

5.8 ASIC activation and epileptic seizure activity

A significant drop of brain pH during intense neuronal excitation or seizure activity (Urbanics et al., 1978; Somjen et al., 1984; Simon et al., 1985, 1987; Chesler & Chan, 1988; Chesler & Kaila, 1992) suggests that ASIC activation might occur and activated ASICs then play a role in the generation/maintenance of epileptic seizures. However, the exact role of ASIC activation in seizure generation, propagation, and termination seems controversial.

Babinski and colleagues first reported a change of ASIC1a and ASIC2b expression in the hippocampal area following pilocarpine-induced epilepticus (Biagini et al., 2001), suggesting that the channels containing ASIC1a and ASIC2b subunits might play a role in the pathology of epilepsy.

Later on, a number of studies showed that amiloride, a commonly used non-selective ASIC blocker, has an anticonvulsant property *in vivo* in pilocarpine and pentylenetetrazole models of seizures (Ali et al., 2004, 2006; N'Gouemo, 2008), suggesting that ASIC activation might be proconvulsant. However, since amiloride also inhibits a number of other channels and ion exchange systems, these findings do not define ASICs as a specific target for amiloride to achieve its anti-epileptic action.

Using a number of *in vitro* epilepsy models, a preliminary study by Chang et al provided additional evidence that ASIC1a activation might be proconvulsant (Chang et al., 2007). In a cell culture model of epilepsy, brief withdrawal of the NMDA antagonist kynurenic acid induces a dramatic increase in the firing of action potentials, in addition to a sustained membrane depolarization. ASIC blockade by amiloride and the selective ASIC1a blocker PcTX1 significantly inhibited the increase of neuronal firing and the sustained membrane depolarization. In hippocampal slices, high frequency electrical stimulation or removal of extracellular Mg^{2+} triggers spontaneous seizure-like bursting. Bath perfusion of amiloride and PcTX1 decreased the amplitude and the frequency of these seizure-like bursting activities. Similarly, slices prepared from the brains of ASIC1a knockout mice demonstrated a reduced sensitivity to low extracellular Mg^{2+}-induced or stimulation-evoked seizure activities (Chang et al., 2007).

In contrast, studies by Ziemann and colleagues, performed largely *in vivo*, have suggested that activation of ASIC1a channels is involved in the termination of epileptic seizure activity (Ziemann et al., 2008). An interesting finding by Ziemann and colleagues was that the level of ASIC1a expression is higher in GABAergic interneurons than in excitatory neurons (Ziemann et al., 2008). Therefore, acidosis generated during seizures might produce more

ASIC activation in inhibitory interneurons and facilitate GABAergic transmission, resulting in seizure termination.

The inconsistent data on the role of ASICs in epileptic seizures may result from the use of different epilepsy models. The different ages of animals used may also contribute to the inconsistency since expression and function of ASICs in CNS neurons undergo dramatic developmental changes (Li et al., 2010). In addition, the finding that hippocampal interneurons are highly diverse with dramatically different expression level of ASICs (Weng et al., 2010) adds additional complexity to this subject.

6. Conclusion

ASICs represent new biological components in peripheral sensory and CNS neurons. Increasing evidence indicates the involvement of these channels in both physiological and pathological processes of CNS (Grunder & Chen, 2010). Therefore, targeting these channels may provide novel and effective therapeutic interventions for a number of CNS diseases. In addition to establishing ASIC-specific small molecule antagonists that can easily pass through the blood brain barrier, alternative strategies may consider targeting endogenous modulators that are known to influence the expression and/or activity of these channels.

7. References

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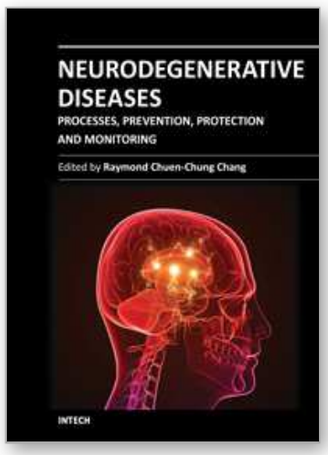

Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring

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Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring focuses on biological mechanisms, prevention, neuroprotection and even monitoring of disease progression. This book emphasizes the general biological processes of neurodegeneration in different neurodegenerative diseases. Although the primary etiology for different neurodegenerative diseases is different, there is a high level of similarity in the disease processes. The first three sections introduce how toxic proteins, intracellular calcium and oxidative stress affect different biological signaling pathways or molecular machineries to inform neurons to undergo degeneration. A section discusses how neighboring glial cells modulate or promote neurodegeneration. In the next section an evaluation is given of how hormonal and metabolic control modulate disease progression, which is followed by a section exploring some preventive methods using natural products and new pharmacological targets. We also explore how medical devices facilitate patient monitoring. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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