Review Article

ACID SENSING ION CHANNELS (ASICS): POTENTIAL TARGETS FOR THE DISCOVERY OF NOVEL THERAPEUTICS IN DISEASE MANAGEMENT

Debendra Nath Roy

Assistant Professor, Department of Pharmacy, Faculty of Biological Science and Technology, Jessore University of Science and Technology, Jessore-7408, Bangladesh.

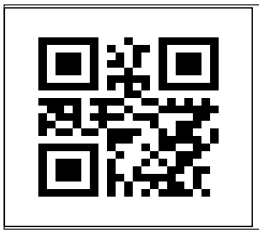
ABSTRACT

Acid sensing ion channels (ASIC) are Na+ channels activated by external protons. Number of neurological (pathological pain, expression of fear, anxiety, depression, and neurodegeneration after ischemic stroke etc) and non -neurological (brain tumor, cardiovascular mechanosensation, hypoxia induced hypertension, glaucoma, etc.) disorders are implicated by various ASICs subtypes. Due to their known and potential roles in many disease pathologies, it is very authentic to explore the importance of new and selective small molecule inhibitors and even activators of ASICs as a research tool in clinical uses for treating these diseases pathogenesis. This review is aimed to find out the therapeutic potentialities of ASICs targeted novel drugs in context of their pathophysiological role in human body. Fluorescent dyes and optical sensors as a means of fast and efficient screening approaches would certainly be used to improve the discovery technology of ASICs modulated drugs.

Keywords: Acid, ion channel, discovery, pharmacological, disease.

INTRODUCTION

The acid-sensing ion channels or ASICs form a distinct branch of the degenerin superfamily (ENaC/DEG) of sodium channels. At least four ASIC genes have been identified in humans so far, numbered 1–4, with a number of splice variants encoding a total of nine unique proteins [1-9]. The channels formed by the ASIC proteins are basically proton-gated cation channels, opening rapidly in the presence of extracellular acid. All ASIC subunit consists of a large extracellular domain, 2 transmembrane helices, and short cytoplasmic N and C termini. Functional ASICs are homo or heterotrimers of ASIC1a, ASIC1bASIC2a, ASIC2b, and/or ASIC3 subunits [10-11]. ASIC2b is not functional as homomultimer but form functional heteromeric channels in combination with other subunits [12]. The activity of ASIC4 channel has been detected very limited yet. It may participate in regulating the membrane availability of other ASIC subunits [13]. ASIC1a and ASIC3 are activated by an acidity range (pH 7.0-6.0) observed in several acute and chronic pain conditions. ASIC3 is particularly sensitive to lactic acidosis and thus is considered to be an important component of acid induced pain [14].



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It has been noticed that the activation of ASIC in neurons induce action potentials. The extent and duration of the ASIC-mediated depolarization depends both on ASIC amplitude activity and the number of charges the channels transport during their opening [15-16]. Among all others, ASIC3 is the most sensitive to increases in proton concentration, with half-maximal pH activation is 6.4 [17]. ASIC2 is the least sensitive, requiring exposure to pH 4.5 for half-maximal activation. ASICs have been detected throughout the nervous system, specifically in areas of high synaptic density, localizing primarily to the soma and processes of neurons [18-19]. Their expression pattern has suggested that these channels play a role in sensory perception and various neural processes [20-21]. ASICs have widespread distribution to many regions in the nervous system including dorsal root ganglia, cortex, hippocampus, basal ganglia, amygdale, olfactory bulb, cerebrum and elsewhere [22-24]. Interestingly, ASICs are increasingly being detected in nonneuronal settings including cancer cells [25], bone [26], intestinal and bladder epithelium cells and smooth muscle [27-30]. Because ASICs are permeable to Na+, their activation leads to membrane depolarization, thus inducing action potentials in neurons ASICs often have an activation effect on neurons. A strong ASIC-mediated depolarization, however, can inhibit an already actively signaling neuron. ASIC1a has a small permeability for Ca2+ in addition to its Na+ permeability, and some of its cellular functions, as for example neurodegeneration after ischem-

Corresponding author: Debendra Nath Roy, Department of Pharmacy, Faculty of Biological Science and Technology, Jessore University of Science and Technology, Jessore-7408, Bangladesh. Email: roydn009@gmail.com

ic stroke are thought to depend on a Ca2+ entry into the cell [31-36]. Expression pattern of ASIC subunits in different cells and tissue types of functional organization are represented in Table 1.

2. Pathophysiological role of acid-sensing ion channels

The abundance of ASICs in human body and their associated causative disorders are recently discovered by a wide range of research expertise. It is interesting to observe that both neurological and non-neurological pathologies these channels have been contributed equally to play their role.

2.1. Synaptic plasticity and learning: It is consistent with ASIC1a induced postsynaptic depolarization, and synaptic plasticity that, depending on the brain area, they either promote or inhibit plasticity.

2.2. Nociception and pain sensation: It occurs in the context of inflammation, mediated by acid-evoked ASIC currents in nociceptive neurons. ASICs in sensory neurons are therefore candidate receptors for acidification inducing pain. ASIC1a and ASIC2 are expressed in pain-processing areas of the CNS whereas peripheral ASIC3 and ASIC1 are involved in pain sensation. ASIC3 is responsible for chronic acidification related forms of pain and inflammation. Inter leukin-1 (IL-1), bradykinin and especially NGF, are called pro inflammatory mediators can enhance ASIC3 expression at the transcriptional level which is reflected by an increase in ASIC current in sensory neurons during pain sensation [37-38].

2.3. Fear and anxiety: It is result of pH change expression and is particularly high in the amygdale induced by ASIC1a. However, overexpression of ASIC1a increased fear related behavior.

2.4. Mechanosensation: Mechanosensation in the gastrointestinal system is important for the control of gastric coordination and emptying, colonic motility, and the sensation of pain. There is evidence of ASIC expression in primary sensory neurons and the afferents of mechanoreception. Heteromeric ASIC2a/ASIC2b channel has been implicated in sour taste sensing which essentially an acid taste type. It has been evident that the activation of the receptor by acid leads to depolarization of taste cells and transmitter release onto gustatory afferent neurons [39].

2.5. Neurodegenerative disorders: Ca2+ ion permeability of ASIC1a and tissue acidification is play a role in a handful number of neurodegenerative disease, including ischemic stroke [40], epileptic seizures [41-43] autoimmune encephalitis [44], Huntington`s [45] and Parkinson`s disease [46-47]. It has been proposed that blocking of ASICs gave a therapeutic time window of more than 5 h in rat models of focal ischemia and therefore makes them a great therapeutic target for stroke treatment [48].

2.6. Angina pain: Angina pain and ischemic damage following cardiac arrest has been associated with ASIC3 response in heart muscle. This is due to the cell bodies of neurons via dorsal root ganglia (DRG) towards heat responded to very low pH [49-50]. Recently it has

Table-1. Expression pattern of ASIC subunits in different cells and tissue types of their functional organization.

Tissue / Cell Type	ASIC Subunit			
	1	2	3	4
Astrocytes	x	x	x	x
Brain	x	x	x	
Chondrocytes, intervertebral discs	x		x	
Dorsal root ganglia	x	x	x	x
Esophagus	x	x	x	
Gastrointestinal tract	x	x	x	
Heart neurons		x	x	
Inner ear		x	x	
Keratinocytes		x		
Lung, AT1/ ATII cells, bronchus, nasal epithelium, Calu-3 cells			x	
Nodose ganglia	x	x		
Osteoblasts	x	x	x	
Pacinian corpuscles	x	x		
Retina	x	x	x	x
Taste buds	x	x	x	
Vascular smooth muscle	x	x	x	

been shown that this kinetics in DRG more closely resemble with currents associated with ASIC 2a/3 heteromers as well [51].

2.7. Development of chronic hypoxia-induced pulmonary hypertension: Although it is unknown whether an increase in ASIC1-mediated Ca2+ influx has a role for developing pulmonary hypertension but ASIC1 obviously contributes to enhanced receptor- mediated vasoconstriction and store operated Ca2+ ion entry in small pulmonary arteries, thereby ASIC1 activates to vasoconstrictor and chronic hypoxia-induced pulmonary hypertension [52] .

2.8: Cardiovascular mechanosensing and chemosensing regulation: The acid-sensing ion channel particularly ASIC1 and ASIC3 and to a lesser extent, ASIC2 proteins may play more ubiquitous roles in cardiovascular regulation considered previously. Recent findings suggest that ASICs may act as mechanosensors and chemosensors in arterial baroreceptor neurons of cardiovascular region. ASIC proteins may be act as chemo transducers in cardiac muscle tissue that can signal to initiate ischemic pain [53-54].

2.9. Cancer cell growth suppression:

2.9.1. Salivary gland metastasis: In salivary gland carcinoma cells, an ASIC2/3 heteromeric conductance has been observed that were absent in normal salivary gland epithelia [55]. To date, in case of colonic and brain malignancies, the involvement of ASICs were best found.

2.9.2. Gliomas: Gliomas are the most common primary brain tumors with a complex biology characterized by antigenic and genomic heterogeneity and tendency for invasion into central nervous system could diffusely infiltrate the normal brain tissues. Large amiloride-sensitive Na+ currents have been detected in aggressive brain tumors while in normal and low grade astrocytic tumors there is none. It was shown that the cells express both ASIC1 and ASIC2 whereas high grade astrocytoma express only ASIC1, indicating that ASIC2 may function as a kind of ASIC current suppressor and therefore a tumor suppressor. ASIC2 is not found in the plasma membrane of grade IV gliomas cells, called glioblastoma multiforme (GBM) thereby, ASIC2 Inhibits the Amiloride-sensitive current and migration of Glioma Cells in metastatic disease [25,56]. It is shown that an active degenerin mutant of ASIC2 could be delivered by virus to express malignant cells leading fast cell death by initiating unregulated influx of sodium ion [57]. A wide variety of disease pathologies in which ASICs are potential therapeutic targets of investigation (inhibition or at activation state) are as follows in Table-2.

Table 2. Major Disease pathologies in which ASICs are potential therapeutic targets of investigation.

Therapeutic Indication	ASIC Subunit			
	1	2	3	4
Angina			x	
Glioma (Tumor suppression)	x	x		
Cardiovascular regulation	x		x	
Pulmonary hypertension	x			
Anxiety	x			
Autoimmune encephalitis	x			
Mechanosensation		x		
Central modulation of pain	x	x		
Dental pain		x	x	
Deafness			x	
Epilepsy	x	x		x
GERD	x	x	x	
Glaucoma	x	x		
Pulmonary hypertension	x			
Huntington's disease	x	x		
IBD	x	x	x	
IBS	x	x	x	
Parkinson's disease	x	x		
Peripheral pain	x		x	
Retinitis pigmentosa		x	x	
Salivary gland carcinoma		x	x	
Stroke	x			
Sour taste sensing		x		

However, given the wide expression of ASICs proteins and their direct implication in multiple neurological and non- neurological disorders, it would be surprising that these channel subtypes form highly attractive targets for the prediction of novel treating outcomes.

Pharmacological agents available

Despite the fact that ASICs are promising pharmacological targets, no potent and selective ASIC inhibitors besides toxins are currently known. PhcrTx1 is the first compound characterized from the sea anemone *Phymanthus crucifer*, and it constitutes a novel ASIC inhibitor PhcrTx1 represents the first member of a new structural group of sea anemones toxins acting on ASIC [58]. These toxins have been instrumental to study the structure, properties, functional expression in above-mentioned physiopathological states. Hcr1b-1 and Hm3a both are peptide toxins similar to PcrTx1 are obtained from spider, snake and sea anemone venoms targeting for ASICs [59-60]. Dendrotoxins (DTx) are a group of peptide toxins purified from the venom of several mamba snakes and α-DTx selectivity and its potential interaction with ASICs should be taken in consideration for inhibiting ASICs induced current [61]. Recently discovered ASIC inhibitor compound 5b, one of the most potent inhibitors known to date, lacks subtype selectivity [62]. Quercetin, a plant derived polyphenolic flavonoid compound blocked homomeric ASIC1a, 2a and ASIC3 with an IC50 of about 2 mM [63].

Acid-sensing ion channels are directly modulated by a variety of compounds of synthetic, endogenous and natural origin. Chemically, there are three classes of ASIC inhibitors: metal ions, polypeptide toxins, and small-molecule inhibitors. Besides Ca2+ and Mg2+, a number of divalent and trivalent metal ions inhibit ASICs. The best know synthetic small molecule inhibitor of ASIC channels is amiloride, which inhibits also other targets and is a clinically used diuretic due to its inhibition of ENaC. Other molecules can also block ASIC channels with IC50 values

of the order of tens to hundreds of micromolar, including A- 317567, non-steroid anti- inflammatory drugs, local anesthetics, voltage-gated K+ channel blockers like 4-aminopyridine, and a few other compounds (streptomycin, neomycin, nafamostat mesilate, chloroquine and diarylamidines). Synthetic molecules like GMQ potentiate, or even activate, ASICs. The most selective modulators of ASIC channels are coming from animal venoms with highly selective cysteine-rich high-affinity polypeptide toxins that inhibit (Mambalgins, and to a certain extent APETx2) and sometimes activate (MitTx) these channels [64]. It has been shown human painful inflammatory exudates, displaying non-acidic pH; induce a slow constitutive activation of human ASIC3 channels. This effect is largely driven by lipids, and we identify lysophosphatidylcholine (LPC) and arachidonic acid (AA) as endogenous activators of ASIC3 in the absence of any extracellular acidification [65].

CONCLUSIONS

This mini review reveals pathophysiological roles of ASICs and their therapeutic candidates isolated in different laboratories. ASICs are containing in all parts of human body having immense desensitization characteristics, pharmacological properties and different abilities to interact with intra and extracellular factors which are making themselves in fact as like as a divers therapeutic indications purposes. These to indicate the ASIC channels an even more appealing drug target however. The fact is that, the ASIC channels are involved in numerous physiological and pathological conditions, their unique characteristics to allow exquisite selectivity makes them more appealing and attractive drug target for seeking lead compounds to predict a novel treatment outcome for severe diseases including vasoconstriction, angina, ischemic stroke, pain and inflammation, many psychiatric disorders and even in benign tumor growth alteration. Since the pharmacology of ASIC channels has made rapid progress in the last years, thereby few compounds have been isolated yet from sources of drugs availability. Unfortunately, still we don't have the selective and potent ASICs modulated drug to combat diseases in upcoming days. Therefore, in this review I have wanted to deliver a message regarding the vast importance of new therapeutic opportunities of ASICs due to their diverse pharmacological implications. It would be good to develop strategies of new screening approaches to discover small selective molecules for treating ASICs modulated disease pathogenesis and it would be achieved by inhibiting as well as possibly stimulation of these ion channels.

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