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Invited review

Acid-Sensing Ion Channels and nociception in the peripheral and central nervous systems

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ABSTRACT

Since their molecular cloning in the late 90's, Acid-Sensing Ion Channels (ASICs) have been shown to be involved in many aspects of nociception, both in peripheral and central neurons. In rodents, the combination of specific or non-specific pharmacological modulators of ASICs, together with *in vivo* knockdown and/or knockout animals has revealed their contribution to the detection, the modulation and the sensitization of the pain message by primary and secondary sensory neurons. Functional ASICs are homo or heterotrimers of different homologous subunits (ASIC1-3). Channels containing ASIC3 or ASIC1 subunits, appear to be important in peripheral nociceptors, where they are subject to intense regulation, while ASIC1a-containing channels also have a prominent role in central neurons, including spinal cord neurons that modulate and transmit the pain signal to the brain. In humans, experiments performed in healthy volunteers using drugs already used in the clinic and acting as poorly-selective inhibitors of ASICs, together with recent *in vitro* data obtained from stem cell–derived sensory neurons both support a role for these channels in nociception. These data thus suggest a real translational potential in the development of inhibitory strategies of ASICs for the treatment of pain.

This article is part of a Special Issue entitled 'ASIC Channels'.

1. Introduction

The first reports of proton-induced depolarizing sodium currents in sensory neurons came from the pioneering work of Krishtal and colleagues (Krishtal and Pidoplichko, 1981a) who suggested a key role for these channels in nociception (Krishtal and Pidoplichko, 1981b,c) (see the review by O. Krishtal in this special issue, Krishtal, 2015). The molecular basis of these currents remained however controversial until the cloning of Acid-Sensing Ion Channels (ASICs) in the late 90's (Waldmann et al., 1997b). Since then, a growing body of evidence has accumulated showing the important role of ASIC channels in nociception in both the peripheral and central nervous systems, which is the focus of this review. The biophysical properties of these channels are discussed in detail in another review by S. Gründer & M. Pusch in this special issue (Gründer and Pusch, 2015).

2. ASIC expression in the pain pathway

ASIC channels are largely expressed throughout the pain pathway, including peripheral and central neurons (Table 1). Most of the ASIC subunits (*i.e.*, ASIC1a and b, ASIC2a and b, and ASIC3) are present in rodent peripheral sensory neurons (Chen et al., 1998b; Mamet et al., 2002; Poirot et al., 2006; Voilley et al., 2001; Waldmann et al., 1997a), where ASIC1b and ASIC3 are almost exclusively expressed (Chen et al., 1998b; Waldmann et al., 1997a). ASICs have been detected in the soma and in the peripheral terminals of Dorsal Root Ganglia (DRG) neurons (Alvarez de la Rosa et al., 2002; Garcia-Anoveros et al., 2001; Price et al., 2000, 2001), but have not been detected (at least for ASIC1a and ASIC2a) in the central terminals in the dorsal horn of the spinal cord (Duan et al., 2007; Garcia-Anoveros et al., 2001).

Native ASIC currents in rat DRG neurons are mainly supported by ASIC1-type and ASIC3-type channels (Deval et al., 2011, 2008; Diochot et al., 2012; Mamet et al., 2002; Poirot et al., 2006). ASICs are also functionally expressed in the trigeminal (TG) (Yan et al., 2011) and nodose (NG) ganglia neurons (Sugiura et al., 2005). The levels of ASIC transcripts, including ASIC1a, ASIC1b, ASIC2a and

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Table 1
Tissue expression profile of the six ASIC subunits. Detection in the different species has been done by at least one of the methods listed in brackets. Note that the list is certainly not exhaustive and does not include functional data (e.g., electrophysiological characterization of native ASIC currents). Expression in some tissues that is based on a limited number of approaches (e.g., RT-PCR only) probably needs to be further characterized and functionally validated. Immunolocalization and Western blot data are highly dependent on the quality of the antibodies being used. Protein and/or transcript detection does not always differentiate between variants a and b of ASIC1 and ASIC2.

Subunits	Tissue expression profile (methods of detection)	References
ASIC1a	Rat, mouse and human brain *(NB, RT-PCR, ISH, WB, IHC)*	(1–4) (7–9) (17)
	Rat, mouse and human spinal cord *(northern blot, ISH, RT-PCR, IHC, WB)*	(7) (13) (14) (17) (19) (28)
	Rat, mouse, guinea pig and human DRG, TG and NG (*NB, RT-PCR, ISH, WB, IHC)*	(1) (3) (6) (7) (10) (11) (17) (27) (54)
	Rat and rabbit retina *(RT-PCR, ISH, WB, IHC)*	(4) (12) (24) (25)
	Rat astrocytes *(IHC, WB)*	(16)
	Human lung epithelial cells (*RT-PCR*)	(20)
	Rat cultured vascular smooth muscle cells (*RT-PCR*, IHC)	(21)
	Mouse immune cells (*RT-PCR, WB*)	(19)
	Rat microglia (*RT-PCR, WB, IHC)*	(18)
	Human bone cells (*RT-PCR)*	(26)
	Human gliomas (*RT-PCR)*	(22)
	Rat and mouse taste receptor cells (*RT-PCR)*	(23)
ASIC1b	Rat and mouse DRG *(NB, ISH, RT-PCR)*	(3) (5–7) (10)
	Mouse and guinea pig NG *(RT-PCR)*	(10) (27)
	Mouse immune cells (*RT-PCR, WB*)	(19)
	Rat taste receptor cells (*RT-PCR)*	(29)
	Rat carotid body (*RT-PCR, IHC)*	(30)
	Mouse cochlear hair cells (stereocilia) (*ISH, IHC)*	(31)
ASIC2a	Rat, mouse and human brain *(NB, ISH, RT-PCR)*	(2) (4) (7) (8) (17) (36)
	Rat, mouse and guinea pig DRG and NG *(RT-PCR, ISH, WB, IHC)*	(4–6) (11) (27) (32) (36) (54)
	Rat and mouse spinal cord *(NB, ISH, RT-PCR, WB, IHC)*	(4) (7) (13) (14) (28)
	Rat, mouse and rabbit retina *(RT-PCR, ISH, WB)*	(24) (25) (33)
	Mice spiral ganglion in the cochlea (*IHC*)	(35)
	Rat astrocytes *(IHC, WB)*	(16)
	Rat microglia (*RT-PCR, WB, IHC)*	(18)
	Human bone cells (*RT-PCR)*	(26) (33)
	Human lung epithelial cells (*RT-PCR*)	(20)
	Rat cultured vascular smooth muscle cells (*RT-PCR*, IHC)	(21)
	Human gliomas (*RT-PCR)*	(22)
	Rat taste receptor cells (*RT-PCR, IHC)*	(23) (34)
	Rat carotid body (*RT-PCR)*	(30)
ASIC2b	Rat and human brain *(NB, ISH, RT-PCR)*	(17) (36)
	Rat and mouse spinal cord *(RT-PCR, ISH)*	(14) (28)
	Rat and mouse DRG *(RT-PCR)*	(5) (6) (36)
	Guinea pig NG and JG *(RT-PCR)*	(27)
	Rat and mouse retina *(RT-PCR, ISH)*	(33) (24)
	Rat taste receptor cells (*RT-PCR, IHC)*	(34)
ASIC3	Rat, mouse and human DRG, TG and NG *(NB, ISH, RT-PCR, IHC)*	(3) (5–7) (11) (17) (37–42) (45–48) (52) (54) (56)
	Human brain, spinal cord, testis *(RT-PCR, NB)*	(17) (38)
	Rat and guinea pig vagal and glossopharyngeal ganglia *(IHC, RT-PCR)*	(27)
	Rat, mouse and rabbit retina *(RT-PCR, IHC)*	(24) (25) (43)
	Mouse chondrocytes and synoviocytes *(RT-PCR, IHC)*	(44) (55)
	Rat brain (hippocampus, amygdala, caudate putamen, cortex, hypothalamus) *(RT-PCR, WB, IHC)*	(46)
	Rat astrocytes *(IHC, WB)*	(16)
	Rat microglia (*RT-PCR, WB, IHC)*	(18)
	Mouse adipocytes (*RT-PCR)*	(49)
	Mouse immune cells (*RT-PCR*)	(19)
	Human lung epithelial cells (*RT-PCR*, IHC)	(20)
	Human bone, cartilage and teeth (*RT-PCR)*	(26) (50)
	Rat cultured vascular smooth muscle cells (*RT-PCR*, IHC)	(21) (26)
	Rat and mouse taste receptor cells (*RT-PCR)*	(23) (44)
	Mouse inner ear (*RT-PCR, ISH, IHC)*	(53)
	Rat carotid body (*RT-PCR, IHC)*	(30)
ASIC4	Mouse brain and spinal cord *(NB)*	(7)
	Human brain, inner ear and pituitary gland (*NB, RT-PCR)*	(51)
	Mouse immune cells (*RT-PCR*)	(19)
	Rat and rabbit retina (*RT-PCR*)	(24) (25)

Abbreviations: DRG: Dorsal Root Ganglia, TG: Trigeminal ganglia, NG: Nodose Ganglia, JG: jugular ganglia; NB: *northern blot*; ISH: *in situ hybridization*; IHC: *immunolocalization*; WB: *Western blot*; RT-PCR: *Reverse Transcriptase – Polymerase Chain Reaction* (quantitative or not).

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