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Two Aspects of ASIC Function: Synaptic Plasticity and Neuronal Injury.

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Abstract

Extracellular brain pH fluctuates in both physiological and disease conditions. The main postsynaptic proton receptor is the acid-sensing ion channels (ASICs). During the past decade, much progress has been made on protons, ASICs, and neurological disease. This review summarizes the recent progress on synaptic role of protons and our current understanding of how ASICs contribute to various types of neuronal injury in the brain.

Keywords

Proton; acidosis; ASIC; neuronal injury; synaptic plasticity

1. Introduction

Acid signaling has attracted more and more attention in recent years. Protons and their receptor-the acid-sensing ion channels (ASICs) play important roles in physiology and neurological diseases. This current review focuses on the role of ASICs in the central nervous system (for a review of ASICs in the periphery, see Deval et al in this issue). We mainly discuss two major aspects of protons: the well established role of acidosis in neuronal injury, and the more recent progress on acid signaling and neural plasticity. For an overview of additional roles of ASICs, see other reviews (Abboud and Benson, 2015; Holzer, 2015; Omerbasic et al., 2014) in this special issue of Neuropharmacology

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2. Expression of ASICs in the brain

ASIC1a, 2a and 2b are the major subunits present in the brain, with the mRNA of ASIC1a and ASIC2 expressed widely throughout the brain (Garcia-Anoveros et al., 1997; Price et al., 1996; Waldmann et al., 1997b; Waldmann et al., 1996). These mRNA expression data are consistent with the immunlocalizaiton studies (Coryell et al., 2009; Price et al., 2014; Wemmie et al., 2003). Some regions, e.g., amygdala, somatosensory cortex, posterior cingular cortex, dentate gyrus in hippocampus, show higher levels of ASIC1a expression than others. For a review of ASIC1a expression in the nervous system, see (Zha, 2013). One recent study performed a thorough immunolocalization analysis of ASIC2 in the brain, and compared it side-by-side with that of ASIC1a (Price et al., 2014). The result shows that the expression of ASIC2 and ASIC1a proteins overlaps in most brain regions, with synaptically dense regions exhibit high staining of both ASIC1a and ASIC2. Consistent with wide expression of both ASIC1a and ASIC2, acid-activated current recorded from brain neurons suggest the contribution from both ASIC1a and ASIC2 in most cases (Alvarez de la Rosa et al., 2002; Askwith et al., 2004; Baron et al., 2002; Chu et al., 2004; Sherwood et al., 2011).

ASICs function as trimers (Jasti et al., 2007) (also see Grunder 2015; Askwith 2015), and can form homomeric and heteromeric channels. Homomeric and heteromeric ASICs show different pH sensitivity (Table 1) and pharmacological properties {Zha, 2013 #1323}. Since three subunits form one functional channel, it is interesting to ask whether heteromeric ASICs favor a specific subunit stoichiometry. One recent study shows that, when expressed in Xenopus oocytes, ASIC1a and 2a heteromers have no special preference for a specific subunit stoichiometry (Bartoi et al., 2014). This result suggests that the subunit stoichiometry in ASIC heteromers is mainly determined by the expression level of the subunits. However, it remains unclear what is the relative subunit ratio of different ASICs in the brain. This question is interesting because it will speak to the relative proportion of homomeric and heteromeric channels in the brain, and will provide insight into subunit stoichiometry of ASIC1a/2 heteromeric channels *in vivo*. The latter can be an important consideration for pharmacological targeting of ASICs in brain neurons (see also Baron 2015).

Besides ASIC1a and ASIC2, some other ASIC family members are also present in the brain, but typically expressed in a more restricted pattern. For example, BLiNaC/BASIC, which stands for Brain Liver Intestine Na+ Channel (Schaefer et al., 2000), is expressed in unipolar brush cells in the ventral uvula and nodulus of the vestibulocerebellum (Boiko et al., 2014). ASIC3 is another subunit that is present in specialized structures in the brain (Babinski et al., 1999; Delaunay et al., 2012; Meng et al., 2009; Wang et al., 2014). The functional importance of these subunits in the brain has not been thoroughly studied.

3. Synaptic role of ASICs

The idea that protons can function as a neurotransmitter has existed for some time. However, it is only recently that we start to obtain evidence directly supporting this hypothesis. In this section, we summarize the recent development on protons as a

neurotransmitter, and our current understanding of protons in synaptic physiology and structural remodeling, and the role of ASICs in fear and anxiety.

3.1. Proton-ASIC as a neurotransmitter-receptor pair

Extracellular acidification can occur during both physiological and disease conditions. Figure 1A illustrates the potential contributors to changes in extracellular proton concentrations. These include glycolysis in neurons, direct release from presynaptic vesicles, lactate and CO_2 production from glial cells, and changed transporter activities in both neurons and glia (Deitmer, 2002; Du et al., 2014; Grichtchenko and Chesler, 1994; Highstein et al., 2014; Krishtal et al., 1987; Miesenbock et al., 1998; Obara et al., 2008; Siesjo, 1982; Siesjo and Wieloch, 1986; Voipio and Kaila, 1993). Many of the same machineries reside around synaptic region as well. Previous studies have assessed the magnitude of pH reduction at synaptic cleft. One approach is based on the fact that acidification inhibits voltage-gated calcium channels (VGCCs). Several groups measured the reduction in presynaptic Ca^{2+} current during neurotransmission, and back-calculated the reduction of synaptic cleft pH to be about 0.2-0.6 pH units (DeVries, 2001; Palmer et al., 2003; Vessey et al., 2005). As discussed below, this magnitude of pH reduction is big enough to regulate several ion channels.

A decrease in pH affects multiple proteins. Besides the above mentioned VGCCs, acidification also inhibits one important class of synaptic channels, the NMDA receptors, with a pKa of 6.9 (Tang et al., 1990; Traynelis and Cull-Candy, 1990). The effects on VGCCs and NMDA receptors are modulatory, and lead to an attenuation of synaptic transmission. In contrast, protons also directly gate several ion channels, including ASICs and TrpV1. However, TrpV1 does not start to open until pH 6.4, and its pH_{50} is about 5.4-5.7 (Ryu et al., 2007; Tominaga et al., 1998). Thus, TrpV1 is unlikely to act as a proton receptor in physiological pH ranges. ASICs are much more pH sensitive, can be activated at pH <= 7.0, and the pH_{50} values for ASIC1a and 3 are around 6.5 (see Table 1). These properties make ASICs a perfect candidate for sensing small to moderate pH reduction in the brain. The subcellular localization of ASICs further supports their role as a neuronal proton receptor (see (Zha, 2013). ASIC1a and ASIC2a show a preferential somatodendritic distribution (Zha et al., 2009; Zha et al., 2006). Moreover, both subunits are enriched in brain synaptosomes (Wemmie et al., 2002; Zha et al., 2009). Immunofluorescence staining further shows a preferential targeting of ASIC1a to dendritic spines (Jing et al., 2012). Consistent with their localization, acute pH 6 application induce $[Ca^{2+}]_i$ rise in dendrites and dendritic spines, and this effect depends upon ASIC1a (Zha et al., 2009; Zha et al., 2006).

Although ASICs localize to dendritic region, early attempts to record ASIC-specific currents during neurotransmission have not been successful (Alvarez de la Rosa et al., 2003). Recently, several groups revisited this idea and have provided new evidence for protons to function as a neurotransmitter and regulate synaptic physiology (Beg et al., 2008; Du et al., 2014; Highstein et al., 2014; Kreple et al., 2014). In turtle lagena, the equivalent of vestibular system in mammals (Highstein et al., 2014), stimulated release from hair cells acidify the synaptic cleft at hair cell calyx and induces excitatory postsynaptic potential (EPSP). In amygdala, increased activity induces pH reduction at the cleft (Du et al., 2014).

Moreover, ASIC1a activity contributes to EPSP in both amygdala and nucleus accumbens (Du et al., 2014; Kreple et al., 2014). Increased pH buffering attenuates the above acid-activated responses while decreased pH buffering has the opposite effect. A similar situation in the nematode shows that protons can function as a neurotransmitter and regulate muscle contraction (Beg et al., 2008).

Consistent with a role as postsynaptic proton receptor, ASICs regulate structural remodeling of synaptic sites. Overexpression of a human ASIC1a, either acutely or chronically, increases the density of dendritic spines in hippocampal slices (Zha et al., 2006). Conversely, ASIC2 deletion or acute knockdown of ASIC1a leads to spine reduction (Zha et al., 2009; Zha et al., 2006). Chronic knockout of ASIC1a, however, has no apparent effect on baseline spine density in organotypic hippocampal slices. In contrast, one recent study showed that deleting ASIC1a increases spine density in nuclear accumbens (Kreple et al., 2014). These data indicate that ASICs are important for spine remodeling, although the exact effect depends on the system studied. Previous studies have further examined the effect of ASIC1 deletion on baseline transmission. Deleting the *ASIC1a* gene has no effect on basal levels of GABA, AMPA and NMDA currents (Cho and Askwith, 2008; Wemmie et al., 2002), but alters the ratio of AMPA:NMDA current. ASIC deletion reduces the AMPA:NMDA ratio in a microisland hippocampal neuron culture but increases the ratio in nucleus accumbens neurons (Cho and Askwith, 2008; Kreple et al., 2014).

In summary, neural activity can acidify synaptic cleft and protons can function as a neurotransmitter. The pH sensitivity and dendritic distribution of ASICs put them in a perfect position to sense pH reduction around pH 7-6. Lastly, both electrophysiological recordings and morphological studies on spines support that ASICs are the main postsynaptic proton receptors in the brain.

3.2. ASICs and synaptic plasticity

While protons activate an inward current at postsynaptic cells, the amplitude of the proton-activated EPSCs is small, about 15-20 times less compared to that generated from glutamate receptors (Du et al., 2014; Highstein et al., 2014; Kreple et al., 2014). These data provide one explanation for why some previous attempts failed to detect a specific proton-activated component during neurotransmission (Alvarez de la Rosa et al., 2003). However, this component probably functions as a boosting mechanism for neurotransmission, and is important for the generation of long-term potentiation (LTP) in amygdala (Du et al., 2014). These results are consistent with a previous report, which shows a similar attenuation of LTP in ASIC1a null hippocampal slices (Wemmie et al., 2002). It is important to note that, while proton inhibits NMDA receptors directly, activation of ASIC1a and the resulting membrane depolarization could help relieve voltage-dependent blockade of NMDA receptors by Mg^{2+}, thus facilitating the activation of NMDA receptors and the expression of LTP. Similar to the effect on LTP, deleting the *ASIC1a* gene reduces paired-pulse responses in microisland hippocampal cultures (Cho and Askwith, 2008). However, the effect on LTP depends on ASIC1a while that on paired-pulse facilitation is not sensitive to amiloride, suggesting that the effect on paired-pulse could be secondary to chronic changes in the knockout. In contrast to the above findings, one study using a CRE-mediated knockout of

ASIC1a does not observe differences in hippocampal LTP between WT and ASIC1a knockout (Wu et al., 2013). These data suggest that ASICs can mediate proton signaling at synaptic sites, but the exact contribution of protons and ASICs to synaptic plasticity may vary, depending on the system and condition.

3.3. ASICs in fear and anxiety

The above studies implicate that ASICs regulate brain physiology. One interesting observation is that ASIC1a and ASIC2 exhibit high levels of expression in “fear structures” such as amygdala and bed nucleus of the stria terminalis (BNST) (Coryell et al., 2007; Price et al., 2014; Wemmie et al., 2003). These data suggest an important role of ASICs in fear and related behavior. Several previous reviews have covered this topic in detail (Sluka et al., 2009; Wemmie et al., 2013). Here, we summarize the key observations and highlight a possible difference between systems. In mice, deleting ASIC1a or inhibiting ASIC1a activity makes the animals less fearful to both conditioned and unconditioned fear. ASIC1a null mice exhibit a reduced acoustic startle, and a reduced freezing in response to CO_2 and TMT, a predator odor (Coryell et al., 2008; Coryell et al., 2007; Ziemann et al., 2009). ASIC1a deletion also reduces learned fear (Wemmie et al., 2003). Viral-mediated expression of ASIC1a in the ASIC1a null mice in amygdala rescues conditioned but not unconditioned fear (Coryell et al., 2008). In another study, site-specific deletion of ASIC1a in BNST is sufficient to abolish CO_2-induced freezing (Taugher et al., 2014). These data indicate that ASICs in different structures have differential effects on fear induced by specific modality.

Consistent with a role in fear, ASIC1a contributes to anxiety and depression-related behavior. In mice, deleting the *ASIC1a* gene or inhibiting ASIC1a shows an anti-depression effect in several assays, including open field test, tail suspension test and forced swim test (Coryell et al., 2008; Coryell et al., 2009). In contrast to the data from mice, injection of ammonium directly into amygdala in rat, which elicits ASIC-type current in these neurons, reduces center avoidance in the open field test and prolonged the time spent in the light compartment in the light/dark test (Pidoplichko et al., 2014). In addition, injecting Psalmotoxin-1 (PcTx1), a specific blocker of 1a-containing ASIC channels (Escoubas et al., 2000), into amygdala in rat increases center avoidance in the open field test. Thus, ASIC activation in rat has anxiolytic effect, which contrasts with the results obtained from the mice. These data indicate that ASICs are clearly important for fear and depression-type behavior, but the exact role they play may depend upon the paradigm.

The role of protons and ASICs in human brain function remains uncertain. In a recent study, Magnotta et al used magnetic resonance imaging to measure changes in proton concentration in the brain (Magnotta et al., 2012). The result shows that normal learning process is sufficient to induce acidification in the brain. Although the magnitude of pH changes in this study is unclear, the data suggests that acid signaling contributes to neural plasticity during normal learning process and possibly to long-term changes in various pathological conditions in human subjects.

4. ASICs and neuronal injury

Extracellular acidosis typically occurs in various injurious conditions in the brain. The range of pH reduction varies, from about pH 6.5 in multiple sclerosis to below pH 6.0 in severe ischemia (Figure 1B). As the main neuronal proton receptor in neurons, ASICs play a critical role in neuronal injury associated with acidosis. We will summarize the main findings in brain ischemia, multiple sclerosis, traumatic brain injury and Parkinson's disease.

4.1. Ischemic brain injury

Multiple mechanisms contribute to ischemia-induced brain injury. Excitotoxicity as a result of massive glutamate release is one main cause of early neurotoxicity (Lai et al., 2014). Following ischemiareperfusion, there is a large increase in reactive oxygen species accompanied by a large reduction in brain pH (Hertz, 2008; Siesjo et al., 1993). Brain pH can reduce to about pH 6.5 in a mild ischemia and to pH 6.0 or lower in severe ischemia (Xiong et al., 2007). These pH reductions are large enough for robust activation of ASIC1a containing channels (see Table 1). Indeed, ASIC1a plays a critical role in ischemia-induced neuronal injury. Deleting the ASIC1a gene protects mice from brain injury induced by middle cerebral artery occlusion (MCAO) (Pignataro et al., 2007; Xiong et al., 2007). Amiloride, a non-specific ASIC inhibitor, and PcTx1, have similar protective effect. The time window for this effect is long, with protection observed up to 5 hrs after MCAO (Pignataro et al., 2007). In addition, one previous study showed that activation of NMDA receptors, through the recruitment of calcium/calmodulin-dependent protein kinase II (CaMKII) signaling, increases ASIC1a current and potentiates ischemia-induced neuronal injury (Gao et al., 2005). Consistent with this result, the protective effect from ASIC inhibition is additive to that of inhibiting NMDA receptors (Mishra et al., 2011; Pignataro et al., 2007). These data suggest that targeting ASICs, especially when combined with other interventions, may be an effective therapeutic strategy for alleviating ischemia-induced brain injury.

It is interesting to note that some chemicals that are present in the brain and/or released during ischemia modulate ASIC channels. Lactate potentiates ASIC currents by “chelating”, thus reducing, the effective concentration of extracellular cations (Immke and McCleskey, 2001). Sperimine is one endogenous polyamine that is found at high concentrations in the brain. Spermine shifts the steady state inactivation of ASIC1a, probably due to a stabilization of the channel at resting state (Babini et al., 2002), and potentiates ischemia-induced injury in the brain (Duan et al., 2011). Inhibiting spermine synthesis with difluromethylornithine (DFMO) attenuated ASIC1a channel-mediated ischemic injury. Dynorphins are another class of endogenous peptides in the brain. Depending on the target, these peptides can be either protective or detrimental to neurons in disease (for a review, see (Hauser et al., 2005). Dynorphin reduces steady-state desensitization of ASIC1a and increases acid-activated current in brain neurons, with an EC50 of 26 nM (Sherwood and Askwith, 2009). In dissociated cultures, 1 μM Dynorphin potentiates acidosis-induced neuronal injury. The exact extracellular dynorphin concentration in the brain remains unclear and the consequence of ischemia on dynorphin levels remains controversial (Andrews et al., 1988; Cheung and Cechetto, 1995; Fried and Nowak, 1987). However, a rat

brain, which has a density of ~1g/cm^3 (Bishop and Wahlsten, 1999; Tajima et al., 1993), contains 10-100 fmol dynorphin per mg tissue (Andrews et al., 1988; Goldstein and Ghazarossian, 1980). Thus, the overall concentration of dynorphin in a rat brain is about 30-300 μM, which suggests that endogneous dynorphin can reach a level to potentiate ASIC currents. In reality, probably multiple endogenous factors work together to regulate ASIC function and acid-induced injury.

4.2. Multiple sclerosis

Multiple sclerosis (MS) is another type of central nervous system disorder associated with prolonged inflammation and acidification. In a mouse experimental autoimmune encephalomyelitis (EAE) model, pH in spinal cord was about pH 6.5-6.6 at 15 days post immunization (Friese et al., 2007), suggesting that there is a prolonged period of acidosis in this paradigm. In healthy axons, ASIC1a expression is relatively low (Vergo et al., 2011; Zha et al., 2009; Zha et al., 2006). However, in both an animal EAE model and human MS patients, inflammation leads to an increase of ASIC1a expression or trafficking to axons, as well as an upregulation of ASIC1a in oligodendrocytes (Arun et al., 2013; Vergo et al., 2011). Deleting the *ASIC1a* gene or inhibiting ASIC1a reduces EAE-induced axonal injury and improves the clinical score (Friese et al., 2007). Amiloride alleviates the severity of the disease, either when applied in the acute model or at the phase of first relapse (Vergo et al., 2011). These data indicate that ASICs mediate inflammation-induced axonal degeneration. A recent three-year clinical study followed up on a group of patient with progressive MS (Arun et al., 2013). Patients were imaged with MRI before, during and after a one-year long oral treatment with amiloride. The result shows that amiloride treatment significantly reduces the rate of brain atrophy, and improves scores reflecting axonal damage and myelin loss. While there are many issues that need to be addressed, this report is exciting because it is the first translational study that illustrates a promising neuroprotective effect of inhibiting ASICs.

4.3. Traumatic Neuronal Injury

Traumatic brain injury (TBI) and spinal cord injury (SCI) affect millions of people worldwide. Following the initial acute phase of injury, extensive neuronal injury can happen during the secondary phase. Multiple mechanisms contribute to the secondary injury observed following trauma. One important factor is the decrease in extracellular pH. Brain pH reduces to about 6.7-6.9 in rodent TBI models and human TBI patients (Gupta et al., 2004; Vink et al., 1987; Yin et al., 2013). Of note, these pH measurements were performed with Magnetic resonance spectroscopy, microelectrode or microdevice, and thus detect the pH changes of at the tissue level. Given that traumatic injuries typically lead to massive disruption of metabolism, it is conceivable that localized pH reduction at the cellular level can be more severe. In TBI patients, the degree of pH reduction is correlated with the outcome, with lower pH associated with higher lethality (Gupta et al., 2004; Timofeev et al., 2011; Zygun et al., 2004). In a mouse lateral fluid percussion injury model of TBI, attenuating pH reduction with bicarbonate alleviates neuronal injury (Yin et al., 2013). These observations suggest that the reduction in pH apparently is one causal factor of TBI-induced secondary injury. In a rat model of TSCI, ASIC1a expression was acutely increased in the penumbra region (Hu et al., 2011). In both the mouse TBI and rat TSCI models,

inhibiting ASIC1a with amiloride or PcTx1 alleviates the severity of the injury (Hu et al., 2011; Yin et al., 2013). Together, these results indicate that ASICs play an important role in traumatic injury. Therefore, inhibiting or down-regulating ASICs can be a therapeutic approach to treat traumatic neuronal injuries.

4.4. Parkinson's Disease

Parkinson's Disease (PD) is common neurodegenerative disease that is characterized by motor impairment, mainly due to a loss of dopaminergic neurons in the substantia nigra (Dauer and Przedborski, 2003). However, the mechanisms that lead to the loss of dopaminergic neurons remain unclear. In PD, increased oxidative stress inhibits mitochondria function and disrupts energy metabolism (Mattson et al., 1999), which results in an increase in lactate production and acidosis (Koga et al., 2006). Neurons in substantia nigra express ASICs and exhibit typical ASIC-type current (Arias et al., 2008; Pidoplichko and Dani, 2006). In a mouse PD model induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), ASIC inhibition with amiloride or PcTx1 attenuates the reduction of immunoreactivity of tyrosine hydroxylase and dopamine transporter- both are markers for dopaminergic neurons (Arias et al., 2008). This result suggests that ASIC-mediated responses contribute to loss of dompaminergic neurons in PD. Since many other degenerative diseases are associated with pH reduction (Chu and Xiong, 2012), it is conceivable that inhibiting ASICs may have similar protective effects in neurodegenerative diseases in general.

5. Summary and speculation

Protons have emerged as an important signaling molecule in neurons. As illustrated in Figure 1A, multiple processes contribute to an increase in extracellular proton concentration. This leads to acidification and inhibition of some synaptic receptors, including NMDA receptor and VGCCs. While these typically dampens synaptic activity, the activation of ASIC family ion channels leads to increased calcium-dependent signaling and boosts neural activity. Depending on the magnitude and duration of acidification, this ASIC-dependent signaling can contribute to synaptic physiology and induce structural changes of the synaptic sites, or contribute to neuronal injury in various neurological disorders. This scheme, though simplified, highlights the importance of protons in both synaptic plasticity and brain injury. It will be interesting to determine what additional players are involved in acid signaling in neurons, and to determine the cross-talk between ASICs and other synaptic signaling pathways. Studies along this line will reveal a more dynamic picture of proton signaling, and will provide important insight into brain physiology and disease.

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Highlights

1. We discussed the general expression of ASICs in the brain.
2. We discussed the synaptic role of ASICs in the brain.
3. We discussed the role of ASICs in neuronal injury.

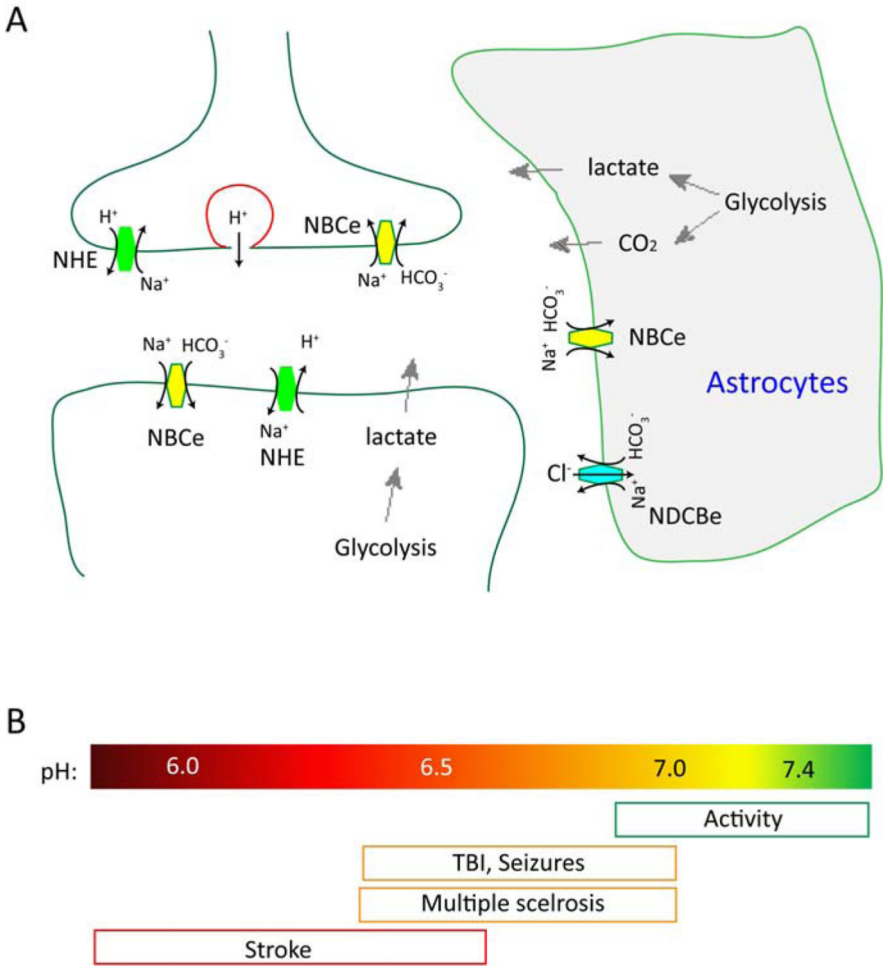

Figure 1. Source of protons and the magnitude of pH changes in the brain

(A) Illustration showing the major contributors to extracellular pH reduction in the brain. Increased glycolysis leads to lactate and CO_2 production, which can acidify interstitial space. In addition, several exchangers actively regulate extracellular pH. Abbreviations: NBCe Na^+/bicarbonate cotransporter; NDCBe Na^+-dependent bicarbonate-chloride exchanger; NHE: Na^+- H^+ exchanger. (B) Illustration showing the magnitude of pH changes in various conditions. Note that neural activity can lead to both alkalinization and acidification.

Table 1

pH_{50} of ASIC homomeric and heteromeric channels.

Subunit composition	1a	1b	2a	2b	3
1a	5.8-6.8	5.8-6.3	5.4-6.1	6.2-6.4	6.3-6.7
1b		5.8-6.1	4.9	N/A	6.3-6.7
2a			3.8-4.5	4.8	5.6-6.1
2b				N/A	6.5
3					6.3-6.7

pH sensitivity data are based on the following literature: (Alijevic and Kellenberger, 2012; Askwith et al., 2004; Babini et al., 2002; Benson et al., 2002; Chen et al., 2005; Hattori et al., 2009; Hesselager et al., 2004; Poirot et al., 2004; Salinas et al., 2005; Sherwood et al., 2011; Sutherland et al., 2001; Waldmann et al., 1997a). ASIC4 is not included in this table because mammalian ASIC4 does not appear to contribute to acid-activated current.