ASICs as potential therapeutic targets for treating neurologic diseases

The various functions of ASICs in the nervous system have yet to be fully understood. ASICs are widely distributed throughout all regions of the brain where they participate in synaptic plasticity, learning, and sensory transduction. In particular, ASIC1a is a known purveyor of synaptic plasticity, especially the facilitation of N-methyl-D-aspartate (NMDA) receptor activation in long-term potentiation (LTP) of hippocampus [44]. However, a recent study by the Lien group showed that disruption of the ASIC1a gene did not impair normal hippocampal LTP and spatial memory in ASIC1a conditional knockout mice [45]. Still, Wemmie et al. recently detected local pH changes during normal brain activity in mouse and human brains, underscoring the potential for ASIC activation in this context [46]. More studies are clearly needed to delineate the roles of ASIC1 in the nervous system (Table 2).

Parkinson's disease

Parkinson's disease (PD) is a disabling disease characterized by selective, gradual apoptosis of midbrain dopaminergic (DA) neurons and progressive motor deterioration. Increasing efforts have been made to identify putative causes of PD, namely oxidative stress, microglial inflammation, and mitochondrial dysfunction. Interestingly, these processes often result in tissue acidification; and lactic acidosis, which further aggravates neuronal damage, has been documented in the brains of patients with PD and in the classic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced animal model of PD [47, 48]. A recently conducted study has demonstrated that mitochondrial ASIC1a may serve as an important regulator of MPT pores, thus contributing to oxidative neuronal cell death [49]. Moreover, Arias and colleagues have found that MPTP-treated mice develop brain tissue acidosis and that ASIC inhibitors amiloride and PcTx-1 protect against substantia nigra neuronal degeneration by reducing levels of DA and its transporter and preventing apoptosis [50]. In addition, mutation of the parkin gene or a lack of endogenous parkin protein results in abnormal ASIC currents, protein degradation, and DA neuronal injury, suggesting that ASIC currents may mediate the fundamental pathology in PD [51]. ASIC inhibitors amiloride and PcTx-1 are also protective of substantia nigra in the mouse PD model, preventing neuronal loss and apoptosis [50]. Lipopolysaccharide (LPS) stimulation likewise increases levels of ASIC1 and ASIC2a expression in rat microglia and induces inflammatory cytokines [52]. Such findings collectively indicate that modulating microglial ASIC function may control neurodegenerative diseases such as PD.

Huntington's disease

In individuals with Huntington's disease (HD), CAG repeats of the huntingtin gene *IT15* (copy number >35–40) produce variations in the huntingtin protein, leading to

Table 2 ASICs in neurologic disorders

Disease	Role of ASICs
Parkinson's disease	Lactic acidosis occurs in the brains of patients with PD.
	Amiloride helps protect against substantia nigra neuronal degeneration, inhibiting apoptosis.
	Parkin gene mutations result in abnormal ASIC currents.
Huntington's disease	ASIC1 inhibition enhances ubiquitin-proteasome system activity and reduces huntingtin-polyglutamine accumulation.
Pain	ASIC3 is involved in: 1) primary afferent gastrointestinal visceral pain, 2) chemical nociception of the upper gastrointestinal system, and 3) mechanical nociception of the colon.
	Blocking neuronal ASIC1a expression in dorsal root ganglia may confer analgesia.
	NSAIDs inhibit sensory neuronal ASIC expression.
Cerebral ischemia	Neuronal ASIC2 expression in the hypothalamus is upregulated after ischemia.
	Blockade of ASIC1a exerts a neuroprotective effect in a middle cerebral artery occlusion model.
Migraine	Most dural afferent nerves express ASICs.
Multiple sclerosis	ASIC1a is upregulated in oligodendrocytes and in axons of an acute autoimmune encephalomyelitis mouse model, as well as in brain tissue from patients with multiple sclerosis.
	Blockade of ASIC1a may attenuate myelin and neuronal damage in multiple sclerosis.
Seizure	Intraventricular injection of PcTX-1 increases the frequency of tonic-clonic seizures.
	Low-pH stimulation increases ASIC1a inhibitory neuronal currents.
Malignant glioma	ASIC1a is widely expressed in malignant glial cells.
	PcTx1 or ASIC1a knock-down inhibits cell migration and cell-cycle progression in gliomas.
	Amiloride analogue benzamil also produces cell-cycle arrest in glioblastoma.