



Triggering of Major Brain Disorders by Protons and ATP: The Role of ASICs and P2X Receptors

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Abstract Adenosine triphosphate (ATP) is well-known as a universal source of energy in living cells. Less known is that this molecule has a variety of important signaling functions: it activates a variety of specific metabotropic (P2Y) and ionotropic (P2X) receptors in neuronal and non-neuronal cell membranes. So, a wide variety of signaling functions well fits the ubiquitous presence of ATP in the tissues. Even more ubiquitous are protons. Apart from the unspecific interaction of protons with any protein, many physiological processes are affected by protons acting on specific ionotropic receptors—acid-sensing ion channels (ASICs). Both protons (acidification) and ATP are locally elevated in various pathological states. Using these fundamentally important molecules as agonists, ASICs and P2X receptors signal a variety of major brain pathologies. Here we briefly outline the physiological roles of ASICs and P2X receptors, focusing on the brain pathologies involving these receptors.

Keywords ASICs · P2X receptors · Stroke · Chronic pain · Epilepsy · Neurodegenerative · Psychiatric diseases

Introduction

Since water is an essential attribute of life, protons are essential ions for the most fundamental biological processes such as pH homeostasis, synaptic transmission, and

the mitochondrial respiratory chain [1]. Slight fluctuations in intracellular or extracellular pH can have marked effects on protein function, synaptic vesicle trafficking, and the electrical machinery of neuronal and glial cells [1]. Apart from nonspecific interactions with biological molecules, numerous physiological processes are triggered by protons acting on their highly specific effectors—acid-sensing ion channels (ASICs) [2, 3].

Adenosine triphosphate (ATP) is well known to be a universal source of energy in cells. Less known, but also a very important function of this molecule, is the activation of specific receptors on the cell membrane, in particular, ionotropic receptors such as P2X (ATP-gated receptor cation channel family).

Both ASICs and P2X receptors are involved in numerous physiological functions [2–5]. Although the amino-acid sequences of ASICs and P2X are substantially different, both channels are trimeric complexes (Fig. 1) sharing a similar pore architecture and conducting monovalent cation currents [6].

Both ASICs and P2X receptors mediate a variety of pathologies [5, 7], the majority of which have a considerable social impact [8–11] (Table 1). Several recent reviews have summarized findings on the role of ASICs in the peripheral nervous system, in particular in nociception and proprioception [2, 12]. The structure–function relationship of ASICs [4, 13] and their evolution [14] has been described as well as developing pharmacology [15]. Similarly, the importance of P2X receptors in the peripheral nervous system, smooth muscle, vascular physiology, and pathology has been the subject of several recent reviews [16–19].

The roles of ASICs and P2X receptors in the brain have also been summarized in several reviews devoted to each of these receptors [20–25]. On the other hand, it is reasonable to review their roles in the framework of the same work.

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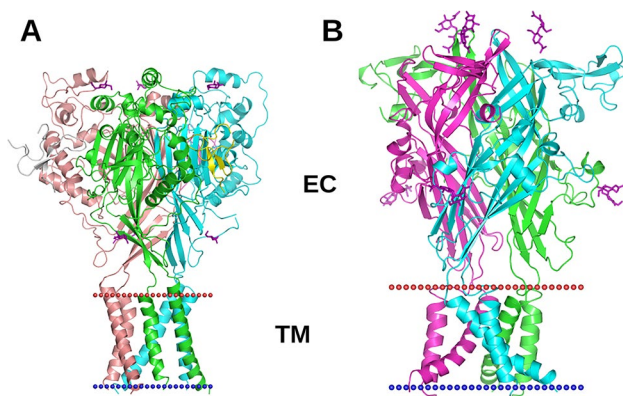


Fig. 1 Structures of ASIC1 in complex with psalmotoxin at a high pH (**A**) and the P2X4 channel in the closed state (**B**). Different colors correspond to different subunits of the channels. TM, transmembrane domain; EC, extracellular domain. Images 4fz1 and 3h9v from the Orientations of Proteins in Membranes database of the University of Michigan (CC BY 3.0) with changes.

Protons and ATP serve as co-transmitters in specific brain areas, and consequently, both ASICs [26–30] and P2X receptors [31, 32] mediate some components of the postsynaptic response. ASICs [26, 28, 33, 34] and P2X receptors [35] are also involved in synaptic plasticity, which makes them important players in this brain function. Furthermore, ASICs and P2X receptors have been shown to form molecular complexes with one another, suggesting the possibility of their functional interaction(s) [36, 37]. In this review, we briefly outline the physiological roles of ASICs and P2X receptors and the brain pathologies involving these receptors.

General Information on ASICs and P2X Receptors

ASICs

ASICs are proton-gated voltage-independent ion channels that are ubiquitous in the nervous system. The existence of receptors for protons was first revealed in 1980 as currents

activated by extracellular acidification of the neuronal membrane [38]. They were named acid-sensing ion channels after being cloned in 1997 [39]. ASICs are members of the epithelial Na^+ channel/degeneration family of amiloride-sensitive ion channels [3].

Currently, at least eight subunits encoded by five genes (*ASIC1-5*) are known. Splice variants of the *ASIC1* gene give ASIC1a, ASIC1b, and ASIC1b2 subunits; and those of *ASIC2* give ASIC2a and ASIC2b subunits [40–43]. There are no known splice variants of the *ASIC3-5* genes. Almost all subunits of these channels are expressed in the mammalian brain, except for ASIC1b [44] and ASIC1b2 [45]. Of them, the most common are ASIC1a, ASIC2a, and ASIC2b [46]. The subunits form homo- or heterotrimeric complexes working as channels with pH-sensing properties [46].

ASIC1a homomers are more sensitive to extracellular protons than other subunits and their combinations [41, 47, 48]. ASIC2b, ASIC4, and ASIC5 are not activated by protons at all [40, 49, 50].

ASICs are found in most regions of the mammalian brain: cerebral cortex, cerebellum, brain stem, amygdala, hippocampus, diencephalic structures, striatum, and olfactory bulb, among other brain structures [24].

Under physiological conditions, the main stimulus known so far to activate ASICs is a rapid drop in pH. ASIC1a is of particular importance since it can be activated by acidosis in the physiological range. In a laboratory setting, the activity of ASICs can be altered by several natural or synthetic substances: amiloride and A-317567 (non-discriminative low-affinity blockers), 2-guanidine-4-methylquinazoline (a pH-independent activator), ammonium ions (an activator), the spider peptide psalmotoxin-1 (PcTx1, complex state-dependent effects on ASIC1), the snake venom components mambalgins (blockers), novel compound **5b** (an orthosteric antagonist of ASIC1a), and others [7, 51–53]. Several endogenous substances such as spermine [54], histamine, or corticosterone [55] also modulate the activity of ASICs.

At the periphery, ASICs are primarily expressed in sensory neurons that innervate tissues and organs, and participate in sensory processes, including mechanotransduction,

Table 1 Some brain pathologies involving ASICs and P2X have a considerable social impact

Pathology	Number of people affected worldwide
Ischemic stroke	Stroke is ranked as the second leading cause of death worldwide with an annual mortality rate of about 5.5 million [8]
Chronic pain	Globally, it is estimated that about one in five [9], or about 1.5 billion people, suffer from chronic pain
Degenerative disorders, including multiple sclerosis (MS) and Parkinson's disease	A total of 2.8 million people was estimated to live with MS worldwide [10], In 2016, 6.1 million had Parkinson's disease globally
Epilepsy	Around 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally [11]

chemoreception, and nociception [2]. Within the brain, ASICs appear to play important roles in synaptic transmission, and its modulation and plasticity [24]. Briefly, the rapid acidification occurring during synaptic transmission [26, 56] activates ASICs on postsynaptic neurons in several brain structures [26–30, 57], implying that some component of postsynaptic current is mediated by ASICs with protons acting as co-transmitters. Before this component was identified, it was already known that ASICs play a functional role in central synapses. Their activation regulates the synaptic strength of glutamatergic and GABAergic synapses and/or contributes to use-dependent synaptic plasticity [24]. Depending on the pattern of neuronal activity, the structure of a given brain region, and downstream signaling pathways, ASICs may contribute to both short-term [29, 58, 59], and long-term [26, 33, 34, 52, 58, 60, 61] plasticity. The involvement of ASICs in the functioning of synapses in the amygdala, hippocampus, striatum, and cingulate cortex determines their role in higher-order functions like learning, memory, and fear conditioning. A detailed review of the behavioral effects of ASIC activation or inactivation can be found in [24]; here we describe the main known effects.

Pharmacological inhibition or genetic elimination of ASICs negatively affects motor performance in tests of high difficulty [57], and, interestingly, this effect decreases after training. Also, ASICs contribute to the freezing component of innate fear reactions. Disruption of ASICs in the amygdala decreases the ability to form long-term potentiation (LTP), which manifests as deficits in both cue and context fear conditioning [33, 44, 62]. In the ventral hippocampus, inhibition of ASIC1a leads to impairment of fear extinction [63], which is mediated by the alteration of NMDA receptors. ASICs influence not only the negative reinforcement system but also the positive. Global (genetic) disruption of ASIC1a leads to a decrease in learning performance in the classical conditioning paradigm based on positive stimuli [64]. In the nucleus accumbens, ASIC1a emphasizes cocaine-seeking behavior [65, 66].

The pH-sensing properties of ASICs determine their role in controlling brain homeostasis related to CO₂ concentration. Systemic blockade or deletion of ASIC1a decreases hypercarbia-induced freezing [62, 67]. Reconsolidation of related memories also depends on the proper functioning of ASICs [68]. Interestingly, suppressing the activity of ASIC2 and ASIC3 in the locus coeruleus disturbs sleep structure [69]. This region is known to be a CO₂-dependent modulator of respiration and sleep-wakefulness cycles.

In general, the contribution of ASICs to complex forms of behavior and brain homeostasis is essential, modulatory, and region-dependent.

P2X

The idea of ATP-mediated intercellular signaling appeared almost immediately after the discovery of this molecule in 1929 [70]. The first information on the release of ATP from sensory nerves was obtained by Pamela Holton in the 1950s [71, 72]. In 1972, Geoffrey Burnstock proposed the existence of "purinergic" nerves [73], thus founding a new research field. We now know that extracellular ATP signaling is widespread among different physiological systems [74]. Much of the early data on purinergic signaling were obtained from experiments on smooth muscles. In 1983, it was shown that extracellular ATP causes depolarizing ionic current in mammalian sensory neurons [75, 76] due to the opening of the membrane ion channels [77, 78] and can mediate rapid synaptic transmission in both peripheral and central parts of the nervous system [74]. Extracellular ATP activates both inotropic P2X and metabotropic P2Y receptors [74]; the latter are not reviewed here.

P2X receptors are ligand-gated ion channels that trigger their open state by binding ATP or related agonists. In mammals, seven genes encoding P2X receptor subunits are known [79]. Their amino-acid sequences are 40%–50% identical. The length of P2X1–6 subunits is 388–471 amino-acids, while the P2X7 receptor is larger (595 amino-acids). Each subunit contains two hydrophobic transmembrane domains separated by an ectodomain (~280 amino-acids). Functional channels are formed as trimers. The pore is formed by six transmembrane domains (two from each subunit). The cytoplasmic part of the channel is formed by the N- and C- termini of the subunits [79]. Due to the larger size of the P2X7 subunit, its intracellular part contains additional domains [80]. The trimers can be homomeric (P2X1, P2X2, P2X3, P2X4, P2X5, or P2X7, but not P2X6) or heteromeric (except P2X7). Common heteromeric variants are P2X1/2, P2X1/4, P2X1/5, P2X2/3, P2X2/6, and P2X4/6 [81]. P2X receptors are widely expressed in the cells of various tissues: smooth (P2X1) and skeletal (P2X5) muscles, immune cells (P2X7), as well as, critical for this review, neurons, glial cells, and brain microvessels (P2X2, P2X3, P2X4, and P2X6) [79, 82].

All P2X receptors are permeable to small monovalent cations, while some have significant permeability to Ca²⁺ (the highest reported for P2X4) [79, 83]. Homomeric P2X7 receptors can transmit even relatively large organic cations such as some fluorescent dyes [83]. However, P2X5 receptors are permeable to Cl⁻ anions too [84].

After activation, P2X receptors undergo desensitization. Based on the speed of this process, we distinguish two groups: with fast (< 1 s; P2X1 and P2X3) and slow (> 20 s; P2X2, P2X4, P2X5, and P2X7) onset [79, 83, 85]. The molecular mechanisms controlling desensitization are insufficiently

studied. The available data indicate that this process is determined mainly by the properties of the channel's cytoplasmic cup [80, 86].

The main physiological agonist of P2X receptors is ATP. The efficient concentration range to activate most P2X receptors is 0.5–12 $\mu\text{mol/L}$. The exception is P2X7, which requires a significantly higher concentration of up to 100 $\mu\text{mol/L}$ [79]. Other efficient agonists of P2X receptors are ATP derivatives: 2-meSATP, ATP γS , α,β -meATP, $\beta\gamma$ -meATP, BzATP, and the like. Many novel compounds act as non-selective (suramin, PPADS, and RB-2) or selective antagonists. A detailed review of the pharmacological properties of P2X receptors can be found in [79].

The wide expression of P2X receptors, in particular their presence on smooth muscle cells (including blood vessels), immune cells, neurons, and glia, determines the broad variety of their physiological effects. Numerous ATP effects are carried out in both the efferent and sensory parts of the peripheral nervous system. ATP is released as the co-transmitter in the terminals of autonomic fibers (along with acetylcholine or norepinephrine), where it acts mainly through the activation of P2X1 receptors. P2X2 and P2X3 receptors of gustatory afferents detect the ATP released from taste receptor cells [87]; modulate the activity of the auditory system [88]; and induce the excitation of nociceptors [89]. In the central nervous system (CNS), P2X receptors contribute to excitatory intercellular communication in the locus coeruleus [90, 91], hippocampus [31, 35, 92], spinal cord [93], hypothalamus [94, 95], and cortex [32, 96]. Of particular interest are P2X4-containing receptors, which have the highest permeability to Ca^{2+} . In the presynapse, their activation may trigger Ca^{2+} -dependent signaling, enhancing, for example, the release of glutamate [97]. The release of ATP under physiological conditions facilitates LTP in the hippocampus, and this facilitation is mediated by Ca^{2+} entry through P2X4 receptors followed by the down-regulation of postsynaptic NMDA receptors [98]. Also, P2X4 receptors are significantly expressed in microglial cells and are involved in immune function [99].

P2X receptors are involved in the interaction of neurons and glial cells and hence may play a role in the development, maintenance, and plasticity of neuronal circuits [100]. In particular, astrocytic P2X7 receptors have the potential to cause rapid non-vesicular glutamate release [101]. Microglial P2X7 receptors are important for immune responses, particularly in the CNS. The role of P2X receptors in pathological processes is discussed in more detail in the following section.

ASICs in Brain Pathology

As outlined in the previous section, ASICs are widely expressed in the mammalian nervous system in general and

the brain in particular. The list of established functions of this receptor family is already long and is rapidly increasing (for instance, reviewed in [102, 103]). ASICs are involved in many important physiological functions, as well as contributing to a variety of pathologies. This is not surprising given that tissue acidosis is a key contributor to neuronal cell death in many neurological diseases, whereas ASICs, namely subtype ASIC1a, are pivotal in acidosis-induced damage to brain neurons. [104, 105]. Chronic pain [106], ischemic stroke [4], epileptic seizures [106, 107], degenerative disorders including multiple sclerosis (MS), Parkinson's disease (PD), and even neonatal hyperbilirubinemia [108] are just a few examples of pathologies involving ASICs. Interestingly, apart from the well-established role of peripheral ASICs in pain, there is emerging evidence that ASIC1a located in the brain is an important player in pain processing [28].

Some of these pathologies affect millions of people worldwide and are still awaiting adequate pharmacological tools for their cure (for instance up to 40% of epilepsy cases are resistant to currently available drug therapy). Emerging evidence from intensive research strongly suggests that the pharmacological modulation of ASICs is a very promising strategy for the treatment of these pathologies.

In this section, we briefly review evidence regarding the role of ASICs in acid-induced toxicity in relation to some brain pathologies. In addition, we outline a potential explanation for the following paradox. ASICs, especially ASIC1a, are typically activated by a rapid drop in pH, whereas slow acidification results in steady-state desensitization without inducing detectable currents [109, 110] (Fig. 2). On the other hand, acidification associated with pathological states is prolonged and typically slow, and thus should not activate ASICs. Still, inhibition of ASICs (especially ASIC1a), is

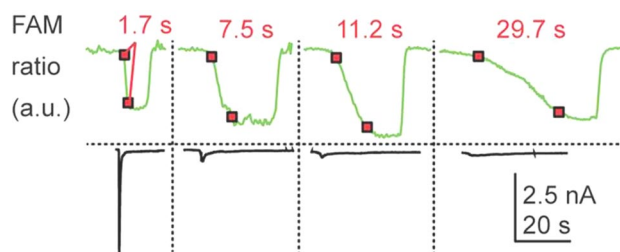


Fig. 2 Slow acidification results in the steady-state desensitization of ASIC currents. ASIC-currents are evoked by acidification with similar amplitudes (from pH 7.4 to pH 6.0) but with different rise times. Upper panel, the pH of the applied solution was measured using pH-sensitive fluorescent dye; the 10–90% fall-time of the fluorescence change corresponds to the interval between the two squares (corresponding values are shown above the traces). Lower panel, ASIC currents evoked by these acidifications. Notice the striking reduction of the amplitudes of ASIC currents evoked by slower acidification. Adapted from [110] (part of Figure 4) published under the terms of the Creative Commons Attribution License (CC BY). Copyright © 2020 Alijevic, Bignucolo, Hichri, Peng, Kucera and Kellenberger.

protective in multiple models of pathological states reported in numerous studies. How to account for this contradiction?

Ischemic Stroke

Acidosis is a common feature of ischemia and is assumed to play a critical role in brain injury [111]. Important evidence regarding the role of Ca^{2+} -permeable ASICs in acidosis-induced brain injury was reported in 2004 by Xiong *et al.* [104]. In particular, it was found that in focal ischemia, intracerebroventricular injection of ASIC1a blockers or knockout of the ASIC1a gene protects the brain from ischemic injury more potently than glutamate antagonism [104]. Since then, the pathological role of ASIC1a in stroke has been confirmed in many studies and extensively reviewed [7, 111, 112]. Still, the exact mechanism of involvement of ASIC1a in stroke requires further investigation because at least two studies [105, 113] that do confirm the important role of ASIC1a in an *in vitro* model of acidotoxicity and an *in vivo* model of ischemic stroke, suggesting that this role involves an ion-conducting independent function of ASIC1a [105]. Authors [105] have reported that extracellular protons trigger a novel form of neuronal necroptosis *via* ASIC1a. Indeed, they identified serine/threonine kinase receptor interaction protein 1 (RIP1) as a critical component of this form of neuronal necroptosis. Acid stimulation recruits RIP1 to the ASIC1a C-terminus, causing RIP1 phosphorylation and subsequent neuronal death [105]. Arguments used to support the point that the role of ASIC1a is independent of the ion-conducting function include the following [105]:

1. Pretreatment of cultured mouse cortical neurons with mild acidification (pH 6.8) greatly suppresses the ASIC currents evoked by greater acidification (pH 6); however, this fails to prevent acid-induced neuronal death [105].
2. Removing Ca^{2+} from the treatment solution has no clear protective effect on acid-induced neuronal death [105].
3. Although co-administration of the non-specific ASIC blocker amiloride with acid significantly inhibits ASIC-currents, it does not show neuroprotection [105].

This study has been recently expanded by revealing an auto-inhibitory mechanism that regulates interactions between the N-terminus (NT) and C-terminus (CT) of the ASIC1a protein, in particular, by using fluorescence resonance energy transfer [113]. Disruption of this auto-inhibition underlies conformational signaling of ASIC1a to induce neuronal necroptosis; a synthetic membrane-penetrating peptide representing the distal NT of ASIC1a has been identified as protective in both acidosis-induced necroptosis *in vitro* and a mouse model of ischemic stroke [113]. These results suggest a therapeutic potential of targeting the

auto-inhibition of ASIC1a for neuroprotection against acidotoxicity [113]. This study also provided additional evidence that the role of ASIC1a in necroptosis is independent of the ion-conducting activity. Indeed, acid treatment mediates cell death in mutants with non-conducting ASIC1a just as in wild-type animals [113].

Chronic Pain

Chronic pain is a challenging clinical problem affecting millions of people worldwide. It is well established that ASICs play important roles in nociception at peripheral and spinal neurons [2, 12]. However, the role of these channels in pain perception at the supraspinal level is less studied. Still, recent findings [28] indicate that brain ASIC1 does contribute to pain perception, making it an attractive therapeutic target for chronic pain management. Several lines of evidence support an important role of cortically-located ASIC1a channels in pain hypersensitivity by promoting long-term synaptic potentiation in the anterior cingulate cortex [28]. In particular, region-specific genetic deletion or pharmacological blockade of ASIC1a results in attenuated heat and mechanical hypersensitivity in the CFA model of inflammatory pain, while at the cellular level it reduces the probability of LTP induction in this brain area [28]. It has been concluded that ASIC1a critically gates pain sensitivity by regulating the probability of cingulate LTP induction, in which $\text{PKC}\lambda$ serves as a crucial mediator [28].

Epilepsy

Epilepsy, a disorder of unprovoked seizures, is a multifaceted disease affecting individuals of all ages with a particular predilection for the very young and old [114]. In addition to seizures, many patients often report cognitive and psychiatric problems associated with both the seizures themselves and their therapy [114]. About 1% of the human population suffers from chronic epilepsy disorder and 30–40% of patients develop drug-resistant epilepsy. Therefore, finding new targets for pharmacological intervention to treat patients with epilepsy is very important.

During and following seizures, lactic and glutamic acids are released into the extracellular space, causing a significant fall in pH that activates ASICs [115–117]. These results imply that ASICs may be involved in the regulation of epileptic discharges. On the other hand, the exact role of ASICs in such discharges is rather controversial. Some authors suggest that acidification diminishes seizure severity due to the more pronounced ASIC-dependent activation of inhibitory GABAergic interneurons by acidification as compared to excitatory glutamatergic cells [118]. Consistent with this idea, ASIC density on hippocampal inhibitory neurons is higher than on principal neurons, and the loss of ASIC1a

reduces postictal depression [118]. Other studies have demonstrated that inhibition of ASIC activity reduces epileptic manifestations in *in vitro* models of epilepsy: perfusion of hippocampal slices with amiloride or PcTx1 reduces the epileptic discharges evoked by electrical stimulation or removal of extracellular Mg^{2+} and hippocampal slices from ASIC1a-knockout mice are less susceptible to seizures [119]. Similarly, the application of the novel ASIC1 antagonist compound **5b** to rat hippocampal slices during epileptic activity significantly and reversibly reduces the frequency of seizure discharges [107]. In addition, in an *in vivo* model of epilepsy, selective ASIC antagonists reduce the seizure-like activity evoked by the injection of kainic acid into the amygdala or hippocampus [107, 119].

Neurodegenerative Diseases

In spite of many differences, neurodegenerative diseases have several similarities including accumulation of misfolded proteins, damage to specific neuronal populations, neuroinflammation, and persistent acidification [120]. Neuroinflammation is a complex process that occurs in various neurodegenerative diseases such as Alzheimer's disease (AD), PD, MS, and Huntington's disease (HD) [120]. Moreover, there is growing evidence suggesting that neuroinflammation is among the important causes of neurodegenerative diseases [120–122]. Inflammatory stimuli, such as ATP, lactic acid, arachidonic acid (AA), agmatine, and hypertonicity, are able to enhance the proton-induced ASIC current [121], whereas persistent acidification accompanies neurodegenerative diseases.

In addition, it has been demonstrated that ASICs: (1) mediate a component of synaptic current at glutamatergic synapses as postsynaptic ionotropic receptors for protons [26–29]; (2) play a role in the regulation of synaptic transmission at glutamatergic [59, 123] and GABAergic [107, 124], synapses; and (3) are involved in short- and long-term plasticity [26, 28, 52, 59].

Therefore, ASICs are considered to be potential targets for the treatment of neurodegenerative diseases, and promising results have been obtained as briefly outlined below.

Alzheimer's Disease

AD is a progressive neurodegenerative disorder, the most common form of dementia, accounting for 60–70% of all cases [125]. In spite of many attempts, currently there are still only symptomatic treatments available for this disease; no drugs capable of arresting or reversing it have so far been identified [125, 126].

While the question regarding the primary cause of the disease is still debated, it is widely accepted that the progression of AD occurs due to multiple factors. There is emerging

evidence that the activation of ASICs may be one of these factors (reviewed recently [22, 120]). Here, we only note that observational studies in humans, though indirect, corroborate this view. Amiloride, a non-specific blocker of ASICs, is a well-known K^+ -sparing diuretic used in medical practice. The use of diuretics, including amiloride, is associated with a reduced risk of AD [127, 128]. Moreover, while all antihypertensive drugs are associated with a decrease in AD risk, K^+ -sparing diuretics (including amiloride) are associated with the greatest reduction of this risk [127].

A selective antagonist of ASIC1a, PcTx1, inhibits the mGlu receptor-dependent long-term depression recorded in hippocampal slices, which were either treated with $A\beta$ oligomers or obtained from the Tg2576 mouse model of AD [129]. Curcuminoids, considered a treatment for AD [126], block ASICs [130]. In this regard, it is also interesting to note that memantine, one of the very few drugs approved for the amelioration of AD, apart from its blocking action on NMDA receptors (believed to be its primary mechanism of action) also affects ASICs [131].

Multiple Sclerosis

MS is a chronic autoimmune inflammatory disease of the CNS that involves demyelination and axonal degeneration [132]. ASIC1a is upregulated in the brain tissue of patients with MS [133]. Similarly, ASIC1a is upregulated in oligodendrocytes and axons in a mouse model of MS (acute autoimmune encephalomyelitis, EAE) [133]. The enhanced expression of ASIC1 is associated with axonal damage while blocking these channels with amiloride protects both myelin and neurons from damage in this model [133]. These results are in line with evidence obtained elsewhere [134]. After induction of EAE, ASIC1-/- mice show both a markedly reduced clinical deficit and reduced axonal degeneration compared to wild-type animals [134]. ASIC1 disruption is also protective against acidosis-mediated injury in nerve explants *in vitro* [134]. Importantly, evidence supporting the neuroprotective effect of amiloride has been obtained from a cohort of MS patients [135].

Parkinson's Disease

PD is a progressive neurodegenerative disorder resulting from a pathological loss or degeneration of dopaminergic neurons in the substantia nigra of the midbrain and the development of neuronal Lewy bodies [136]. The potential role of ASICs in PD has been studied in a mouse model of degeneration induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [137]. Amiloride has been found to protect substantia nigra neurons from MPTP-induced degeneration. Administration of the selective ASIC1a antagonist

PcTx1 is also protective, resulting, however, in a much more modest effect [137].

Huntington's Disease

HD is a neurodegenerative disease caused by CAG (cytosine, adenine, and guanine) repeat expansion in the *huntingtin* gene and involves multiple pathogenic mechanisms [138]. There is evidence indicating that acidification-induced activation of ASIC1a may be one of these mechanisms [139]. In particular, in the R6/2 mouse model of HD, it has been shown that the amiloride derivative benzamil increases the activity of the ubiquitin–proteasome system, resulting in enhanced degradation of soluble huntingtin–polyglutamine aggregation [139]. Similarly, blocking the expression of ASIC1a leads to an enhancement of ubiquitin–proteasome system activity and this blockade also decreases huntingtin–polyglutamine aggregation in the striatum of R6/2 mice [139].

Psychiatric Disorders

There is not much data on the role of ASICs in psychiatric disorders. Nonetheless, ASIC1a inhibition (genetic or pharmacological) reduces depression-like behavior in mice [140] and rats [141]. Thus, ASIC1a has been proposed as a potential target to combat depression. At the same time, there is no evidence of the role of ASICs in anxiety or depressive behavior in patients. Despite this fact, using the ASIC blocker amiloride in the form of a nasal spray is considered to be a treatment for anxiety disorders [142].

ASIC1/2 inhibition reduces the freezing response to hypercarbia [62, 67]. An increase in CO₂ in the inhaled air can induce a panic attack. Interestingly, the genetic variation of ASIC1a and ASIC2 structure is related to the individual differences in the panic response to an increased CO₂ concentration [143]. In addition, a specific ASIC1 polymorphism (rs685012) is more frequent in patients with panic disorder than in healthy controls [144].

Protective Effects of Blocking ASICs in Spite of Slow Acidification in Pathologies: Potential Explanations

The roles of ASICs in several fundamental physiological processes as well as in numerous pathologies have been well documented. However, in contrast to pathologies, the roles of ASICs in physiological processes are easier to explain because rapid (though brief) changes in pH occur under physiological conditions. In particular, the latter is applicable to synapses ([56, 145, 146], but see [147] for conflicting evidence), where rapid acidification occurring during

synaptic vesicle release can activate ASICs on both pre- and postsynaptic neurons [24]. Pathologies, on the other hand, are typically associated with slow and prolonged acidification, raising the question of how rapidly inactivating ASICs can contribute substantially to these pathologies.

Evidence regarding potential mechanisms relevant to this question can be subdivided into two broad categories: (1) conformational signaling of the ASIC independent of its ion-conducting function (as suggested for the role of ASIC1a in necroptosis [105, 113]), and (2) activation and decreased steady-state desensitization of ASICs by pro-inflammatory and algescic endogenous mediators.

Regarding conformational signaling *via* ASIC1a, the above results of Wang and colleagues [105, 113] indicate that conformational signaling involving ASIC1a induces neuronal necroptosis in *in vitro* and *in vivo* models of ischemic stroke. This signaling recruits RIP1 and is independent of the ion-conducting function of ASIC1a [113]. At the same time, these studies do not exclude the therapeutic potential of targeting ASIC1a in ischemic stroke with known blockers of this channel. Indeed, in contrast to co-administration, pretreatment with amiloride did show neuroprotection in the same study [105]. PcTx1, which is believed to inhibit ASIC1a activation by causing steady-state channel desensitization at neutral and alkaline pH (in contrast to mild acidification) is also neuroprotective [105]. An explanation of these results taken altogether is not straightforward. In addition, it should be noted that, while no clear protective effect of removing Ca²⁺ from the treatment solution on acid-induced neuronal death was reported by Wang *et al.* [105], the opposite results were reported in another study [104]. Thus, further studies are required to address these controversial issues.

As for pro-inflammatory and algescic endogenous mediators that enhance the activity of ASICs, there is growing evidence that numerous endogenous substances (such as lactate, AA, FMRFamide-related peptides—peptides related to mammalian RFamide transmitters, dynorphins, nitric oxide, and histamine), up-modulate ASICs, and the extracellular levels of these substances are increased in pathological states (see [121, 148, 149] for reviews). For instance, endogenous cationic polyamine spermine enhances ASIC1a and ASIC1b currents by decreasing the pH sensitivity of channel steady-state desensitization [54]. Moreover, *via* its effect on ASIC1a, increased extracellular spermine exacerbates neuronal damage following ischemic stroke [54]. AA, a polyunsaturated fatty acid, involved in cellular signaling activities as a lipid second messenger, plays a critical role in pathological conditions such as inflammation and neurological disorders [149]. AA regulates the activity of ASICs [150]. Indeed, in the cerebellum, AA significantly enhances the sustained component of current induced by acidification and increases the fraction of cells exhibiting

a sustained component [150]. It should be noted, however, that this sustained component of current is insensitive to amiloride [150], raising the question of whether it is mediated by ASICs. The ASIC currents are also potentiated by lactate, and released in ischemia, and by FMRFamide [150]. Another endogenous mediator, histamine, directly and selectively potentiates ASIC1a homomers, most effectively when applied at modest levels of acidification [151].

P2X Receptors in Brain Pathologies

P2X receptors are widely expressed by both neurons and glia in various brain regions, indicating their crucial role in physiological and pathophysiological brain function. Following world pharma's patent applications [152, 153] and recent numerous studies [154, 155], the P2X7 receptor is the most prominent drug target for numerous CNS diseases, especially those accompanied by inflammation [155, 156]. Brain P2X7 and P2X3 receptors participate in central pain transmission. P2X7 receptors are involved in the modulation of diabetes-induced neuropathic pain [157], whereas P2X3 (traditional primary nociception receptor) expressed in the midbrain periaqueductal gray is involved in the modulation of central post-stroke pain [158]. One could think that the P2X7 subunit is the sole one involved in almost all brain disorders. However, we suggest that the role of other subtypes of these receptors in brain disorders, particularly P2X4, which is more sensitive to ATP than P2X7 [79], is still underestimated.

Neuroinflammation, Ischemia, Stroke, Epilepsy, and COVID-19

Under healthy conditions, the concentration of extracellular ATP in tissues is in the nanomolar range [159]. However, under stress, hyperexcitability, ischemia, and cellular damage, the ATP concentration increases considerably, resulting in the activation of P2X receptors. In high concentrations, extracellular ATP activates P2X7 receptors that are highly expressed in microglial cells [159–161]. This results in the activation of transcription factor NF- κ B, which consequently promotes the upregulation of the pro-inflammatory cytokines, pro-IL-1 β and pro-IL-18, and NLRP3 protein. It has been shown that the P2X7 receptor is one of the most potent activators of the NLRP3-associated inflammasome [160]. The latter triggers the activation of caspase-1, which causes the maturation of IL-1 β and IL-18 and, consequently, increases pro-inflammatory cytokine release [160, 162]. A recent study demonstrated that inhibition of P2X7 by the selective antagonist, JNJ-55308942, suppresses the development of neuroinflammation induced in different rodent

models by lipopolysaccharide, Bacillus Calmette–Guerin, or chronic stress [162].

Brain ischemia induces ATP release and the subsequent activation of P2X receptors that conduct inward cationic current through the plasma membrane. However, despite their higher sensitivity to ATP than P2X7 [79], the contribution of P2X4 receptors to this current is virtually undetermined. Acute ischemia promotes the upregulation of P2X4 receptors in microglia or infiltrating macrophages [163, 164]. Activation of these receptors modulates the inflammatory response after stroke [165]. Correspondingly, a potent inhibitor of inflammation, minocycline, attenuates the upregulation of P2X4 receptors induced by hypoxia-ischemia [166]. Specific deletion of P2X4 is acutely neuroprotective and leads to a substantial reduction of infarct volume [165]. On the other hand, it predisposes depression-like behavior chronically after stroke due reduced expression of brain-derived neurotrophic factor (BDNF) [165]. Recent data show that P2X4 receptors are required for ischemic tolerance following middle cerebral artery occlusion in mice [167]. In contrast, blocking P2X4 receptors by TNP-ATP (but not PPADS that presumably inhibits P2X1-3 and P2X5-7 receptors) in a rat model of neonatal hypoxia shows a profound neuroprotective effect, pointing to the differences in P2X receptor function in ontogenesis [168].

There is a growing body of evidence for the role of ATP as well as P2X receptors in status epilepticus (SE) and epilepsy. Some studies report that extracellular ATP increases during SE and seizures, but this effect requires further examination [169]. Mice lacking P2X4 receptors display a decrease in neuronal death after SE, although seizure activity is not altered by the knockout of the corresponding gene [170]. In addition, the administration of P2X7 antagonists has been shown to have anticonvulsive effects in several experimental models of SE and acute seizures [171–175]. Genetic deletion of P2X7 receptors and inhibition of their activity by antibodies also suppress seizures in the kainic acid model of epilepsy [171]. Following SE, there is a prominent increase in P2X7 receptors and downregulation of P2X2 receptors in hippocampal neurons, particularly granule neurons, and microglia [171, 176]. It has also been reported that P2X4 receptors are upregulated in hippocampal microglia after SE in rats [170]. Upregulation of P2X3 receptor expression has also been shown in the LiCl-pilocarpine rat model of chronic epilepsy, as well as in patients with temporal lobe epilepsy [177]. The authors found that activation of P2X3 receptors accelerates sustained repetitive firing, while their inhibition results in relatively low-frequency discharges [177]. These data were later confirmed using the pentylene-tetrazole-induced animal model of epilepsy. Administration of the P2X3 antagonist NF110 significantly and dose-dependently ameliorates pentylene-tetrazole-induced impairments in behavior, learning, memory,

locomotion, motor activity, discrimination, neuronal damage, hippocampal inflammation, oxidative stress, and mitochondrial dysfunction. These effects of NF10 are notably abolished by administration of the selective P2X3 agonist α,β -methylene ATP [178]. Growing data indicate that certain P2X receptors may be novel drug targets for seizure control.

The ATP release induced by the SARS-CoV-2 virus has recently been proposed to play a key role in the genesis of both the main symptoms and sequelae of the novel coronavirus disease COVID-19 [179]. According to recent findings, COVID-19 is associated with a number of severe consequences, including "brain fog", depression, confusion, stroke, and more [180–182]. The metallopeptidase named angiotensin-converting enzyme 2 has been identified as the functional receptor for SARS-CoV-2. It is highly expressed in lung alveolar epithelial cells and enterocytes of the small intestine, being also present in the brain neurons, glial cells, and microglia [181–184]. P2X7 receptors, which are known to induce the secretion of pro-inflammatory cytokines in response to elevated ATP levels, are abundantly expressed in both macrophages and microglia, suggesting that these receptors can be a potential target for treating COVID-19 [185].

Neurodegenerative Disorders

Alzheimer's Disease

Some authors have proposed that ATP participates in the inflammatory process widely described in AD [186, 187] while others suggest that ATP, leaking through cell membrane pores made by soluble amyloid- β (A β) peptide, could participate directly through some P2X receptors [188, 189]. Numerous reports indicate that the P2X7 receptor plays a crucial role in AD, and its inhibition ameliorates the neuronal damage induced by both neuroimmune response activation [190–192] and reactive oxygen species production [193, 194]. There has been some conflicting information on the effect of these receptors on α -secretase activity, which cleaves amyloid precursor protein within the A β domain, thereby preventing the generation of A β . Two studies have shown that inhibition of P2X7 receptors leads to an increase in α -secretase activity through inhibition of glycogen synthase kinase 3 [195, 196]. However, results from Delarasse *et al.* revealed the opposite effect: P2X7 receptor stimulation may enhance α -secretase activity [197]. It has been reported that systemic administration of a P2X7 receptor antagonist, Brilliant Blue G, diminishes the spatial memory impairment and cognitive deficits induced by the injection of soluble A β 1-42 into the hippocampal CA1 region of mice, which is an animal model of AD [198]. P2X4 overexpression in the neurons enhances the toxic effect of A β 1-42, whereas

its silencing decreases cellular death after exposure to A β 1-42, indicating that this P2X subtype also contributes to the neuronal cell death induced by A β [199]. A recent paper suggests that P2X2 receptor expression increases in the brain of patients with AD, so it may participate in the toxic cellular and molecular events induced by A β [200]. In addition, the overexpression of P2X2 increases A β levels in a cellular model of AD [200]. We can conclude that the P2X4 and P2X7 receptors are important prospective targets in the treatment of AD.

Parkinson's Disease

The cause and pathogenesis of PD remain elusive. The neurotoxin 6-hydroxydopamine (6-OHDA) is widely used to induce models of PD. Recently it has been shown that 6-OHDA increases ATP release and its extracellular conversion into adenosine through CD73 upregulation in SH-SY5Y cells [201]. P2X7 receptor inhibition has neuroprotective and neuroregenerative effects in various models of PD through anti-inflammatory actions along with modulation of the microglial activation state and cytokine release [202–205]. Also, overexpression of P2X4 receptors upregulates IL-6 and exacerbates 6-OHDA-induced dopaminergic degeneration in the rat model of PD [206]. A very recent paper suggests that P2X4 receptor activation might inhibit neuronal autophagy through regulation of the BDNF/TrkB signaling pathway, leading to dopaminergic neuron damage in the substantia nigra and the further inhibition of P2X4-mediated autophagy [207]. A role for P2X1 receptors in PD pathogenesis has also been reported, perhaps identifying a new therapeutic target [208, 209]. Consequently, P2X7, P2X4, and P2X1 receptors are interesting research subjects and might be possible targets for PD treatment.

Huntington's Disease

We found only a few reports on the role of P2X receptors in HD. The first study demonstrated that P2X7 receptor expression is substantially increased in two HD animal models, also its channel pore has augmented Ca²⁺ permeability, and finally, its inhibition with Brilliant Blue G lessens the motor coordination deficits and cachexia and decreases neuronal loss [210]. The most recent paper reported elevated expression of the P2X7 receptor in the human postmortem striatum as well as alteration of its splicing [211], pointing to the important role of this receptor in HD.

Amyotrophic Lateral Sclerosis

The first experimental findings on the role of P2X receptors in ALS demonstrated a significant increase in P2X7 immunoreactivity in active microglia from postmortem

spinal cords of patients with sporadic ALS [212]. Similarly, increased immunoreactivity for P2X7 has been found in an animal model of familial ALS, the SOD1-G93A mouse [213], while increased P2X4 receptor immunoreactivity is associated with degenerating neurons [214]. In addition, it has been shown that the allosteric modulator of the P2X4 receptor ivermectin extends the lifespan of SOD1-G93A mice by almost 10% [215]. P2X7 is known to play a complex role in ALS [216]: while knockout of P2X7 accelerates the disease in SOD1-G93A mice [217], antagonism immediately preceding the onset of symptoms partially ameliorates the motor neuron loss and inflammation [217]. Later it has been reported that P2X7 participates in ALS pathogenesis by directly modulating autophagy and particularly the expression of autophagosome component LC3-II and the autophagy receptor p62 in SOD1-G93A microglia [218]. These findings support the idea that P2X7 receptors might be one of the top targets in a multidrug strategy for ALS treatment.

Multiple Sclerosis

MS is an autoimmune disease with an unknown etiology. It is characterized by massive infiltration of immune cells, demyelination, axonal loss, and chronic inflammation that induces ATP release in lesions. It has been reported that both P2X4 [219] and P2X7 [220] receptors are strongly overexpressed in MS lesions in humans. Recently-found genetic mutations of P2X receptors support their role in MS: a rare P2X7 variant, Arg307Gln, with absent pore formation and function protects against neuroinflammation in MS [221]; and a rare P2X7 Gly150Arg–P2X4 Tyr315Cys haplotype which inhibits P2X7-mediated phagocytosis has been suggested as a risk factor for MS [222]. EAE has been extensively used as a model of MS for many decades. It has been shown that in chronic EAE in mice, inhibition of P2X4 receptors with TNP-ATP leads to exacerbation of the clinical signs, whereas their allosteric potentiation with ivermectin has the opposite effect [223]. Blockade of P2X7 receptors results in suppression of demyelination and axonal damage, reduction of gliosis, and amelioration of neurological symptoms in chronic EAE [224–226]. These data support the crucial role of P2X4 and P2X7 in MS pathology.

Psychiatric Disorders

There is growing evidence of a possible role of P2X receptors in various psychiatric disorders including major depressive disorder (MDD), bipolar disorder (BD), schizophrenia (SCZ), anxiety, and autism spectrum disorder (ASD) [99, 154, 227, 228]. For several psychiatric diseases, such as MDD, SCZ, and BD, it has been postulated that activation

of the P2X7 receptor by ATP release mediates brain inflammation [229–231].

Both P2X2 and P2X7 receptors play an important role in depression disorders. P2X2 receptors in the medial prefrontal cortex mediate the antidepressant-like effects of ATP [232], whereas P2X7 receptors activated by synaptic ATP release stimulate the hyperactivation of microglia and interleukin-1 β production reported in depressive-like behaviors [231]. In turn, their inhibition by Brilliant Blue G as well as knockout of the corresponding gene has antidepressant effects [233–235]. Only a few data are available on the role of P2X7 receptors in SCZ. One study showed that the tricyclic antipsychotics prochlorperazine and trifluoperazine induce allosteric inhibition of human P2X7 receptor activity [236]. Therefore, one may speculate that the antipsychotic-induced inhibition of the P2X7 receptor contributes to therapeutic efficacy [230, 237]. P2X receptors are also involved in BD: the animal model of mania induced by chronic administration of amphetamine, pharmacological blockade with A-438079 and genetic deletion of P2X7 receptor completely reverses the increased locomotor activity induced by amphetamine [229]. A-438079 also abolishes the release of the pro-inflammatory cytokines IL-1 β and TNF- α as well as lipid peroxidation in the hippocampus [229]. P2X receptor actions have also been implicated in ASD. Genetic deletion of the P2X4 receptor results in a significant reduction in sensory and social task performance, vocalization responses, and plausible deficit in the ability to extract and filter relevant information from the external milieu, suggesting that P2X4 receptors regulate information processing [238] as well as perceptual and socio-communicative functions [239]. Downregulation of P2X7 and P2Y2 receptor expression has been described as a compensatory response in an animal model of ASD [240].

In summary, the role of P2X receptors in psychiatric disorders requires additional studies, especially regarding P2X2, P2X3, P2X4, and P2X7 subtypes that are strongly associated with neurodevelopment and psychiatric disorders [241, 242].

A Plausible Link between ASICs and P2X Receptors in Brain Disorders

Apart from the differences between ASICs and P2X receptors, as previously stated, there are also similarities, including trimeric structure, similarity in the pore architecture, and ionic permeability [6]. While emerging evidence indicates interactions of ASICs and P2X receptors in sensory neurons [36, 37], their possible roles in brain functions and pathologies are still virtually unexplored. The overlap of brain pathologies mediated (potentially) by ASICs/P2X receptors (Table 2, Fig. 3) suggests that such interactions may be relevant to brain pathologies as well.

Table 2 Evidence supporting the involvement of brain ASICs or P2X receptors in pathologies

Pathology	ASICs	P2X receptors
Ischemic stroke	Inhibition of ASIC1a protects the brain from ischemic injury [104, 112], ASIC1a is involved in ischemic-induced damage [105, 113]	Acute ischemia up-regulates P2X4R in microglia or macrophages [163, 164] P2X4R inhibition has a neuroprotective effect [165, 168]
Chronic pain	Brain ASIC1a contributes to the processing of pain, its block may be analgesic [28]	Brain P2X7R contributes to central post-stroke pain [158] whereas brain P2X3R in diabetes-induced neuropathic pain [157]
Epilepsy	Inhibition of ASIC1a reduces the probability of paroxysmal discharges [107, 112] (However) ASIC1a activation limits the duration and progression of seizures [118]	P2X4R is up-regulated, and its deletion decreases neuronal death [170] P2X7R inactivation has the anticonvulsive effect [171–175]
Alzheimer's disease	Use of amiloride is associated with reduced risk of AD [127, 128] PcTx1 rescued the synaptic plasticity associated with genetic and non-genetic models of AD [129] Memantine, one of the very few drugs approved for amelioration of AD, apart from its blocking action on NMDA-receptor also affects ASICs [131]	P2X7R mediates neuroinflammation, and its inhibition ameliorates neuronal damage [190–194] and diminishes spatial memory impairment and cognitive deficits [198] Overexpression of P2X4R in neurons enhanced the A β toxic effect, while its silencing decreased A β associated cellular death [199] P2X2R is up-regulated in AD [200]
Multiple sclerosis	Upregulation of ASIC1a is associated with the disease, and ASIC1 inhibition has a protective role [133–135]	P2X4R and P2X7R are overexpressed in human patients [219, 220] P2X7R genetic variants may be neuroprotective [221] or a risk factor [222] P2X7R inactivation reduces the symptoms in EAE [224–226] P2X4 inhibition potentiates the symptoms in EAE, allosteric potentiation with ivermectin has the opposite effect [223]
Parkinson's disease	ASIC1a inhibition has a protective effect [137]	P2X7R inhibition shows a neuroprotective effect [202–205] Overexpression or activation of P2X4Rs is associated with increased dopaminergic degeneration [206, 207] P2X1R mediates an increase in alpha-synuclein in response to ATP [208]
Huntington's disease	Amiloride derivative benzamil enhances the activity of the ubiquitin-proteasome system [139] Blocking the expression of ASIC1a has a similar effect [139]	P2X7 expression is increased in HD, its inhibition decreases symptoms and neuronal loss [210, 211]
Amyotrophic lateral sclerosis		P2X7R is up-regulated in mice [213] and human patients [212] Its role in ALS genesis and progression is dual and complex [217] P2X4 is increased in degenerating motoneurons [214] P2X4 allosteric modulator ivermectin extends the life span in ALS mice [215]
Psychiatric disorders	ASIC1a inhibition decrease depression-like behavior in mice [140, 141] ASIC1/2 genetic variation is related to individual differences in panic response [143, 144]	P2X2Rs mediate the antidepressant-like effects of ATP [232] P2X7Rs stimulate the hyperactivation of microglia associated with depressive-like behaviors [231] P2X7 inhibition has antidepressant effects [233–235] P2X7R inhibition normalizes locomotor activity in the bipolar disorder model [229] P2X7R mediates the positive effects of antipurinergic therapy in the autism spectrum disorder model [240]

In this regard, it seems to be of interest to study the following questions: are ASICs and P2X co-localized in the brain? Are there interactions between ASICs and P2X in the brain? In particular, it may be of interest to study whether

such interactions could contribute to the enigma noted above as to how rapidly inactivating ASICs can substantially contribute to the pathologies that are typically associated with slow acidification. Regarding these issues, it should be

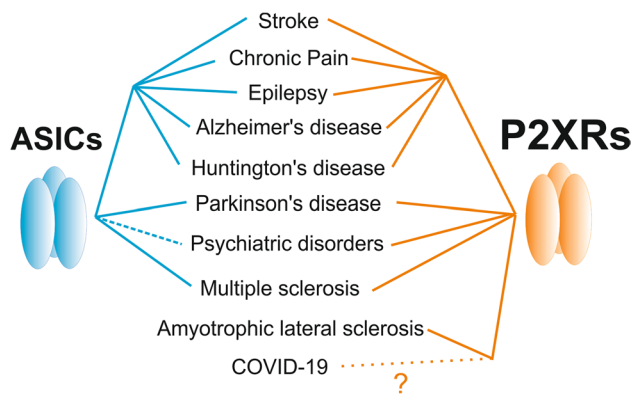


Fig. 3 ASICs and P2X receptors contribute to almost the same set of brain pathologies. Dashed lines indicate weak evidence or not much data available.

emphasized that although interactions of ASIC3 with P2X receptors have been a major focus of research in sensory neurons [36], nevertheless, “ASIC1 can also be sensitized through P2X receptors” [36].

Furthermore, given that novel technologies for investigating functional cell-surface ASIC1a channels have recently been developed and used to investigate the physiological roles of these channels in brain neurons [243], the application of such tools to investigating brain pathologies would be fascinating.

Conclusions

We felt the necessity of this review due to the quickly-expanding evidence on the physiological significance of the two receptor/channel families. This seems especially relevant for the ASICs.

Both families entered the “market of knowledge” substantially later than the more canonical families like cholino- or adrenoceptors. In both cases, the path to recognition of ASICs or P2 receptors was quite difficult and long. Geoffrey Burnstock made prolonged efforts to demonstrate the importance of the dual metabo- and ionotropic roles of purinoreceptors. After being cloned [39], ASICs became a subject of widespread interest 14 years after their initial discovery [38].

The last decade demonstrated that this subject was a long shot: it became clear that every neuron in the mammalian nervous system expresses at least one member of the ASIC family. Correspondingly, we are bound to expect a great variety of functional roles and new possibilities for pharmacology. Thus, new pharmacological tools, not only ASIC-specific but ASIC subunit-specific, will allow the specification of new roles of these receptors in known functions or even reveal new functions.

Both receptor families examined here provide intriguing opportunities in the novel realm of research connected with the roles of receptors traditionally regarded as ion channels. Growing evidence indicates that these receptors play important roles connected with intimate intermolecular machinery in the brain rather than just allowing ions passage.

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Conflict of interest The authors declare no competing interests.

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