We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



20

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

Chu Xiang-Ping[1], Wang John Q.[1] and Xiong Zhi-Gang[2]
[1]*Department of Basic Medical Science, University of Missouri-Kansas City, Kansas City, Missouri;*
[2]*Department of Neurobiology, Morehouse School of Medicine, Atlanta, Georgia; USA*

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.

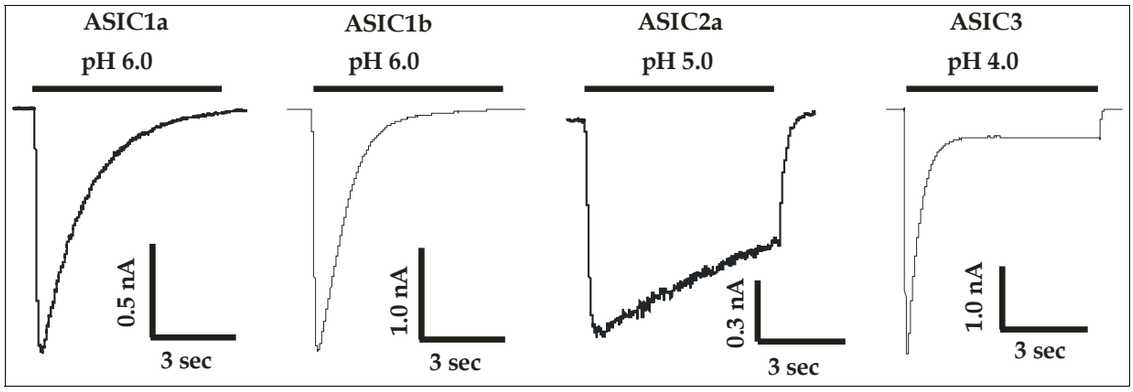


Fig. 1. Acid-triggered inward currents in CHO cells expressing indicated ASIC subunits

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

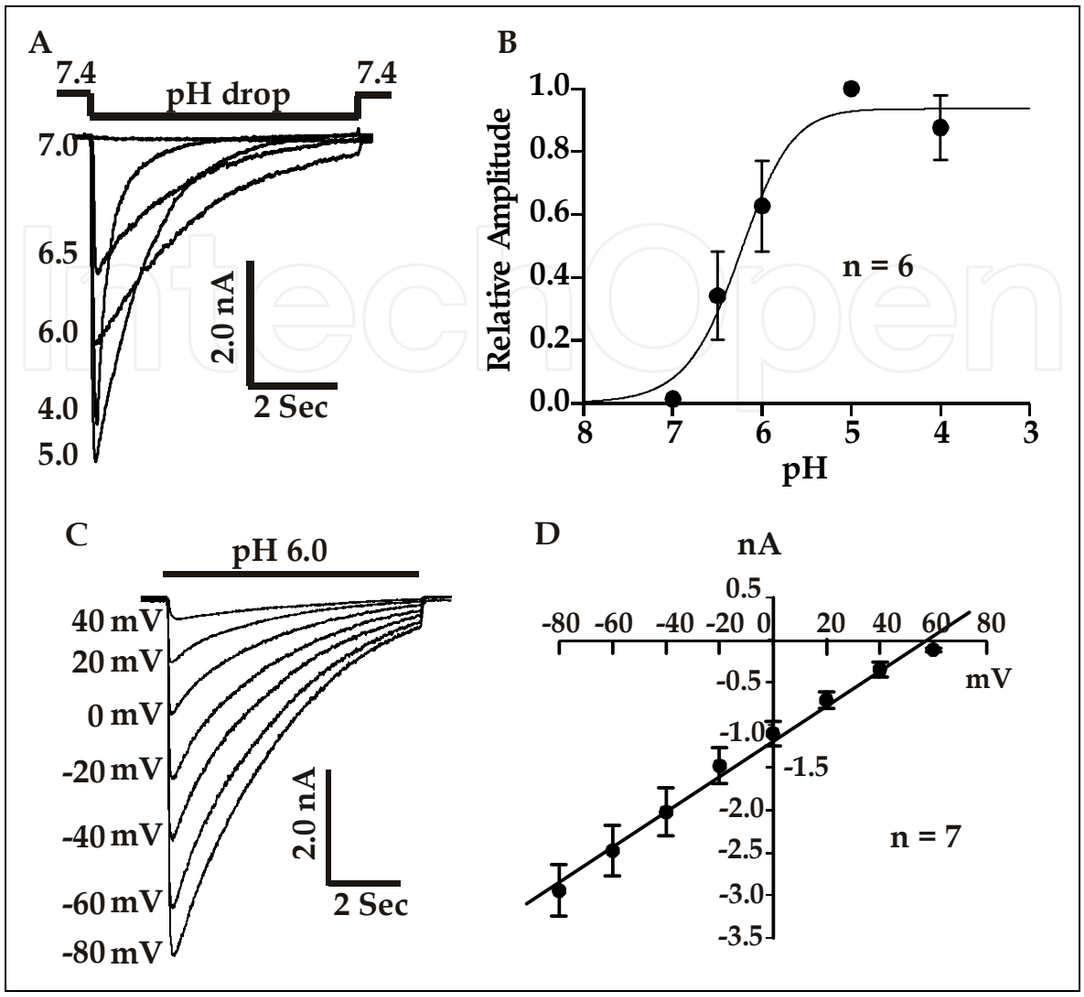


Fig. 2. Electrophysiological properties of ASICs in cultured mouse MSNs. (A) pH-dependent activation of ASIC currentsin in MSNs. (B) Dose-response curve for activation of the currents by pH drops. The pH_{50} value is 6.25 and the Hill coeficient is 0.94. (C) The I-V relationship of acid-activated currents 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).

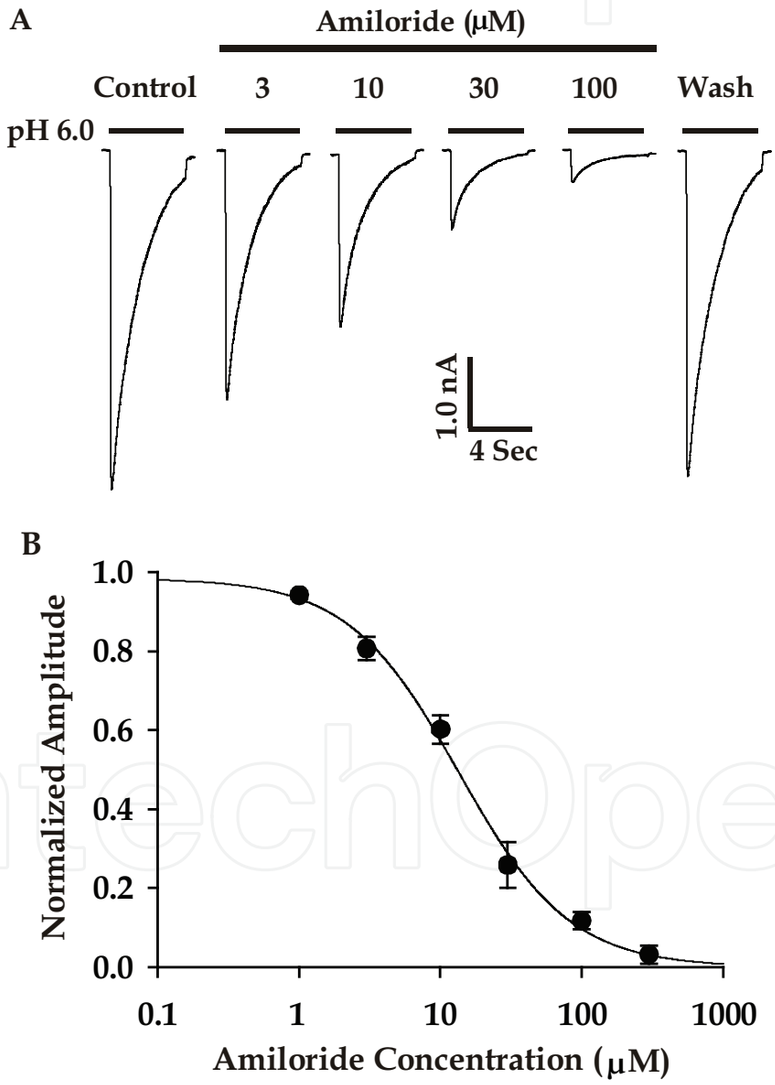


Fig. 3. Dose-dependent blockade of ASIC currents in cultured MSNs by amiloride, a non-specific ASIC blocker. (A) Amiloride dose-dependently inhibits the ASIC currents activated by pH 6.0. (B) Dose-inhibition curve of the acid-induced currents by amiloride. The IC_{50} of amiloride is 13.6 μM

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.

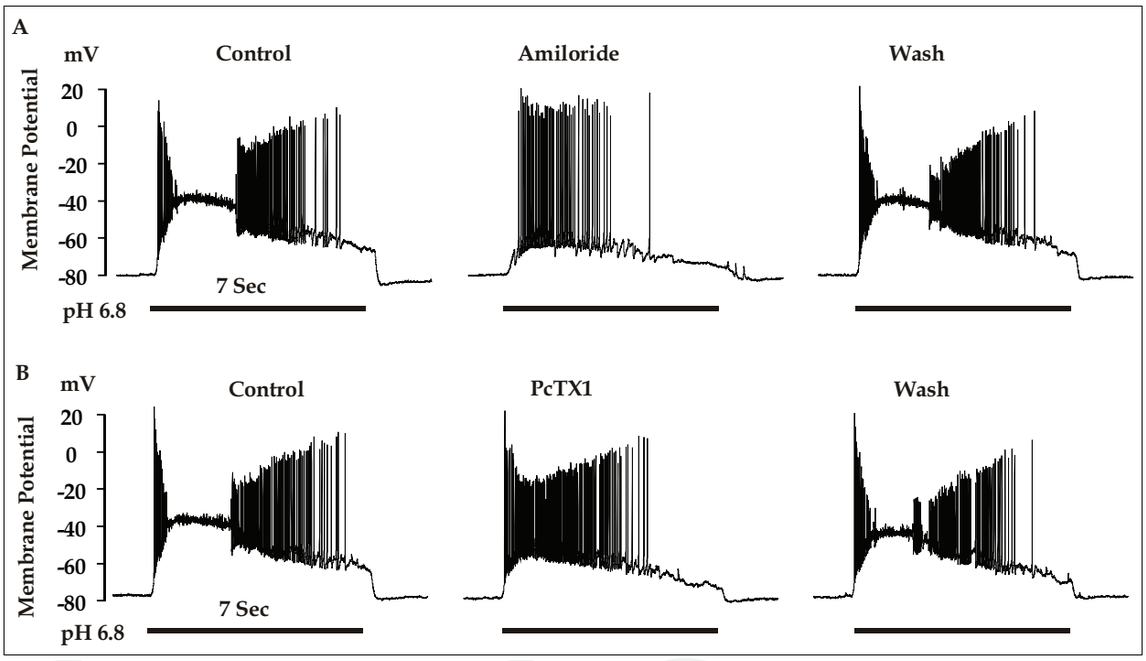


Fig. 4. pH drop triggered membrane depolarization and action potentials by activation of ASICs in cultured MSNs. Membrane depolarization by a drop in pH from 7.4 to 6.8 subsequently triggered trains of action potentials. The membrane depolarization was inhibited by amiloride (A) and PcTX1 (B)

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

Adams, C.M.; Snyder, P.M. & Welsh, M.J. (1999). Paradoxical Stimulation of a DEG/ENaC Channel by Amiloride. *Journal of Biological Chemistry*, Vol. 274, No. 22, pp.15500-15504, ISSN 0021-9258

Akopian, A.N.; Chen, C.C.; Ding, Y. Cesare, P. & Wood, J.N. (2000). A New Member of the Acid-Sensing Ion Channel Family. *Neuroreport,* Vol.11, No.10, pp. 2217 – 2222, ISSN 0959-4956

Ali, A.; Ahmad, F.J.; Pillai, K.K. & Vohora, D. (2004). Evidence of the Antiepileptic Potential of Amiloride With Neuropharmacological Benefits in Rodent Models of Epilepsy and Behavior. *Epilepsy & Behavior,* Vol. 5, No. 3, pp. 322-328, ISSN 1525-5050

Ali, A.; Pillai, K.P.; Ahmad, F.J.; Dua, Y. & Vohora, D. (2006). Anticonvulsant Effect of Amiloride in Pentetrazole-Induced Status Epilepticus in Mice. *Pharmacological Reports,* Vol. 58, No.2, pp. 242-245, ISSN 1734-1140

Allen, N.J. & Attwell, D. (2002). Modulation of ASIC Channels in Rat Crebellar Purkinje Nurons by Ichemia-Rlated Sgnals. *Journal of Phsiology,* Vol. 543, No. 2, pp. 521 – 529, ISSN 0022-3751

Alvarez de la Rosa, D.; Canessa, C.M.; Fyfe, G.K. & Zhang, P. (2000). Structure and Regulation of Amiloride Sensitive Sodium Channels. *Annual Review of Physiology,* Vol. 62, No.1, pp.573-594, ISSN 0066-4278

Arias, R.L.; Sung, M.L.; Vasylyev, D.; Zhang, M.Y.; Albinson, K.; Kubek, K.; Kagan, N.; Beyer, C.; Lin, Q.; Dwyer, J.M.; Zaleska, M.M.; Bowlby, M.R.; Dunlop, J. & Monaghan, M. (2008). Amiloride is Neuroprotective in an MPTP Model of Parkinson's Disease. *Neurobiology of Disease,* Vol. 31, No. 3, pp. 334-341, ISSN 0969-9961

Askwith, C.C.; Wemmie, J.A.; Price, M.P.; Rokhlina, T. & Welsh, M.J. (2004). Acid-Sensing Ion Channel 2 (ASIC2) Modulates ASIC1 H^+-Activated Currents in Hippocampal

Neurons. *Journal of Biological Chemistry*, Vol. 279, No. 18, pp.18296-18305, ISSN 0021-9258

Babini, E.; Paukert, M.; Geisler, H.S. & Grunder, S. (2002). Alternative Splicing and Interaction with Di- and Polyvalent Cations Control the Dynamic Range of Acid-Sensing Ion Channel 1 (ASIC1). *Journal of Biological Chemistry*, Vol. 277, No. 44, pp.41597-41603, ISSN 0021-9258

Bano, D.; Young, K.W.; Guerin, C.J.; Lefeuvre, R.; Rothwell, N.J.; Naldini, L.; Rizzuto, R.; Carafoli, E. & Nicotera, P. (2005). Cleavage of the Plasma Membrane Na^+/Ca^{2+} Exchanger in Excitotoxicity. *Cell,* Vol. 120,No.2, pp. 275-285, ISSN 0092-8674

Baraldi, P.G.; Bovero, A.; Fruttarolo, F.; Preti, D.; Tabrizi, M.A.; Pavani, M.G. & Romagnoli, R. (2004). DNA Minor Groove Binders as Potential Antitumor and Antimicrobial Agents. *Medicinal Research Reviews,* Vol. 24, No. 4, pp. 475-528, ISSN 0198-6325

Baron, A.; Voilley, N.; Lazdunski, M. & Lingueglia, E. (2008). Acid Sensing Ion Channels in Dorsal Spinal Cord Neurons. *Journal of Neuroscience*, Vol.28, No.6, pp.1498-1508, ISSN 0270-6474

Baron, A.; Waldmann, R. & Lazdunski, M. (2002). ASIC-Like, Proton-Activated Currents in Rat Hippocampal Neurons. *Journal of Physiology,* Vol. 539, No.2, pp.485-494, ISSN 0022-3751

Bässler, E.L.; Ngo-Anh, T.J.; Geisler, H.S.; Ruppersberg, J.P. & Gründer, S. (2001). Molecular and Functional Characterization of Acid-Sensing Ion Channel (ASIC) 1b. *Journal of Biological Chemistry*, Vol. 276, No. 36, pp. 33782-33787, ISSN 0021-9258

Benson, C.J.; Eckert, S.P. & McCleskey, E.W. (1999). Acid-Evoked Currents in Cardiac Sensory Neurons: A Possible Mediator of Myocardial Ischemic Sensation. *Circulation Research,* Vol. 84, No. 8, pp. 921-928, ISSN 0009-7330

Benson, C.J.; Xie, J.; Wemmie, J.A.; Price, M.P.; Henss, J.M.; Welsh, M.J. & Snyder, P.M. (2002). Heteromultimers of DEG/ENaC Subunits Form H^+-Gated Channels in Mouse Sensory Neurons. *Proceedings of National Academy of Science U.S.A.,* Vol. 99, No. 4, pp. 2338-2343, ISSN 0027-8424

Benveniste, M. & Dingledine, R. (2005). Limiting Stroke-Induced Damage by Targeting an Acid Channel. *New England Journal of Medicine*, Vol. 352, No. 1, pp. 85-86, ISSN 0028-4793

Biagini, G.; Babinski, K.; Avoli, M.; Marcinkiewicz, M. & Seguela, P. (2001). Regional and Subunit Specific Down-Regulation of Acid-Sensing Ion Channels in the Pilocarpine Model of Epilepsy. *Neurobiology of Disease,* Vol. 8, No. 1, pp.45-58, ISSN 0969-9961

Champigny, G.; Voilley, N.; Waldmann, R. & Lazdunski, M. (1998). Mutations Causing Neurodegeneration in Caenorhabditis Elegans Drastically Alter the PH Sensitivity and Inactivation of the Mammalian H^+-Gated Na^+ Channel MDEG1. *Journal of Biological Chemistry,* Vol. 273, No. 25, pp. 15418-15422, ISSN 0021-9258

Chang, S.Y.; Li, M.H.; Li, T.F.; Chu, X.P.; Lan, J.Q.; Thomson, S.; Jessick, V.; Meller, R.; Simon, R.P. & Xiong, Z.G. (2007). Involvement of Acid-Sensing Ion Channels in the Generation of Epileptic Seizure Activity [abstract]. 37th *Society for Neuroscience Annual Meeting*, 257.5. ISBN 0-916110-04-4, San Diego, California, USA, November 3-7, 2007

Chen, C.C.; England, S.; Akopian, A.N. & Wood, J.N. (1998). A Sensory Neuron Specific, Proton-Gated Ion Channel. *Proceedings of National Academy of Science U.S.A.,* Vol. 95, No. 17, pp.10240 – 10245, ISSN 0027-8424

Chen, X.; Kalbacher, H. & Gründer, S. (2006). Interaction of Acid-Sensing Ion Channel (ASIC) 1 with the Tarantula Toxin Psalmotoxin 1 is State Dependent. *Journal of General Physiology,* Vol.127, No.3, pp.267-76, ISSN 0022-1295

Chen, X.; Kalbacher, H. & Gründer, S. (2005). The Tarantula Toxin Psalmotoxin 1 Inhibits Acid-Sensing Ion Channel (ASIC) 1a by Increasing its Apparent H^+ Affinity. *Journal of General Physiology,* Vol.126, No.1, pp. 71-79, ISSN 0022-1295

Chen, X.; Qiu, L.; Li, M.; Dürrnagel, S.; Orser, B.A.; Xiong, Z.G. & MacDonald, J. F. (2010). Diarylamidines: High Potency Inhibitors of Acid-Sensing Ion Channels. *Neuropharmacology,* Vol. 58, No. 7, pp.1045-1053, ISSN 0028-3908

Chesler, M. & Chan, C.Y. (1988). Stimulus-Induced Extracellular PH Transients in the In Vitro Turtle Cerebellum. *Neuroscience,* Vol. 27, No. 3, pp. 941-948, ISSN 0306-4522

Chesler, M. & Kaila, K. (1992). Modulation of PH by Neuronal Activity. *Trends in Neuroscience*, Vol, 15, No. 10, pp. 396-402, ISSN 0166-2236

Cho, J.H. & Askwith, C.C. (2008). Presynaptic Release Probability Is Increased in Hippocampal Neurons From ASIC1 Knockout Mice. *Journal of Neurophysiology,* Vol. 99, No. 2, pp.426-441, ISSN 0022-3077

Chu, X.P.; Close, N.; Saugstad, J.A. & Xiong, Z.G. (2006). ASIC1a-Specific Modulation of Acid-Sensing Ion Channels in Mouse Cortical Neurons by Redox Reagents. *Journal of Neuroscience*, Vol. 26, No. 20, pp. 5329 – 5339, ISSN 0270-6474

Chu, X.P.; Miesch, J.; Johnson, M.; Root, L.; Zhu, X.M.; Chen, D.; Simon, R.P. & Xiong, Z.G. (2002). Proton-Gated Channels in PC12 Cells. *Journal of Neurophysiology,* Vol. 87, No. 5, pp.2555-2561, ISSN 0022-3077

Chu, X.P.; Wemmie, J.A.; Wang, W.Z.; Zhu, X.M.; Saugstad, J.A.; Price, M.P.; Simon, R.P. & Xiong, Z.G. (2004). Subunit-Dependent High-Affinity Zinc Inhibition of Acid-Sensing Ion Channels. *Journal of Neuroscience*, Vol.24, No. 40, pp. 8678 – 8689, ISSN 0270-6474

Coryell, M.W.; Wunsch, A.M.; Haenfler, J.M.; Allen, J.E.; McBride, J.L.; Davidson, B.L. & Wemmie, J.A. (2008). Restoring Acid-Sensing Ion Channel-1a in the Amygdala of Knock-out Mice Rescues Fear Memory but not Unconditioned Fear Responses. *Journal of Neuroscience,* Vol. 28, No. 51, pp. 13738-13741, ISSN 0270-6474

Coryell, M.W.; Wunsch, A.M.; Haenfler, J.M.; Allen, J.E.; Schnizler, M.; Ziemann, A.E.; Cook, M.N.; Dunning, J.P.; Price, M.P.; Rainier, J.D.; Liu, Z.; Light, A.R.; Langbehn, D.R. & Wemmie, J.A. (2009). Acid-Sensing Ion Channel-1a in the Amygdala, a Novel Therapeutic Target in Depression-Related Behavior. *Journal of Neuroscience,* Vol. 29, No. 17, pp. 5381-5388, ISSN 0270-6474

Coryell, M.W.; Ziemann, A.E.; Westmoreland, P.J.; Haenfler, J.M.; Kurjakovic, Z.; Zha, X.M.; Price, M.; Schnizler, M.K. & Wemmie, J.A. (2007). Targeting ASIC1a Reduces Innate Fear and Alters Neuronal Activity in the Fear Circuit. *Biological Psychiatry.* Vol.62, No. 10, pp.1140-1148, ISSN 0006-3223

Dauer, W. & Przedborski, S. (2003). Parkinson's Disease: Mechanisms and Models. *Neuron*, Vol. 39, No. 6, pp. 889-909, ISSN 0896-6273

Deval, E.; Noël, J.; Lay, N.; Alloui, A.; Diochot, S.; Friend, V.; Jodar, M.; Lazdunski, M. & Lingueglia, E. (2008). ASIC3, A Sensor of Acidic and Primary Inflammatory Pain. *EMBO Journal*, Vol. 27, No. 22, pp. 3047– 3055, ISSN 0261-4189

Diochot, S.; Baron, A.; Rash, L.D.; Deval, E.; Escoubas, P.; Scarzello, S.; Salinas, M. & Lazdunski, M. (2004). A New Sea Anemone Peptide, APETx2, Inhibits ASIC3, A Major Acid-Sensitive Channel in Sensory Neurons. *EMBO Journal,* Vol. 23, No.7, pp.1516-1525, ISSN 0261-4189

Deval, E.; Salinas, M.; Baron, A.; Lingueglia, E. & Lazdunski, M. (2004). ASIC2b-Dependent Regulation of ASIC3, An Essential Acid-Sensing Ion Channel Subunit in Sensory Neurons via the Partner Protein PICK-1. *Journal of Biological Chemistry,* Vol. 279, No. 19, pp. 19531-19539, ISSN 0021-9258

de Weille, J.R.; Bassilana, F.; Lazdunski, M. & Waldmann, R. (1998). Identification, Functional Expression and Chromosomal Localisation of a Sustained Human Proton-Gated Cation Channel. *FEBS Letters,* Vol.433, No.3, pp.257-60, ISSN 0014-5793

Dubé, G.R.; Lehto, S.G.; Breese, N.M.; Baker, S.J.; Wang, X.; Matulenko, M.A.; Honoré, P.; Stewart, A.O.; Moreland, R.B. & Brioni, J.D. (2005). Electrophysiological and In Vivo Characterization of A-317567, a Novel Blocker of Acid Sensing Ion Channels. *Pain,* Vol. 117, No. 1-2, pp. 88-96. ISSN 0885-3294

Dwyer, J.M.; Rizzo, S.J.; Neal, S.J.; Lin, Q.; Jow, F.; Arias, R.L.; Rosenzweig-Lipson, S.; Dunlop, J. & Beyer, C.E. (2009). Acid Sensing Ion Channel (ASIC) Inhibitors Exhibit Anxiolytic-Like Activity in Preclinical Pharmacological Models. *Psychopharmacology (Berl),* Vol.203, No. 1, pp. 41-52, ISSN 1432-2072

Escoubas, P.; de Weille, J.R.; Lecoq, A.; Diochot, S.; Waldmann, R.; Champigny, G.; Moinier, D.; Ménez, A. & Lazdunski, M. (2000). Isolation of a Tarantula Toxin Specific for a Class of Proton-Gated Na^+ Channels. *Journal of Biological Chemistry,* Vol. 275, No. 33, pp. 25116-25121, ISSN 0021-9258

Ettaiche, M.; Deval, E.; Cougnon, M.; Lazdunski, M. & Voilley, N. (2006). Silencing Acid-Sensing Ion Channel 1a Alters Cone-Mediated Retinal Function. *Journal of Neuroscience,* Vol. 26, No. 21, pp.5800-5809, ISSN 0270-6474

Ettaiche, M.; Deval, E.; Pagnotta, S.; Lazdunski, M. & Lingueglia, E. (2009). Acid-Sensing Ion Channel 3 in Retinal Function and Survival. *Investigative Ophthalmology & Visual Science,* Vol. 50, No.5, pp. 2417-2426, ISSN 0146-0404

Ettaiche, M.; Guy, N.; Hofman, P.; Lazdunski, M. & Waldmann, R. (2004). Acid-Sensing Ion Channel 2 is Important For Retinal Function and Protects Against Light-Induced Retinal Degeneration. *Journal of Neuroscience,* Vol. 24, No. 5, pp. 1005-1012, ISSN 0270-6474

Friese, M.A.; Craner, M.J.; Etzensperger, R.; Vergo, S.; Wemmie, J.A.; Welsh, M.J.; Vincent, A. & Fugger, L. (2007). Acid-Sensing Ion Channel-1 Contributes to Axonal Degeneration in Autoimmune Inflammation of the Central Nervous System. *Nature Medicine,* Vol.13, No. 12, pp.1483-1489, ISSN 1078-8956

Gao, J.; Duan, B.; Wang, D.G.; Deng, X.H.; Zhang, G.Y.; Xu, L. & Xu, T.L. (2005). Coupling Between NMDA Receptor and Acid-Sensing Ion Channel Contributes to Ischemic Neuronal Death. *Neuron*, Vol. 48, No.4, pp.635-646, ISSN 0896-6273

Garza, A.; López-Ramírez, O.; Vega, R. & Soto, E. (2010). The Aminoglycosides Modulate the Acid-Sensing Ionic Channel Currents in Dorsal Root Ganglion Neurons from the Rat. *Journal of Pharmacology & Experimental Therapeutics,* Vol. 332, No. 2, pp. 489-499. ISSN 0022-3565

Giffard, R.G.; Monyer, H. & Choi, D.W. (1990). Selective Vulnerability of Cultured Cortical Glia to Injury by Extracellular Acidosis. *Brain Research,* 1990; Vol. 530, No.1, pp. 138-141, ISSN 0006-8993

Gonzales, E.B.; Kawate, T. & Gouaux, E. (2009). Pore Architecture and Ion Sites in Acid-Sensing Ion Channels and P2X Receptors. *Nature,* Vol. 460, No. 7255, pp.599-604, ISSN 0028-0836

Grunder, S. & Chen, X. (2010). Structure, Function, and Pharmacology of Acid-Sensing Ion Channels (ASICs): Focus on ASIC1a. *International Journal of Physiology, Pathophysiology and Pharmacology,* Vol. 2, No.2 , pp. 73-94, ISSN 1944-8171

Grunder, S.; Geissler, H.S.; Bassler, E.L. & Ruppersberg, J.P. (2000). A New Member of Acid-Sensing Ion Channels from Pituitary Gland. *Neuroreport,* Vol.11, No.8, pp. 1607 – 1611, ISSN 0959-4956

Gu, L.; Liu, X.; Yang, Y.; Luo, D. & Zheng, X. (2010). ASICs Aggravate Acidosis-Induced Injuries During Ischemic Reperfusion. *Neuroscience Letters,* Vol. 479, No. 1, pp. 63-68, ISSN 0304-3940

Hattori, T.; Chen, J.; Harding, A.M.; Price, M.P.; Lu, Y.; Abboud, F.M. & Benson, C.J. (2009). ASIC2a and ASIC3 Heteromultimerize to Form PH-Sensitive Channels in Mouse Cardiac Dorsal Root Ganglia Neurons. *Circulation Research,* Vol. 105, No.3, pp. 279-286, ISSN 0009-7330

Hesselager, M.; Timmermann, D.B. & Ahring, P.K. (2004). PH Dependency and Desensitization Kinetics of Heterologously Expressed Combinations of Acid-Sensing Ion Channel Subunits. *Journal of Biological Chemistry,* Vol. 279, No. 12, pp. 11006-11015, ISSN 0021-9258

Hillered, L.; Smith, M.L. & Siesjo, B.K. (1985). Lactic Acidosis and Recovery of Mitochondrial Function Following Forebrain Ischemia in the Rat. *Journal of Cerebral Blood Flow & Metabolism,* Vol. 5, No. 2, pp.259-266, ISSN 0271-678X

Hoagland, E.N.; Sherwood, T.W.; Lee, K.G.; Walker, C.J. & Askwith, C.C. (2010). Identification of a Calcium Permeable Human Acid-Sensing Ion Channel 1 Transcript Variant. *Journal of Biological Chemistry,* Vol. 285, No. 53, pp. 41852-41862, ISSN 0021-9258

Huang, Y. & McNamara, J.O. (2004). Ischemic Stroke: "Acidotoxicity" is a Perpetrator. *Cell,* Vol. 118, No.6, pp.665-666, ISSN 0092-8674

Hruska-Hageman, A.M.; Wemmie, J.A.; Price, M.P. & Welsh, M.J. (2002). Interaction of the Synaptic Protein PICK1 (Protein Interacting with C Kinase 1) with the Non-Voltage Gated Sodium Channels BNC1 (Brain Na^+ Channel 1) and ASIC (Acid-Sensing Ion Channel). *Biochemical Journal,* Vol. 361, No. 3, pp. 443-450, ISSN 0264-6021

Ikeuchi, M.; Kolker, S.J. & Sluka, K.A. (2009). Acid-Sensing Ion Channel 3 Expression in Mouse Knee Joint Afferents and Effects of Carrageenan-Induced Arthritis. *Journal of Pain,* Vol.10, No. 3, pp. 336 – 342, ISSN 1256-5900

Immke, D.C. & McCleskey, E.W. (2001). Lactate Enhances the Acid-Sensing Na+ Channel on Ischemia-Sensing Neurons. *Nature Neuroscience,* Vol.4, No. 9, pp. 869-870, ISSN 1097- 6256

Jasti, J.; Furukawa, H.; Gonzales, E.B. & Gouaux, E. (2007). Structure of Acid-Sensing Ion Channel 1 at 1.9 A Resolution and Low pH. *Nature,* Vol. 449, No. 7160, pp.316-323, ISSN 0028-0836

Jetti, S.K.; Swain, S.M.; Majumder, S.; Chatterjee, S.; Poornima, V. & Bera, A.K. (2010). Evaluation of the Role of Nitric Oxide in Acid Sensing Ion Channel Mediated Cell Death. *Nitric Oxide,* Vol. 22, No. 3, pp. 213-219, ISSN 1089-8603

Jiang, Q.; Li, M.H.; Papasian, C.J.; Branigan, D.; Xiong, Z.G.; Wang, J.Q. & Chu, X.P. (2009). Characterization of Acid-Sensing Ion Channels in Medium Spiny Neurons of Mouse Striatum. *Neuroscience,* Vol.162, No.1, pp. 55 – 66, ISSN 0306-4522

Johnson, M.B.; Jin, K.; Minami, M.; Chen, D. & Simon, R.P. (2001). Global Ischemia Induces Expression of Acid-Sensing Ion Channel 2a in Rat Brain. *Journal of Cerebral Blood Flow & Metabolism,* Vol. 21, No. 6, pp.734-740, ISSN 0271-678X

Jones, N.G.; Slater, R.; Cadiou, H.; McNaughton, P. & McMahon, S.B. (2004). Acid-Induced Pain and its Modulation in Humans. *Journal of Neuroscience*, Vol.24, No. 48, pp. 10974 – 10979, ISSN 0270-6474

Kalimo, H.; Rehncrona, S.; Soderfeldt, B.; Olsson, Y. & Siesjo, B.K. (1981). Brain Lactic Acidosis and Ischemic Cell Damage: 2. Histopathology. *Journal of Cerebral Blood Flow & Metabolism,* Vol. 1, No. 3, pp.313-327, ISSN 0271-678X

Kellenberger, S. & Schild, L. (2002). Epithelial Sodium Channel/Degenerin Family of Ion Channels: a Variety of Functions for a Shared Structure. *Physiological Review,* Vol. 82, No. 3, pp. 735 – 767, ISSN 0031-9333

Kimelberg, H.K.; Barron, K.D.; Bourke, R.S.; Nelson, L.R. & Cragoe, E.J. (1990). Brain Anti-cytoxic Edema Agents. *Progress in Clinical and Biological Research* Vol. 361, No.1, pp. 363-385, ISSN 0361-7742

Krishtal, O. (2003). The ASICs: Signaling Molecules? Modulators? *Trends in Neuroscience*, Vol, 26, No. 9, pp. 477-483, ISSN 0166-2236

Li, M.; Inoue, K.; Branigan, D.; Kratzer, E.; Hansen, J.C.; Chen, J.W.; Simon, R.P. & Xiong, Z.G. (2010). Acid-Sensing Ion Channels in Acidosis-Induced Injury of Human Brain Neurons. *Journal of Cerebral Blood Flow & Metabolism,* Vol. 30, No. 6, pp.1247-1260, ISSN 0271-678X

Li, M.; Kratzer, E.; Inoue, K.; Simon, R.P. & Xiong, Z.G. (2010). Developmental Change in the Electrophysiological and Pharmacological Properties of Acid-Sensing Ion Channels in CNS Neurons. *Journal of Physiology,* Vol. 588, No.20, pp.3883-3900, ISSN 0022-3751

Lilley, S.; LeTissier, P. & Robbins, J. (2004). The Discovery and Characterization of a Proton-Gated Sodium Current in Rat Retinal Ganglion Cells. *Journal of Neuroscience,* Vol. 24, No. 5, pp. 1013 – 1022, ISSN 0270-6474

Lin, Y.W.; Min, M.Y.; Lin, C.C.; Chen, W.N.; Wu, W.L.; Yu, H.M. & Chen, C.C. (2008). Identification and Characterization of a Subset of Mouse Sensory Neurons That Express Acid-Sensing Ion Channel 3. *Neuroscience,* Vol.151, No.2, pp.544-557, ISSN 0306-4522

Lingueglia, E. (2007). Acid-Sensing Ion Channels in Sensory Perception. *Journal of Biological Chemistry,* Vol. 282, No. 24, pp. 17325–17329, ISSN 0021-9258

Lingueglia, E.; de Weille, J.R.; Bassilana, F.; Heurteaux, C.; Sakai, H.; Waldmann, R. & Lazdunski, M. (1997). A Modulatory Subunit of Acid Sensing Ion Channels in Brain and Dorsal Root Ganglion Cells. *Journal of Biological Chemistry,* Vol. 272, No. 47, pp. 29778–29783, ISSN 0021-9258

Lu, Y.; Ma, X.; Sabharwal, R.; Snitsarev, V.; Morgan, D.; Rahmouni, K.; Drummond, H.A.; Whiteis, C.A.; Costa, V.; Price, M.; Benson, C.; Welsh, M.J.; Chapleau, M.W. & Abboud, F.M. (2009). The Ion Channel ASIC2 is Required for Baroreceptor and Autonomic Control of the Circulation. *Neuron*, Vol. 64, No.6, pp. 885-897, ISSN 0896-6273

Mamet, J.; Lazdunski, M. & Voilley, N. (2003). How Nerve Growth Factor Drives Physiological and Inflammatory Expressions of Acid-Sensing Ion Channel 3 in Sensory Neurons. *Journal of Biological Chemistry,* Vol. 278, No. 49, pp. 48907 – 48913, ISSN 0021-9258

Mari, Y.; Katnik, C. & Cuevas, J. (2010). ASIC1a Channels are Activated by Endogenous Protons During Ischemia and Contribute to Synergistic Potentiation of Intracellular Ca(2+) Overload During Ischemia and Acidosis. *Cell Calcium,* Vol. 48, No. 1, pp. 70-82, ISSN 0143-4160

Maysami, S.; Branigan, D.; Simon, R.P. & Xiong, Z,G. (2009). Amyloid Beta Peptide Modulates the Activity of Acid-Sensing Ion Channels in Neurons [abstract]. 39th *Society for Neuroscience Annual Meeting*, 237.8. ISBN 0-916110-04-4, Chicago, Illinois, USA, October 17-21, 2009

Meng, Q.Y.; Wang, W.; Chen, X.N.; Xu, T.L. & Zhou, J.N. (2009). Distribution of Acid-Sensing Ion Channel 3 in the Rat Hypothalamus. *Neuroscience,* Vol. 159, No. 3, pp.1126-1134, ISSN 0306-4522

Mishra, J.; Saxena, A. & Singh, S. (2007). Chemotherapy of Leishmaniasis: Past, Present and Future. *Current Medicinal Chemistry,* Vol. 14, No. 10, pp. 1153-1169, ISSN 0929-8673

Molliver, D.C.; Immke, D.C.; Fierro, L.; Paré, M.; Rice, F.L. & McCleskey, E.W. (2005). ASIC3, An Acid-Sensing Ion Channel, is Expressed in Metaboreceptive Sensory Neurons. *Molecular Pain,* Vol.1, No. 1, pp. 35, ISSN 1744-8069

Nedergaard, M.; Kraig, R.P.; Tanabe, J. & Pulsinelli, W.A. (1991). Dynamics of Interstitial and Intracellular PH in Evolving Brain Infarct. *American Journal of Physiology,* Vol. 260, No. 3, pp. R581-R588, ISSN 0363-6119

N'Gouemo, P. (2008). Amiloride Delays the Onset of Pilocarpine-Induced Seizures in Rats. *Brain Research,* Vol. 1222, No. 1, pp. 230-232, ISSN 0006-8993

Papp, L.A.; Klein, D.F. & Gorman, J.M. (1993). Carbon Dioxide Hypersensitivity, Hyperventilation, and Panic Disorder. *American Journal of Psychiatry,* Vol. 150, No. 8, pp. 1149-1157, ISSN 0002-953X

Pidoplichko, V.I. & Dani, J.A. (2006). Acid-Sensitive Ionic Channels in Midbrain Dopamine Neurons are Sensitive to Ammonium, Which May Contribute to Hyperammonemia Damage. *Proceedings of National Academy of Science U.S.A.,* Vol. 103, No. 30, pp. 11376-11380, ISSN 0027-8424

Pignataro, G.; Simon, R.P. & Xiong, Z.G. (2007). Prolonged Activation of ASIC1a and the Time Window for Neuroprotection in Cerebral Ischaemia. *Brain,* Vol. 130, No.1, pp.151-158, ISSN 0006-8950

Pérez, M.E.; Soto, E. & Vega, R. (1991). Streptomycin Blocks the Postsynaptic Effects of Excitatory Amino Acids on the Vestibular System Primary Afferents. *Brain Research,* Vol. 563, No. 1-2, pp. 221-226, ISSN 0006-8993

Price, M.P.; Lewin, G.R.; McIlwrath, S.L.; Cheng, C.; Xie, J.; Heppenstall, P.A.; Stucky, C.L.; Mannsfeldt, A.G.; Brennan, T.J.; Drummond, H.A.; Qiao, J.; Benson, C.J.; Tarr, D.E.; Hrstka, R.F.; Yang, B.; Williamson, R.A. & Welsh, M.J. (2000). The Mammalian Sodium Channel BNC1 is Required for Normal Touch Sensation. *Nature,* Vol. 407, No. 6807, pp. 1007-1011, ISSN 0028-0836

Price, M.P.; McIlwrath, S.L.; Xie, J.; Cheng, C.; Qiao, J.; Tarr, D.E.; Sluka, K.A.; Brennan, T.J.; Lewin, G.R. & Welsh, M.J. (2001). The DRASIC Cation Channel Contributes to the Detection of Cutaneous Touch and Acid Stimuli in Mice. *Neuron*, Vol. 32, No. 6, pp. 1071-1083, ISSN 0896-6273

Price, M.P.; Snyder, P.M. & Welsh, M.J. (1996). Cloning and Expression of a Novel Human Brain Na^+ Channel. *Journal of Biological Chemistry,* Vol. 271, No.14, pp.7879-7882, ISSN 0021-9258

Raisinghani, M. & Premkumar, L.S. (2005). Block of Native and Cloned Vanilloid Receptor 1 (TRPV1) by Aminoglycoside Antibiotics. *Pain,* Vol. 113, No. 1-2, pp. 123-33, ISSN 0885-3924

Rehncrona, S. (1985). Brain Acidosis. *Annals of Emergency Medicine,* Vol.14, No. 8, pp. 770-776, ISSN 0196-0644

Rehncrona, S.; Hauge, H.N. & Siesjo, B.K. (1989). Enhancement of Iron Catalyzed Free Radical Formation by Acidosis in Brain Homogenates: Differences in Effect by Lactic Acid and CO_2. *Journal of Cerebral Blood Flow & Metabolism,* Vol. 9, No. 1, pp. 65-70, ISSN 0271-678X

Render, J.A.; Howe, K.R.; Wunsch, A.M.; Guionaud, S.; Cox, P.J. & Wemmie, J.A. (2010). Histologic Examination of the Eye of Acid-Sensing Ion Channel 1a Knockout Mice. *International Journal of Physiology,Pathophysiology and Pharmacology,* Vol. 2, No.2 , pp. 69-72, ISSN 1944-8171

Salinas, M.; Lazdunski, M. & Lingueglia, E. (2009). Structural Elements for the Generation of Sustained Currents by the Acid Pain Sensor ASIC3. *Journal of Biological Chemistry,* Vol. 284, No., pp. 31851– 31859, ISSN 0021-9258

Schild, J.H. & Kunze, D.L. (1997). Experimental and Modeling Study of Na+ Current Heterogeneity in Rat Nodose Neurons and Its Impact on Neuronal Discharge. *Journal of Neurophysiology,* Vol. 78, No.6, pp.3198-209, ISSN 0022-3077

Sherwood, T.W. & Askwith, C.C. (2009). Dynorphin Opioid Peptides Enhance Acid-Sensing Ion Channel 1a Activity and Acidosis-Induced Neuronal Death. *Journal of Neuroscience,* Vol.29, No. 45, pp.14371-14380, ISSN 0270-6474

Sherwood, T.W.; Lee, K.G.; Gormley, M.G. & Askwith, C.C. (2011). Heteromeric Acid-Sensing Ion Channels (ASICs) Composed of ASIC2b and ASIC1a Display Novel Channel Properties and Contribute to Acidosis-Induced Neuronal Death. *Journal of Neuroscience,* Vol. 31, No. 26, pp. 9723-9734, ISSN 0270-6474

Siesjo, B.K. (1988). Acidosis and Ischemic Brain Damage. *Neurochemical Pathology* Vol. 9, No. pp.31-88, ISSN 0734-600X

Siesjo, B.K.; Katsura, K. & Kristian, T. (1996). Acidosis-Related Damage. *Advance in Neurology,* Vol. 71, No. 1, pp.209-233, ISSN 0091-3952

Simon, R.P.; Copeland, J.R.; Benowitz, N.L.; Jacob, P. III. & Bronstein, J. (1987). Brain Phenobarbital Uptake During Prolonged Status Epilepticus. *Journal of Cerebral Blood Flow & Metabolism,* Vol. 7, No. 6, pp. 783-788, ISSN 0271-678X

Simon, R.P.; Benowitz, N.; Hedlund, R. & Copeland, J. (1985). Influence of the Blood-Brain PH Gradient on Brain Phenobarbital Uptake During Status Epilepticus. *Journal of Pharmacology & Experimental Therapeutics,* Vol. 234, No. 3, pp. 830-835, ISSN 0022-3565

Sluka, K.A.; Price, M.P.; Breese, N.M.; Stucky, C.L.; Wemmie, J.A. & Welsh, M.J. (2003). Chronic Hyperalgesia Induced by Repeated Acid Injections in Muscle is Abolished by the Loss of ASIC3, but not ASIC1. *Pain,* Vol. 106, No.3, pp. 229-239, ISSN 0885-3924

Sluka, K.A.; Radhakrishnan, R.; Benson, C.J.; Eshcol, J.O.; Price, M.P.; Babinski, K.; Audette, K.M.; Yeomans, D.C. & Wilson, S.P. (2007). ASIC3 in Muscle Mediates Mechanical, but not Heat, Hyperalgesia Associated with Muscle Inflammation. *Pain,* Vol. 129, No. 1-2, pp. 102 – 112, ISSN 0885-3294

Sluka, K.A.; Winter, O.C. & Wemmie, J.A. (2009). Acid-Sensing Ion Channels: A New Target for Pain and CNS Diseases. *Current Opinion in Drug Discovery & Development,* Vol. 12, No.5, pp.693-704, ISSN 1367-6733

Somjen, G.G. (1984). Acidification of Interstitial Fluid in Hippocampal Formation Caused by Seizures and by Spreading Depression. *Brain Research,* Vol. 311, No. 1, pp. 186-188, ISSN 0006-8993

Stys, P.K. & LoPachin, R.M. (1998). Mechanisms of Calcium and Sodium Fluxes in Anoxic Myelinated Central Nervous System Axons. *Neuroscience*, Vol. 82, No. 1, pp. 21-32, ISSN

Sutherland, S.P.; Benson, C.J.; Adelman, J.P. & McCleskey, E.W. (2001). Acid-Sensing Ion Channel 3 Matches the Acid-Gated Current in Cardiac Ischemia-Sensing Neurons. *Proceedings of National Academy of Science U.S.A.,* Vol.98, No. 2, pp.711-766, ISSN 0027-8424

Swanson, R.A.; Farrell, K. & Simon, R.P. (1995). Acidosis Causes Failure of Astrocyte Glutamate Uptake During Hypoxia. *Journal of Cerebral Blood Flow & Metabolism,* Vol. 15, No. 3, pp. 417-424, ISSN 0271-678X

Tombaugh, G.C. & Sapolsky, R.M. (1993). Evolving Concepts About the Role of Acidosis in Ischemic Neuropathology. *Journal of Neurochemistry,* Vol. 61, No. 3, pp. 793-803, ISSN 0022-3042

Ugawa, S.; Ueda, T.; Ishida, Y.; Nishigaki, M.; Shibata, Y. & Shimada, S. (2002). Amiloride-Blockable Acid-Sensing Ion Channels are Leading Acid Sensors Expressed in Human Nociceptors. *Journal of Clinical Investigation,* Vol.110, No. 8, pp.1185-1190, ISSN 0021-9738

Ugawa, S.; Yamamoto, T.; Ueda, T.; Ishida, Y.; Inagaki, A.; Nishigaki, M. & Shimada, S. (2003). Amiloride-Insensitive Currents of the Acid-Sensing Ion Channel-2a

(ASIC2a)/ASIC2b Heteromeric Sour-Taste Receptor Channel. *Journal of Neuroscience,* Vol. 23, No. 9, pp. 3616-3622, ISSN 0270-6474

Urbanics, R.; Leniger-Follert, E. & Lubbers, D.W. (1978). Time Course of Changes of Extracellular H^+ and K^+ Activities During and After Direct Electrical Stimulation of the Brain Cortex. *Pflugers Archiv,* Vol. 378, No.1, pp. 47-53, ISSN 0365-267X

Varming, T. (1999). Proton-Gated Ion Channels in Cultured Mouse Cortical Neurons. *Neuropharmacology*, Vol. 38, No.12 , pp. 1875-1881, ISSN 0028-3908

Vergo, S.; Craner, M.J.; Etzensperger, R.; Attfield, K.; Friese, M.A.; Newcombe, J.; Esiri. M. & Fugger, L. (2011). Acid-Sensing Ion Channel 1 is Involved in Both Axonal Injury and Demyelination in Multiple Sclerosis and Its Animal Model. *Brain,* Vol.134, No. 2, pp. 571-584, ISSN 0006-8950

Voilley, N.; de Weille, J.; Mamet, J. & Lazdunski, M. (2001). Nonsteroid Anti-Inflammatory Drugs Inhibit Both the Activity and the Inflammation-Induced Expression of Acid-Sensing Ion Channels in Nociceptors. *Journal of Neuroscience,* Vol. 21, No. 20, pp. 8026-8033, ISSN 0270-6474

Waldmann, R.; Bassilana, F.; de Weille, J.; Champigny, G.; Heurteaux, C. & Lazdunski, M. (1997a). Molecular Cloning of a Non-Inactivating Proton-Gated Na+ Channel Specific for Sensory Neurons. *Journal of Biological Chemistry,* Vol. 272, No. 34, pp. 20975–20978, ISSN 0021-9258

Waldmann, R. & Lazdunski, M. (1998). H(+)-Gated Cation Channels: Neuronal Acid Sensors in the ENaC/DEG Family of Ion Channels. *Current Opinion in Neurobiology,* Vol. 8, No.3, pp. 418-424, ISSN 0959- 4388

Waldmann, R.; Champigny, G.; Bassilana, F.; Heurteaux, C. & Lazdunski, M. (1997b). A Proton-Gated Cation Channel Involved in Acid-Sensing. *Nature,* Vol. 386, No. 6621, pp.173-177, ISSN 0028-0836

Waldmann, R.; Champigny, G.; Voilley, N.; Lauritzen, I. & Lazdunski, M. (1996). The Mammalian Degenerin MDEG, An Amiloride-Sensitive Cation Channel Activated by Mutations Causing Neurodegeneration in Caenorhabditis Elegans. *Journal of Biological Chemistry,* Vol. 271, No. 18, pp. 10433–10436, ISSN 0021-9258

Waxman, S.G. (2006). Axonal Conduction and Injury in Multiple Sclerosis: the Role of Sodium Channels. *Nature Reviews Neuroscience, Vol.* 7, No.12, pp. 932-941, ISSN 1741-0048

Wemmie, J.A.; Askwith, C.C.; Lamani, E.; Cassell, M.D.; Freeman, J.H., Jr. & Welsh, M.J. (2003). Acid Sensing Ion Channel 1 is Localized in Brain Regions with High Synaptic Density and Contributes to Fear Conditioning. *Journal of Neuroscience,* Vol. 23, No. 13, pp.5496-5502, ISSN 0270-6474

Wemmie, J.A.; Chen. J.; Askwith, C.C.; Hruska-Hageman, A.M.; Price, M.P.; Nolan, B.C.; Yoder, P.G.; Lamani, E.; Hoshi, T.; Freeman, J.H. & Welsh, M.J. (2002). The Acid-Activated Ion Channel ASIC Contributes to Synaptic Plasticity, Learning, and Memory. *Neuron,* Vol. 34, No.3, pp.463-477, ISSN 0896-6273

Wemmie, J.A.; Coryell, M.W.; Askwith, C.C.; Lamani, E.; Leonard, A.S.; Sigmund, C.D. & Welsh, M.J. (2004). Overexpression of Acid-Sensing Ion Channel 1a in Transgenic Mice Increases Acquired Fear-Related Behavior. *Proceedings of National Academy of Science U.S.A.,* Vol. 101, No. 10, pp.3621-3626, ISSN 0027-8424

Wemmie, J.A.; Price, M.P. & Welsh, M.J. (2006). Acid-Sensing Ion Channels: Advances, Questions and Therapeutic Opportunities. *Trends in Neuroscience*, Vol. 29, No. 10, pp. 578-586, ISSN 0166-2236

Weng, J.Y.; Lin, Y.C. & Lien, C.C. (2010). Cell Type-Specific Expression of Acid-Sensing Ion Channels in Hippocampal Interneurons. *Journal of Neuroscience,* Vol. 30, No. 19, pp.6548-6558, ISSN 0270-6474

Wong, H.K.; Bauer, P.O.; Kurosawa, M.; Goswami, A.; Washizu, C.; Machida, Y.; Tosaki, A.; Yamada, M.; Knopfel, T.; Nakamura, T. & Nukina, N. (2008). Blocking Acid-Sensing Ion Channel 1 Alleviates Huntington's Disease Pathology via an Ubiquitin-Proteasome System Dependent Mechanism. *Human Molecular Genetics,* Vol.17, No. 20, pp. 3223-3235, ISSN 0964-6906

Wu, L.J.; Duan, B.; Mei, Y.D.; Gao, J.; Chen, J.G.; Zhuo, M.; Xu, L.; Wu, M. & Xu, T.L. (2004). Characterization of Acid-Sensing Ion Channels in Dorsal Horn Neurons of Rat Spinal Cord. *Journal of Biological Chemistry,* Vol. 279, No. 42, pp. 43716–43724, ISSN 0021-9258

Wu, W.L.; Lin, Y.W.; Min, M.Y. & Chen, C.C. (2010). Mice Lacking Asic3 Show Reduced Anxiety-Like Behavior on the Elevated Plus Maze and Reduced Aggression. *Genes, Brain and Behavior,* Vol. 9, No. 6, pp. 603-614, ISSN 1601-1848

Xiong, Z.G.; Chu, X.P. & Simon, R.P. (2007). Acid Sensing Ion Channels--Novel Therapeutic Targets for Ischemic Brain Injury. *Frontier in Bioscience,* Vol. 12, No. pp. 1376-1386, ISSN 1093-9946

Xiong, Z.G.; Zhu, X.M.; Chu, X.P.; Minami, M.; Hey, J., Wei, W.L.; MacDonald, J.F.; Wemmie, J.A.; Price, M.P.; Welsh, M.J. & Simon, R.P. (2004). Neuroprotection in Ischemia: Blocking Calcium Permeable Acid-Sensing Ion Channels, *Cell*, Vol. 118, No.6, pp. 687-698, ISSN 0092-8674

Xiong, Z.G.; Pignataro, G.; Li, M.; Chang, S.Y. & Simon, R.P. (2008). Acid-Sensing Ion Channels (ASICs) as Pharmacological Targets for Neurodegenerative Diseases. *Current Opinion in Pharmacology*, Vol.8, No. 1, pp.25-32, ISSN 1471- 4892

Xu, T.L. & Xiong, Z.G. (2007). Dynamic Regulation of Acid-Sensing Ion Channels by Extracellular and Intracellular Modulators. *Current Medicinal Chemistry,* Vol. 14, No.16, pp.1753-1763, ISSN 0929-8673

Yagi, J.; Wenk, H.N.; Naves, L.A. & McCleskey, E.W. (2006). Sustained Currents Through ASIC3 Ion Channels at the Modest pH Changes that Occur During Myocardial Ischemia. *Circulation Research,* Vol.99, No. 5, pp. 501 – 509, ISSN 0009-7330

Yermolaieva, O.; Leonard, A.S.; Schnizler, M.K.; Abboud, F.M. & Welsh, M.J. (2004). Extracellular Acidosis Increases Neuronal Cell Calcium by Activating Acid-Sensing Ion Channel 1a. *Proceedings of National Academy of Science U.S.A.,* Vol. 101, No. 17, pp.6752-6757, ISSN 0027-8424

Zha, X.M.; Costa, V.; Harding, A.M.; Reznikov, L.; Benson, C.J. & Welsh, M.J. (2009). ASIC2 Subunits Target Acid-Sensing Ion Channels to the Synapse via an Association with PSD-95. *Journal of Neuroscience,* Vol. 29, No. 26, pp. 8438 – 8446, ISSN 0270-6474

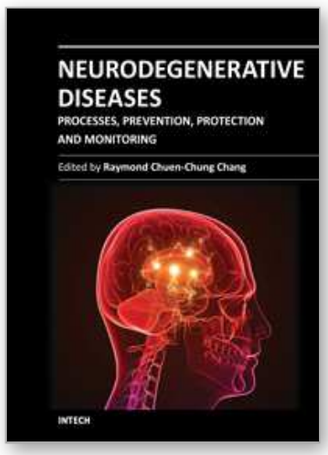
Zha, X.M.; Wemmie, J.A.; Green, S.H. & Welsh, M.J. (2006). Acid-Sensing Ion Channel 1A is a Postsynaptic Proton Receptor That Affects the Density of Dendritic Spines. *Proceedings of National Academy of Science U.S.A.,* Vol. 103, No. 44, pp. 16556-16561, ISSN 0027-8424

Zhou, Y. & Zhao, Z.Q. (2002). Effects of Neomycin on High-Threshold Ca(2+) Currents and Tetrodotoxin-Resistant Na(+) Currents in Rat Dorsal Root Ganglion Neuron. *European Journal of Pharmacology,* Vol. 450, No. 1, pp. 29-35, ISSN 0014-2999

Ziemann, A.E.; Allen, J.E.; Dahdaleh, N.S.; Drebot, I.I.; Coryell, M.W.; Wunsch, A.M.; Lynch, C.M.; Faraci, F.M.; Howard, M.A. III; Welsh, M.J. & Wemmie, J.A. (2009). The Amygdala is a Chemosensor that Detects Carbon Dioxide and Acidosis to Elicit Fear Behavior. *Cell,* Vol.139, No. 5, pp.1012-1021, ISSN 0092-8674

Ziemann, A.E.; Schnizler, M.K.; Albert, G.W.; Severson, M.A.; Howard, M.A. III.; Welsh, M.J. & Wemmie, J.A. (2008). Seizure Termination by Acidosis Depends on ASIC1a. *Nature Neuroscience*, Vol.11, No.7, pp. 816-822, ISSN 1097- 6256

IntechOpen



Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring

Edited by Dr Raymond Chuen-Chung Chang

ISBN 978-953-307-485-6
Hard cover, 558 pages
Publisher InTech
Published online 09, December, 2011
Published in print edition December, 2011

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Chu Xiang-Ping, Wang John Q. and Xiong Zhi-Gang (2011). Acid-Sensing Ion Channels in Neurodegenerative Diseases: Potential Therapeutic Target, Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring, Dr Raymond Chuen-Chung Chang (Ed.), ISBN: 978-953-307-485-6, InTech, Available from: http://www.intechopen.com/books/neurodegenerative-diseases-processes-prevention-protection-and-monitoring/acid-sensing-ion-channels-in-neurodegenerative-diseases-potential-therapeutic-target

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

www.intechopen.com

IntechOpen

IntechOpen

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen