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Acid-sensitive ion channels and receptors

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Abstract

Acidosis is a noxious condition associated with inflammation, ischaemia or defective acid containment. As a consequence, acid sensing has evolved as an important property of afferent neurons with unmyelinated and thinly myelinated nerve fibres. Protons evoke multiple currents in primary afferent neurons, which are carried by several acid-sensitive ion channels. Among these, acid-sensing ion channels (ASICs) and transient receptor potential (TRP) vanilloid-1 (TRPV1) ion channels have been most thoroughly studied. ASICs survey moderate decreases in extracellular pH whereas TRPV1 is activated only by severe acidosis resulting in pH values below 6. Two-pore domain K^+ (K_{2P}) channels are differentially regulated by small deviations of extra- or intracellular pH from physiological levels. Other acid-sensitive channels comprise TRPV4, TRPC4, TRPC5, TRPP2 (PKD2L1), ionotropic purinoceptors (P2X), inward rectifier K^+ channels, voltage-activated K^+ channels, L-type Ca^{2+} channels, hyperpolarization-activated cyclic nucleotide-gated channels, gap junction channels, and Cl^- channels. In addition, acid-sensitive G protein-coupled receptors have also been identified. Most of these molecular acid sensors are expressed by primary sensory neurons, although to different degrees and in various combinations. Emerging evidence indicates that many of the acid-sensitive ion channels and receptors play a role in acid sensing, acid-induced pain and acid-evoked feedback regulation of homeostatic reactions. The existence and apparent redundancy of multiple pH surveillance systems attests to the concept that acid-base regulation is a vital issue for cell and tissue homeostasis. Since upregulation and overactivity of acid sensors appear to contribute to various forms of chronic pain, acid-sensitive ion channels and receptors are considered as targets for novel analgesic drugs. This approach will only be successful if the pathological implications of acid sensors can be differentiated pharmacologically from their physiological function.

1. ACID SENSING BY SENSORY NEURONS

1.1 Acid as a noxious stimulus

Regulation of the acid-base balance and maintenance of pH at a narrow range around 7.4 is one of the basic principles of cellular homeostasis. This balance can be put into danger by many circumstances including, for instance, excess intake of acid, excess gastric acid secretion, defective acid containment in the gastrointestinal and urogenital tracts, metabolic acidosis and acidosis due to ischaemia (hypoxia) or inflammation. To meet with these

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challenges, there are not only cellular mechanisms of acid-base regulation but also systemic monitoring systems to detect harmful acidosis, to initiate appropriate emergency reactions, and thereby to limit any tissue damage that may arise. The most important systemic acid sensors are primary afferent neurons and the taste receptor cells mediating the sour taste.

It has long been known that acid can elicit pain (Steen and Reeh 1993; Steen et al. 1995), and there is plausible evidence that acidosis contributes to the pain associated with inflammation and ischaemia. Several reports summarized by Steen et al. (1992), Kress and Waldmann (2006) and Wemmie et al. (2006) indicate that interstitial pH values can fall to 4.7 in fracture-related haematomas, to 5.4 in inflammation, to 5.7 in cardiac ischaemia, and to 6.2 during exhausting skeletal muscle contractions. In the lumen of the stomach, gastric acid secretion causes the pH to drop down to 1, and this acid load can only be managed by compartmentalization and a strong mucosal acid barrier in the foregut (Holzer 2007). Intrusion of acid into the mucosa of the oesophagus, stomach or duodenum contributes not only to mucosal injury but also to the pain associated with gastro-oesophageal reflux and peptic ulcer disease (Kang and Yap 1991). Acid may likewise be a factor in the pain accompanying cystitis, in which a breakdown of the uroethelial barrier exposes sensory nerve endings to the acidic and hyperosmotic urine (Chuang et al. 2003). There is now ample evidence that the pain associated with angina pectoris is due to ischaemia-induced acidosis (Sutherland et al. 2001; Yagi et al. 2006), that pulmonary acidosis is associated with asthma (Ricciardolo et al. 2004; Hunt 2006), and that acid is a stimulus to elicit the cough reflex (Kollarik et al. 2007). Acidosis also occurs in and around malignant tumours (Vaupel et al. 1989; Newell et al. 1993). Metastases in bone are particularly painful, an instance that is related to enhanced activity of osteoclasts which resorb bone by decreasing interstitial pH below 5 (Honore et al. 2000; Luger et al. 2001; Ghilardi et al. 2005; Nagae et al. 2007).

1.2 Proton-gated currents in sensory neurons

Consistent with the ability of acidosis to induce pain is its capacity to excite primary sensory neurons and to sensitize them to other noxious stimuli (Clarke and Davison 1978; Krishtal and Pidoplichko 1981; Bevan and Yeats 1991; Steen et al. 1992; Bevan and Geppetti 1994; Reeh and Kress 2001; Krishtal 2003; Kress and Waldmann 2006). The molecular basis of acid sensing was discovered when proton-activated cationic currents were described in dorsal root ganglion (DRG) neurons (Krishtal and Pidoplichko 1981; Bevan and Yeats 1991). As reviewed by Kress and Waldmann (2006), two principal types of proton-gated inward currents are observed. The first type is characterized by a fast and rapidly inactivating inward current carried by Na^+ and by a high sensitivity to H^+, threshold activation occurring at a pH of 7 and maximum activation taking place at a pH around 6 (Krishtal and Pidoplichko 1981; Konnerth et al. 1987; Davies et al. 1988). While this type of proton-gated current is seen in most DRG neurons, the second type is observed only in DRG neurons that are also excited by capsaicin (Bevan and Yeats 1991; Bevan and Geppetti 1994). Unlike the first type, this current is less sensitive to acidosis, activated only at pH levels below 6.2, sustained, slowly inactivating and developing tachyphylaxis on repeated activation (Bevan and Yeats 1991; Petersen and LaMotte 1993). Further studies showed that the sustained currrent is due to an increase in cation conductance that allows Na^+, K^+ and Ca^{2+} to pass (Bevan and Yeats 1991; Zeilhofer et al. 1996; Zeilhofer et al. 1997).

Molecular analysis has shown that several acid-sensitive ion channels contribute to the capacity of afferent neurons to monitor acidosis (Figure 1). In some cases, accessory cells (such as the chemoreceptor cells in the taste buds or carotid bodies) survey the pH of their environment and transmit any aberration to adjacent sensory neurons. Among the molecular acid sensors, acid-sensing ion channels (ASICs) and transient receptor potential (TRP) vanilloid-1 (TRPV1) ion channels have been most thoroughly studied (Caterina and Julius 2001; Kress and Waldmann 2006; Wemmie et al. 2006; Diochot et al. 2007; Lingueglia 2007; Szallasi et al. 2007). While the slow proton-activated conductance in DRG neurons shares many similarities with the acidosis-evoked current through TRPV1, the fast acid-induced current resembles currents carried by ASICs (Kress and Waldmann 2006). However, the characteristics of proton-gated currents in sensory neurons are complex and subject to regional and species differences (Leffler et al. 2006; Smith et al. 2007; Sugiura et al. 2007). Accordingly, there is increasing evidence that further acid-sensitive ion channels are involved in monitoring acidosis (Figure 1). These include TRPV4, TRPC4, TRPC5, and PKD2L1, another member of the TRP ion channel that is relevant to the perception of the sour taste (Chandrashekar et al. 2006). Other candidates comprise members of the two-pore domain K^+ (K_{2P}) channel family, inward rectifier K^+ channels, voltage-gated K^+ channels, ionotropic purinoceptors (P2X) containing the $P2X_2$ subunit (Reeh and Kress 2001; Holzer 2003; Duprat et al. 2007) and proton-sensing G protein-coupled receptors (Ludwig et al. 2003; Tomura et al. 2005).

The objective of this article is to give an overview of the ability of primary sensory neurons to monitor acidosis, to describe the molecular acid sensors involved (Figure 1), and to address the physiological and pathophysiological implications of acid-sensitive ion channels and receptors in nociception with a pharmacological perspective.

2. ACID SENSORS ON SENSORY NEURONS

2.1 Acid-sensing ion channels (ASICs)

ASICs belong to the voltage-insensitive, amiloride-sensitive epithelial Na^+ channel/degenerin family of cation channels (Waldmann and Lazdunski 1998; Kellenberger and Schild 2002; Waldmann 2001; Welsh et al. 2002). The *proton-sensitive* members of this family expressed in mammals are encoded by 3 different genes (*ACCN1*, *ACCN2* and *ACCN3*) which are alternatively spliced to produce 5 subunits: ASIC1a, ASIC1b, ASIC2a, ASIC2b and ASIC3 (Kress and Waldmann 2006; Wemmie et al. 2006; Lingueglia 2007). These subunits are characterized by two membrane-spanning α-helical sequences (transmembrane domains 1 and 2), a large cysteine-rich extracellular loop and short intracellular N- and C-termini (Waldmann and Lazdunski 1998; Kellenberger and Schild 2002; Welsh et al. 2002; Lingueglia 2007). With this transmembrane topology (Figure 2), ASICs have the same structure as the ionotropic purinoceptors (P2X) but, since they lack significant sequence homology, do not seem to share a common ancestor (Kress and Waldmann 2006). The different subunits form distinct homomultimeric and heteromultimeric complexes which differ in their kinetics, external pH sensitivity, tissue distribution and pharmacological properties (Waldmann et al. 1999; Alvarez de la Rosa et al. 2002; Benson et al. 2002; Welsh et al. 2002; Kress and Waldmann 2006; Wemmie et al.

2006). Although it is not known precisely how many subunits are required to form a functional channel, there is increasing evidence that ASICs are arranged as homo- or heterotetramers (Gao Y et al. 2007; Lingueglia 2007). When activated, ASICs are preferentially permeable to Na^+ but some of them can also carry other cations such as Ca^{2+} (ASIC1a) and K^+ (ASIC1b) (Kress and Waldmann 2006; Wemmie et al. 2006; Lingueglia 2007).

The functional properties of the different ASIC subunits have been characterized following heterologous expression in *Xenopous laevis* oocytes and mammalian cell lines. Mutational analyses indicate that their pH sensitivity resides in several regions of the ASIC protein, particularly with His-72 and Gly-430 in the extracellular loop (Waldmann 2001; Diochot et al. 2007). ASIC1a, ASIC1b, ASIC2a and ASIC3 are directly gated by protons, whereas ASIC2b does not respond to acidosis when expressed as a homomultimer but can form functional heteromultimers with other ASIC subunits, particularly ASIC3 (Kress and Waldmann 2006; Wemmie et al. 2006). ASICS are activated by changes in pH only if they occur extracellularly, the threshold for activation of ASIC3 being as low as a fall of pH to 7.2 (Kress and Waldmann 2006; Wemmie et al. 2006). The pH values required for half-maximal activation are 6.2 - 6.8 for ASIC1a, 5.9 - 6.2 for ASIC1b, around 4.9 for ASIC2a and 6.5 - 6.7 for ASIC3 (Benson et al. 2002; Kress and Waldmann 2006). Under physiological pH, ASIC3 is blocked by Ca^{2+} bound to a high-affinity binding site on the extracellular side of the channel pore, and protons open ASIC3 by relieving this Ca^{2+} block (Immke and McCleskey 2003).

The proton-gated ASICs are highly sensitive acid sensors as deduced from the steepness of the their stimulus–response relationship. Although ASIC currents are in general fast and rapidly inactivating, there is evidence that they can also monitor prolonged acidosis. ASIC3 homomultimers and ASIC2a/ASIC3 as well as ASIC2b/ASIC3 heteromultimers produce two types of a sustained current: (i) a current that occurs at low acidic or even neutral pH and is thought to result from an overlap of activation and desensitization kinetics (Benson et al. 1999; Kress and Waldmann 2006; Wemmie et al. 2006; Yagi et al. 2006), and (ii) a current that is seen only at pH values below 5 (Kellenberger and Schild 2002; Kress and Waldmann 2006). In addition, persistent currents are observed when ASIC1 and ASIC3 channels are activated by protons in the presence of the neuropeptides NPFF or FMRFamide (Askwith et al. 2000; Catarsi et al. 2001; Deval et al. 2003).

The properties of ASIC channel currents delineated above resemble the fast and rapidly inactivating inward Na^+ current that is evoked by minor acidosis in native DRG neurons (Krishtal and Pidoplichko 1981; Konnerth et al. 1987; Davies et al. 1988; Kellenberger and Schild 2002; Leffler et al. 2006; Poirot et al. 2006). The question as to which ASIC subunits contribute to the native ASIC-like current in sensory neurons has been addressed by comparing the currents carried by ASIC homo- and heteromultimers with the native currents and by analyzing the expression of ASICs in sensory neurons. The pertinent studies revealed distinct regional differences, proton-gated currents being mediated by ASIC1a or ASIC3 homomultimers in some instances (Escoubas et al. 2000; Sutherland et al. 2001) and by ASIC2a/ASIC3 as well as ASIC2b/ASIC3 heteromultimers in other instances (Waldmann et al. 1999; Xie et al. 2002; Diochot et al. 2004; Yagi et al. 2006).

This heterogeneity in function is paralleled by a heterogeneity in the expression of ASIC1a, ASIC1b, ASIC2a, ASIC2b and ASIC3 by different populations of afferent neurons (Waldmann et al. 1999; Voilley et al. 2001; Alvarez de la Rosa et al. 2002; Benson et al. 2002; Mamet et al. 2002; Schicho et al. 2004; Kress and Waldmann 2006). While ASIC1a is present in both sensory neurons and neurons of the central nervous system (CNS), ASIC1b is largely confined to primary afferent neurons (Chen et al. 1998; Alvarez de la Rosa et al. 2002). In contrast, the levels of ASIC2a in sensory neurons are quite low, whereas ASIC2b occurs in both sensory and CNS neurons, and ASIC3 is almost exclusively expressed by sensory neurons (Lingueglia et al. 1997; Waldmann et al. 1999; Price et al. 2001; Voilley et al. 2001; Alvarez de la Rosa et al. 2002; Chen et al. 2002; Xie et al. 2002). The various ASIC subunits have been localized to primary afferent neurons of small, medium and large diameter innervating skin, eye, ear, taste buds, heart, gut, skeletal muscle and bone (Kress and Waldmann 2006; Wemmie et al. 2006; Holzer 2007). Their expression has been analyzed in greatest detail in the sensory innervation of the skin in which ASIC-like immunoreactivity occurs not only in free nerve endings but, as is particularly true for ASIC2, also in specialized mechanosensitive nerve endings (Jiang et al. 2006; Kress and Waldmann 2006; Wemmie et al. 2006). ASIC1, ASIC 2 and ASIC3 have also been localized to glossopharyngeal, vagal and spinal afferent neurons innervating the gut and other visceral organs (Page et al. 2005; Fukuda et al. 2006; Holzer 2007; Hughes et al. 2007), and retrograde tracing has revealed that 75 % of the nodose ganglion neurons and 82 % of the DRG neurons projecting to the rat stomach express ASIC3-like immunoreactivity (Schicho et al. 2004). Analysis of mouse thoracolumbar DRG has revealed that ASIC3 is expressed in 73 %, ASIC2 in 47 % and ASIC1 in 30 % of the somata projecting to the mouse colon (Hughes et al. 2007).

2.2 Transient receptor potential (TRP) ion channels

The transient receptor potential (TRP) ion channels are named after the role these channels have in *Drosophila* phototransduction. At least 28 different TRP subunit genes have been identified in mammals (Clapham et al. 2005), comprising 6 subfamilies of the mammalian TRP superfamily (Figure 3). The primary structure of the TRP channels consists of 6 transmembrane domains with a pore domain between transmembrane domains 5 and 6 and with both the C- and N-termini located intracellularly (Clapham et al. 2005). This architecture (Figure 2) is common to hundreds of ion channels but, despite the topographic similarities between the TRPs and the voltage-gated K^+ channels, the TRPs are only distantly related to these channels (Clapham et al. 2005). Since TRP channels are the subject of another chapter in this book, only TRP channels that are sensitive to pH changes (Figure 3) are considered here.

2.2.1 TRPV1—The existence of TRPV1 (initially termed vanilloid receptor 1, VR1), also known as the *capsaicin receptor*, has long been envisaged from the specific action of capsaicin on nociceptive afferent neurons (Jancsó 1960; Holzer 1991; Szallasi and Blumberg 1999). It is now known as a polymodal nocisensor par *excellence*, being receptive to noxious heat (above 43 °C), capsaicin, endovanilloids, and acid (Caterina et al. 1997; Tominaga et al. 1998; Jordt et al. 2000; Caterina and Julius 2001; Patapoutian et al. 2003). Assembled most likely as a homotetramer, TRPV1 is a non-selective cation channel with high permeability

for Ca^{2+} (Caterina and Julius 2001; Gunthorpe et al. 2002; Patapoutian et al. 2003; García-Sanz et al. 2004). In addition, TRPV1 has also been recognized as a channel that allows protons to enter the cell in an acidic environment (Hellwig et al. 2004; Vulcu et al. 2004). The conductance of H^+ through TRPV1 results in intracellular acidification (Hellwig et al. 2004), which in turn may act on membrane channels that are sensitive to changes in intracellular pH, e.g., certain two-pore domain K^+ channels. How TRPV1 regulates an acid-sensitive Cl^- channel in Sertoli cells (Auzanneau et al. 2008) has not yet been elucidated.

The pH sensitivity of TRPV1 is fundamentally different from that of ASICs, because TRPV1 is gated open only if the extracellular pH is reduced below 6, in which case a sustained channel current is generated (Caterina et al. 1997; Tominaga et al. 1998; Jordt et al. 2000). However, mild acidosis in the range of pH 7 - 6 can sensitize TRPV1 to other stimuli such as capsaicin and heat (Tominaga et al. 1998; McLatchie and Bevan 2001; Ryu et al. 2003; Neelands et al. 2005). As a result, the temperature threshold for TRPV1 activation is lowered under acidotic circumstances so that this cation channel becomes active at normal body temperature (Tominaga et al. 1998). Proton-induced sensitization involves both an increase in current activation rate and a decrease in current deactivation rate (Ryu et al. 2003; Neelands et al. 2005). Besides mild acidosis, many other signalling pathways (stimulated, e.g., by inflammatory mediators such as prostaglandins, bradykinin, adenosine triphosphate, 5-hydroxytryptamine and nerve growth factor) converge on TRPV1 and enhance the probability of channel gating by protons, capsaicin and heat (Caterina and Julius 2001; Vellani et al. 2001; Gunthorpe et al. 2002; Szallasi et al. 2007).

The ability of protons to sensitize TRPV1 to heat and other stimuli, on the one hand, and to activate TRPV1 *per se*, on the other hand, is mediated by different amino acid residues of the channel protein. Glu-600 on the extracellular side of transmembrane segment 5 is crucial for proton-induced sensitization of TRPV1, while Val-538 in the extracellular linker between transmembrane segments 3 and 4, Thr-633 in the pore helix and Glu-648 in the linker between the selectivity filter of the pore and transmembrane segment 6 are essential for proton-induced gating of TRPV1 (Jordt et al. 2000; Ryu et al. 2007). Mutation of these amino acid residues selectively abrogates proton-evoked currents but preserves the current responses to capsaicin and heat and their potentiation by mildly acidic pH (Jordt et al. 2000; Ryu et al. 2007). Thus, the sites in the TRPV1 protein targeted by protons differ from those targeted by other stimuli (Jordt et al. 2000; Welch et al. 2000; McLatchie and Bevan 2001; Gavva et al. 2004; Ryu et al. 2007). This instance allows for the development of TRPV1 blockers that inhibit TRPV1 activation by capsaicin but not acid (Gavva et al. 2005a).

DRG neurons of TRPV1 null mice lack the slow and non-desensitizing proton-gated currents that are seen in DRG neurons of wild-type animals, whereas the fast and rapidly inactivating proton-gated currents mediated by ASICs are maintained (Caterina et al. 2000; Davis et al. 2000). The TRPV1-mediated currents due to acidification are largely confined to DRG neurons with unmyelinated fibres whereas the ASIC-mediated currents are also found on DRG neurons with thinly myelinated axons (Leffler et al. 2006). This is consistent with the predominant expression of TRPV1 in unmyelinated primary afferent nerve fibres originating from the trigeminal, nodose and DRG ganglia although some thinly myelinated fibres also stain for TRPV1 (Caterina et al. 1997; Guo et al. 1999; Michael and Priestley

1999; Patterson et al. 2003; Schicho et al. 2004; Szallasi et al. 2007). Of the nodose ganglion neurons that innervate the rat stomach, 42 - 80 % stain for TRPV1, whereas 71 - 82 % of the DRG neurons projecting to the rat stomach and mouse colon express TRPV1 (Patterson et al. 2003; Robinson et al. 2004; Schicho et al. 2004). In addition, TRPV1 is present on afferent neuron-associated cells such as epithelial cells in the urinary bladder (Birder et al. 2001).

2.2.2 TRPV4—Much like TRPV1, TRPV4 is gated by a drop of pH below 6 and the channel current reaches a maximum at a pH of about 4 (Suzuki et al. 2003a). TRPV4 is also activated by citrate, but not lactate (Suzuki et al. 2003a), and has turned out to play a role in mechano- and osmosensation (Güler et al. 2002; Mizuno et al. 2003; Suzuki et al. 2003a). As TRPV4 has been localized to DRG neurons with both low- and high-threshold mechanosensitive afferent nerve fibres in the skin (Suzuki et al. 2003b), a role of this TRP channel in acid sensing warrants further exploration.

2.2.3 TRPC4 and TRPC5—The TRPC subfamily, specified as *canonical* or *classical* because TRPC1 has been the first member of the mammalian TRP family known to form an ion channel, can be divided into three subgroups by sequence homology and functional similarities: C1/C4/C5, C3/C6/C7, and C2 (Clapham et al. 2005). Accordingly, TRPC4 and TRPC5 are most closely related to TRPC1 which is a component of different heteromeric TRP complexes (Clapham et al. 2005). As other TRP channels, TRPC4 and TRPC5 form Ca^{2+}-permeable cation channels that are involved in receptor-mediated increases in intracellular Ca^{2+}. Their mode of activation has remained somewhat elusive, as TRPC4 and TRPC5 are activated in a phospholipase C-dependent manner by an unidentified messenger.

It has recently been reported that TRPC4 and TRPC5 respond to changes in extracellular pH, given that small decreases in pH (from 7.4 to 7.0) increase both G protein-activated and spontaneous TRPC5 currents (Semtner et al. 2007). TRPC4 channel activity is likewise potentiated by decreases in pH. The effects of a pH decrease on TRPC4 and TRPC5 activity are biphasic, the currents being increased by a reduction of pH down to about 6.5 but inhibited when pH is decreased further (Semtner et al. 2007). H^+ modifies TRPC5 currents by interacting with the Gd^{3+} binding site typical of TRPC4 and TRPC5 (Semtner et al. 2007). These findings clearly indicate that TRPC4 and TRPC5 can act as acid sensors that link decreases in extracellular pH to Ca^{2+} entry and depolarization. The expression of these TRP subunits in acid-sensitive cells and their functional implications in acid monitoring await to be shown.

2.2.4 TRPP2 (PKD2L1, polycystic kidney disease-like ion channel)—PKD2L1 is a member of the polycystin (TRPP) subfamily of TRP channels. Apart from PKD2L1 (TRPP2), the *polycystic kidney disease* (PKD) proteins or polycystins also comprise PKD2 (TRPP1) and PKD2L2 (TRPP3) (Clapham et al. 2005). The term polycystin is derived from the association of a PKD2 gene mutation with autosomal dominant polycystic kidney disease (Delmas 2005). Accordingly, the mouse ortholog of TRPP2 is deleted in *krd* mice which suffer from defects in the kidney and retina (Nomura et al. 1998).

PKD2L1 has recently joined the network of acid-sensitive ion channels after it has been discovered to play a major role in sour taste sensing (Huang et al. 2006; Ishimaru et al. 2006; LopezJimenez et al. 2006). In order to form functional channels, PKD2L1 needs to associate as heteromer with related proteins of the PKD1 family (Delmas 2005; Ishimaru et al. 2006). The PKD1 polycystins (PKD1, PKD1L1, PKD1L2, PKD1L3 and PKDREJ) are not included in the TRP channel family (Clapham et al. 2005) because they are large proteins with a very long N-terminal extracellular domain and 11 transmembrane domains that include a 6-transmembrane TRP-like channel domain at the C terminus. The expression of PKD2L1 in a select class of taste chemoreceptor cells and the deleterious effect of PKD2L1 deletion on the sour taste have led to the concept that PKD2L1is the molecular sour sensor (Huang et al. 2006; Ishimaru et al. 2006; LopezJimenez et al. 2006).

2.3 Two-pore domain K^+ (K_{2P}) channels

Two-pore (or tandem-pore) domain potassium (K_{2P}) channels, encoded by the *KCNK* genes, represent one of the subfamilies of the large superfamily of K^+ channels. Defined by their membrane topology (Figure 2), these channels possess four transmembrane domains, two pore-forming loops between transmembrane domains 1 and 2 as well as 3 and 4, and a large extracellular linker region between transmembrane domain 1 and the first pore-forming loop, which forms the K^+ selectivity filter (Lesage and Lazdunski 2000; Goldstein et al. 2001; Patel and Honoré 2001; Goldstein et al. 2005; Duprat et al. 2007). Functional K_{2P} channels are made up as homo- or heterodimers (Duprat et al. 2007). Thus far, 15 human K_{2P} channel subunits (Figure 4) have been identified and grouped into 6 structurally and functionally different subclasses (Goldstein et al. 2005; Duprat et al. 2007). Many of these channels are background channels that are independent of membrane voltage, constitutively active and non-inactivating. With these properties, K_{2P} channels play a key role in setting the resting membrane potential as well as membrane input resistance and, consequently, the excitability of neurons (Lesage and Lazdunski 2000; Goldstein et al. 2001; Patel and Honoré 2001; Duprat et al. 2007). In addition, many K_{2P} channels possess receptor properties, given that they are responsive to mechanical and chemical stimuli and are increasingly considered to be sensors for hypoxia, hypercapnia, glucose and modifications of intra- and extracellular pH (Duprat et al. 2007). As summarized in Figure 4, acidification or alkalinization modulates the activity of most K_{2P} subunits (Holzer 2003; Goldstein et al. 2005).

As their abbreviation for “TWIK-related acid-sensitive K^+ channels” implies, TASK channels are remarkably sensitive to variations in extracellular pH (Figure 4). TASK-1, TASK-2 and TASK-3 homo- and heteromers are inhibited by extracellular acidification but left unaffected by intracellular pH changes, while TASK-5 is inactive when expressed as homomer (Duprat et al. 1997; Reyes et al. 1998; Chapman et al. 2000; Kim et al. 2000; Rajan et al. 2000; Meadows and Randall 2001; Kang and Kim 2004; Goldstein et al. 2005; Duprat et al. 2007). TASK-1 is particularly sensitive, given that only 10 % of the maximal current is recorded at pH 6.7, 50 % at pH 7.3 and 90 % at pH 7.7 (Duprat et al. 1997). The pH sensitivity of TASK-3 is critically dependent on His-98 in the first pore-forming loop, an amino acid residue that is also present in TASK-1 but absent in TASK-2 (Kim et al. 2000; Rajan et al. 2000). In addition, His-72, Lys-73, Ile-94, Gly-95, Asp-204 and Lys-210 contribute to the acid sensing capacity of TASK-1 and TASK-3 subunits (Kim et al. 2000;

Morton et al. 2003; Yuill et al. 2004; Yuill et al. 2007). TASK-2 differs from TASK-1 and TASK-3 not only by the amino acid residues critical to its pH sensitivity (Glu28, Lys-32, Lys-35, Lys-47 and Arg-224), but also by its property of being an alkaline-activated K_{2P} channel (Morton et al. 2005; Duprat et al. 2007; Niemeyer et al. 2007).

Acid-induced inhibition of TASK channel activity will enhance nerve excitability and hence indirectly encode the presence of acid. The high proton sensitivity of TASK subunits points to a role in surveillance of tissue acidification by ischaemia, inflammation or backdiffusion of luminal acid into the mucosa of the foregut (Lesage and Lazdunski 2000; Holzer 2003: Duprat et al. 2007). This possibility is strongly envisaged from the expression of TASK-1, TASK-2 and TASK-3 mRNA and protein in rat and human DRG neurons with nociceptive properties and in areas of the spinal cord (dorsal horn) and brainstem that receive afferent input from the periphery (Duprat et al. 1997; Bayliss et al. 2001; Medhurst et al. 2001; Talley et al. 2001; Gabriel et al. 2002; Baumann et al. 2004; Cooper et al. 2004; Rau et al. 2006).

TRESK channels are blocked by extra- and intracellular acidification and activated by extra- and intracellular alkalinization (Sano et al. 2003). TRESK is a major background K_{2P} channel in DRG neurons, and disruption of the TRESK gene has revealed that this channel plays a role in the regulation of DRG neuron excitability (Kang and Kim 2006; Dobler et al. 2007).

TREK-1 and TREK-2 do not respond to changes in extracellular pH but are inhibited by intracellular alkalinization and activated by intracellular acidification such that they become constitutively active (Maingret et al. 1999; Bang et al. 2000; Lesage et al. 2000; Kim et al. 2001a; Patel and Honoré 2001; Honoré et al. 2002; Miller et al. 2004). Activation of TREK-1 by intracellular acidification depends critically on protonation of Glu-306 (Honoré et al. 2002). TREK channels are also activated by a number of extracellular stimuli (including arachidonic acid, other unsaturated fatty acids, heat, stretch, negative pressure and heat) and inhibited by intracellular signalling cascades involving protein kinases A and C. A sensory role of TREK channels may be deduced from the expression of TREK-1 and TREK-2 in human DRG neurons as well as in neurons of the spinal cord and brainstem (Bearzatto et al. 2000; Maingret et al. 2000; Hervieu et al. 2001; Medhurst et al. 2001; Talley et al. 2001; Gu et al. 2002; Kang and Kim 2006). In the mouse DRG, TREK-1 is present in small to medium-sized primary afferent neurons (Maingret et al. 2000).

The activity of TWIK-1, but not TWIK-2, is depressed by extracellular acidification (Goldstein et al. 2005; Rajan et al. 2005), whereas intracellular acidification inhibits both TWIK-1 and TWIK-2 (Chavez et al. 1999; Patel et al. 2000). A possible role in sensory mechanisms can be envisaged from the expression of TWIK-1 and TWIK-2 mRNA in human and rat DRG neurons as well as in neurons of the spinal cord (Medhurst et al. 2001; Talley et al. 2001).

TRAAK channels are activated by intracellular alkalinization but not acidification (Lesage and Lazdunski 2000; Kim et al. 2001b; Patel and Honoré 2001). TRAAK mRNA and protein are appreciably expressed in human and rat DRG neurons as well as in the human,

mouse and rat spinal cord (Bearzatto et al. 2000; Reyes et al. 2000; Medhurst et al. 2001; Talley et al. 2001; Kang and Kim 2006).

TALK-1, TALK-2 and their splice variants are blocked by extracellular acidification but gated open by extracellular alkalinization, with Lys-224 playing a critical role in their pH sensitivity (Decher et al. 2001; Girard et al. 2001; Han et al. 2003; Duprat et al. 2005; Goldstein et al. 2005; Niemeyer et al. 2007).

Taken together, the activity of many K_{2P} channels (TASK-1, TASK-2, TASK-3, TRESK, TWIK-1, TALK-1 and TALK-2) is modified by changes in extracellular pH. Although their functional implications in acid sensing await to be explored, K_{2P} channels could play a multimodal sensory role in the peripheral and central nervous system as has been envisaged for the TASK subfamily (Duprat et al. 2007).

2.4 Proton-sensing G-protein-coupled receptors (GPCRs)

Proton-sensitive G-protein-coupled receptors (GPCRs) are emerging as a new class of acid sensors on nociceptive afferent neurons (Figure 1). These receptors comprise the ovarian cancer G-protein-coupled receptor 1 (OGR1), G-protein-coupled receptor 4 (GPR4), the G2 accumulation (G2A) receptor, and the T-cell death-associated gene 8 (TDAG8) receptor. Initially described as receptors for lipid molecules such as sphingosylphosphorylcholine, lysophosphatidylcholine, and psychosine, some of these GPCRs have turned out to be sensors for extracellular acidosis (Ludwig et al. 2003; Tomura et al. 2005). As other GPCRs, these acid-sentitive receptors are composed of 7 transmembrane domains, their signalling involving G_s, G_i, G_q, and $G_{12/13}$ pathways. The sensitivity of OGR1 to extracellular pH changes resides with several histidine residues and is extremely high, given that half-maximum activation occurs at pH 7.2 - 7.5 and full activation at pH 6.4 - 6.8 (Ludwig et al. 2003; Tomura et al. 2005). The transcripts of proton-sensing GPCRs are widely distributed and, importantly, also expressed by DRG neurons, particularly by small-diameter afferent neurons that are involved in nociception (Huang et al. 2007). Although the physiological and pathophysiological roles of proton-sensitive GPCRs are - for the time being - speculative, they could add significantly to the network of acid sensors of afferent neurons and their associated cells.

2.5 Ionotropic purinoceptors (P2X)

P2X purinoceptors are ligand-gated membrane cation channels that open when extracellular adenosine triphosphate (ATP) is bound. They are assembled as homo- or heteromultimers (trimers or hexamers) of P2X subunits, seven of which ($P2X_1$ - $P2X_7$) have been identified at the gene and protein level (Chizh and Illes 2001; Dunn et al. 2001; North 2002; Burnstock 2007). Their membrane topology (Figure 2) is characterized by a very long extracellular polypeptide loop, which consists of about 280 amino acids and is rich in cystein, between two transmembrane domains, with both the N- and C-termini located intracellularly (Dunn et al. 2001; North 2002). Since the role of purinoceptors in sensory neuron physiology and pharmacology is the topic of another chapter in this volume, only aspects relating to the acid sensitivity of P2X purinoceptors are discussed here.

Of the various P2X subunits, $P2X_1$, $P2X_2$, $P2X_3$, $P2X_4$, $P2X_5$ and $P2X_7$ (Figure 1) are modulated by alterations in the extracellular pH (Holzer 2003). Thus, acidification reduces the potency of ATP to gate homomultimeric $P2X_1$, $P2X_3$, $P2X_4$ and $P2X_7$ receptors usually without a change in the maximal response, while alkalinization has no effect on agonist potency and efficacy (Stoop et al. 1997; Dunn et al. 2001; Liu et al. 2001; Gerevich et al. 2007). In $P2X_5$ homomultimers, however, protons reduce both the potency and efficacy of ATP to gate the channel (Wildman et al. 2002). In contrast, acidification sensitizes homomultimeric $P2X_2$ receptors to the excitatory effect of ATP, whereas agonist potency at homomultimeric P2X2 receptors is decreased at alkaline pH levels above 7.5 (Stoop et al. 1997; Ding and Sachs 1999; North 2002; Burnstock 2007). The maximal response of $P2X_2$ receptors to ATP is not altered by alkalinization or acidification. His-319 is particularly important for the effect of protons to potentiate the agonist effect of ATP on $P2X_2$ (Clyne et al. 2002), while protonation of His-206 and His-286 accounts for the inhibition of agonist-induced currents in $P2X_3$ and $P2X_4$, respectively (Clarke et al. 2000; Gerevich et al. 2007).

Acidification has a dual effect on $P2X_3$ channels in response to agonist application. While at low agonist concentrations the current amplitude is reduced due to a decrease in the activation rate, it is enhanced at high agonist concentrations due to a decrease in the desensitization rate (Gerevich et al. 2007). It has therefore been proposed that the effect of low ATP concentrations on $P2X_3$ channels may be attenuated during inflammatory acidosis, whereas the effects of a massive release of ATP by tissue damage may be potentiated by acidosis (Gerevich et al. 2007).

When $P2X_1$, $P2X_2$ or $P2X_3$ subunits are coexpressed with each other, the resultant heteromultimers show a pH sensitivity that is different from that of P2X homomers (Surprenant et al. 2000; Dunn et al. 2001; Liu et al. 2001; Brown et al. 2002). For instance, the potency and efficacy of ATP to gate heteromeric $P2X_{1/2}$ receptors expressed in *Xenopous* oocytes is increased under both acidic and alkaline conditions (Brown et al. 2002). While the agonist-induced currents in $P2X_{2/3}$ heteromers are less enhanced by protons than the equivalent responses in $P2X_2$ homomers (Liu et al. 2001), the ligand-induced currents in $P2X_{2/6}$ heteromers are potentiated by pH levels down to 6.5, but are inhibited by pH levels lower than 6.3 (King et al. 2000). The ATP-evoked currents in $P2X_{4/6}$ heteromers are inhibited in the presence of protons (Dunn et al. 2001), and the ligand-evoked stimulation of $P2X_{1/5}$ heteromers is inhibited by either an increase or a decrease of the extracellular pH, both in terms of potency and efficacy (Surprenant et al. 2000).

P2X receptors are expressed by many cells including primary afferent neurons. The P2X receptors on nodose ganglion neurons comprise predominantly homomultimeric $P2X_2$ and some heteromultimeric $P2X_{2/3}$ receptors whereas on DRG neurons homomultimeric $P2X_3$ prevail over heteromultimeric $P2X_{2/3}$ receptors (Cockayne et al. 2000; Dunn et al. 2001; Burnstock 2007). The different P2X subunit distribution in spinal and vagal sensory neurons explains why the ATP-evoked inward currents in nodose ganglion neurons are persistent whereas those in DRG neurons exhibit transient, persistent or biphasic components (Dunn et al. 2001). Since only $P2X_2$ homomultimers and heteromultimers involving $P2X_2$, i.e., $P2X_{1/2}$, $P2X_{2/3}$ and $P2X_{2/6}$ receptors, are sensitized by acid, it is primarily $P2X_2$-containing purinoceptors that function as indirect acid sensors. The monitoring of acidification depends

on the concomitant release and/or presence of ATP or related purines whose agonist action is enhanced by a decrease of the extracellular pH. This scenario may be of functional significance, given that ATP is liberated from a number of cellular sources in response to both physiological and pathological stimuli. As a result, P2X receptors have been envisaged as potential targets in pain research because, firstly, $P2X_3$ receptors are preferentially expressed by a group of primary afferent neurons that subserve a nociceptor function and, secondly, P2X receptors on these neurons are upregulated by inflammation and nerve injury (Cockayne et al. 2000; Hamilton et al. 2001; Yiangou et al. 2001a; Xu and Huang 2002; Burnstock 2007).

2.6 Other acid-sensitive ion channels

There is an increasing network of ion channels, receptors and other membrane proteins whose activity is modified by changes in the extra- and/or intracellular pH (Figure 1). To review these many principles is beyond the scope of the current article which focuses on acid sensing as an important property of sensory neurons and associated cells. Mention needs to be made, however, of a number of mechanisms that have been discussed as contributing to the acid-monitoring capacity of chemosensory neurons both in the periphery and brain.

Several members of the inward rectifier K^+ channel (Kir) family, such as Kir1.1, Kir4.1, Kir5.1 and Kir6.1 are highly sensitive to changes in the intra- or extracellular pH at near physiological levels. While the activity of Kir1.1, Kir4.1 and Kir5.1 channels is inhibited by a decrease in intracellular pH (Jiang et al. 1999; Claydon et al. 2000; Putnam et al. 2004; Jiang et al. 2005; Liu et al. 2005; Lopez-Lopez and Perez-Garcia 2007), Kir6.1 (K_{ATP}) channels are activated by intracellular acidosis (Xu et al. 2001; Wang et al. 2003). Similarly, G-protein-coupled inward rectifier K^+ channels are activated by extracellular acidification (Mao et al. 2002). The inactivation of the voltage-activated K^+ channel $K_v1.3$ is delayed when extracellular pH is lowered (Somodi et al. 2004), whereas the inactivation of $K_v1.4$ and and $K_v11.1$ channels is facilitated by extracellular acidosis (Jiang et al. 1999; Claydon et al. 2000; Somodi et al. 2004; Chandrashekar et al. 2006).

Nifedipine-sensitive L-type Ca^{2+} channels can be activated by extracellular acidification (Filosa and Putnam 2003), although there are also reports that high voltage-gated Ca^{2+} channels and tetrodotoxin-sensitive Na^+ channels are blocked by a drop of extracellular pH (Reeh and Kress 2001). Hyperpolarization-activated cyclic nucleotide-gated channels (Stevens et al. 2001; Zong et al. 2001; Mistrík and Torre 2004) and gap junction channels (connexins) (Dean et al. 2002) are inhibited by intracellular acidosis. Sertoli cells express an acid-sensitive Cl^- channel which is outwardly rectifying and activated only at acidic pH values in the extracellular space (Auzanneau et al. 2003; Auzaneeau et al. 2008). Neurotransmitter receptors other than P2X purinoceptors are likewise modulated by pH changes. This is true for $GABA_A$ receptors which can be modified by extracellular pH changes, the effect depending on the stage of development and the receptor subunit composition (Krishek and Smart 2001). Given that intracellular pH is regulated by ion pumps, it needs to be envisaged that many transporters including Na^+/H^+ exchangers can

modify the acid sensitivity of chemosensory cells (Lyall et al. 2004; Shimokawa et al. 2005; Montrose et al. 2006).

3. PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL IMPLICATIONS OF ACID SENSORS

In most tissues, stimulation of sensory neurons by acidosis and other noxious stimuli has two different effects: local release of neuropeptides from the peripheral nerve fibres in the tissue and induction of autonomic reflexes, sensation and pain (Holzer 1988; Holzer and Maggi 1998). By releasing peptide transmitters in the periphery, sensory nerve fibres can regulate vascular and other tissue activities embodied in the term *neurogenic inflammation*. This efferent-like mode of operation may take place independently of nociception, and it has been hypothesized that some DRG neurons are specialized in controlling peripheral effector mechanisms only, while other DRG neurons may be specialized in the afferent mode of action or both (Holzer and Maggi 1998). The neuropeptides involved in the efferent-like mode of operation include calcitonin gene-related peptide (CGRP) and the tachykinins substance P and neurokinin A. Acidosis-evoked release of CGRP, one of the most potent vasodilator peptides, has been demonstrated in a variety of tissues including the dental pulp (Goodis et al. 2006), the gastric mucosa (Geppetti et al. 1991; Manela et al. 2005) and the myocardium (Strecker et al. 2005). Pharmacological antagonist and gene disruption studies provide increasing evidence that acid-sensitive ion channels and receptors are involved in a number of physiological and pathophysiological reactions to acidosis (Figure 5).

3.1 Sour taste

The detection of sour taste plays an important role in warning against ingestion of acidic (e.g., spoiled or unripe) food sources (Huang et al. 2006). Taste reception occurs at the apical tip of taste receptor cells that form taste buds composed of 50 - 100 taste receptor cells. After transduction of one of the 5 distinct taste modalities (bitter, sweet, umami, salty, and sour), the taste receptor cells transmit their information to afferent neurons. Several receptors and receptor mechanisms have been proposed to mediate the sour taste (Chandrashekar et al. 2006). These comprise ASIC2a and ASIC2b (Ugawa et al. 2003; Shimada et al. 2006), K_{2P} channels (Lin et al. 2004; Richter et al. 2004a), inward rectifier K^+ channels (Liu et al. 2005), proton-activated voltage-dependent Ca^{2+} channels (Chandrashekar et al. 2006), hyperpolarization-activated cyclic nucleotide-gated channels (Stevens et al. 2001), Na^+/H^+ exchangers (Lyall et al. 2004) and acid-induced inactivation of K^+ channels (Chandrashekar et al. 2006). However, ASIC2 knockout mice respond normally to sour taste stimuli (Richter et al. 2004b), and there is also a lack of conclusive evidence for the other receptor mechanisms.

Histological, genetic and functional studies demonstrate that the TRP channel PKD2L1 (TRPP2) is probably the most important sour taste receptor (Huang et al. 2006; Ishimaru et al. 2006; LopezJimenez et al. 2006; Kataoka et al. 2008). PKD2L1 and the related PKD1L3 are selectively coexpressed in a population of taste receptor cells distinct from those mediating sweet, umami and bitter tastes (Huang et al. 2006; Ishimaru et al. 2006; LopezJimenez et al. 2006). PKD2L1 is accumulated at the taste pore region where taste

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chemicals are detected, and coexpression of PKD2L1 and PKD1L3 is necessary for their functional cell surface expression (Ishimaru et al. 2006). In addition, PKD2L1 and PKD1L3 are activated by various acids when coexpressed in heterologous cells but not by other classes of tastants (Ishimaru et al. 2006). Targeted ablation of PKD2L1-expressing taste receptor cells results in a specific and total loss of the sour taste, whereas responses to sweet, umami, bitter or salty tastants remain indistuinguishable from those in wild-type animals (Huang et al. 2006). These findings firmly establish PKD2L1-expressing cells as specific sour taste receptors. Since PKD2L1 is expressed in neurons surrounding the central canal of the spinal cord, this channel has also been suggested to serve as a chemoreceptor monitoring the acidity of the cerebrospinal fluid (Huang et al. 2006).

3.2 Acidosis in the gastrointestinal tract

3.2.1 Acidity and acidosis in the gastrointestinal tract—The stomach is the most productive source of acid in the body. The gastric parietal cells can secrete hydrochloric acid (HCl) to yield a H^+ concentration in the gastric lumen that - with an average diurnal pH of 1.5 - is 6 orders of magnitude higher than in the interstitial space of the gastric lamina propria (Holzer 2007). Most tissues would rapidly disintegrate if exposed to this pH, yet gastric acid is essential for the digestive breakdown of food and elimination of ingested pathogens. The autoaggressive potential of HCl is kept in check by an elaborate network of mucosal defence mechanisms and by the functional compartmentalization of the oesophago-gastro-duodenal region (Holzer 2007). Both strategies require an acid surveillance system among which acid-sensitive afferent neurons play a important role. If the pathophysiological impact of gastric acid gets out of control, acid-related diseases including gastritis, gastroduodenal ulceration, dyspepsia and gastro-oesophageal reflux disease may ensue.

Acid sensors are not only relevant to control the secretion and actions of gastric acid but also to detect tissue acidosis resulting from ischaemia, inflammation, microbial activity, malignant tumour growth and gastrointestinal motor stasis. The pH profile in the gastrointestinal lumen of healthy subjects shows a distinct shape (Fallingborg 1999; Nugent et al. 2001), with peaks of acidity in the stomach and proximal large bowel. While HCl and bicarbonate (HCO_3^-) secretion are the major determinants of luminal pH in the foregut, luminal pH in the colon depends on mucosal HCO_3^- and lactate production as well as on microbial transformation of carbohydrates to short chain fatty acids and formation of ammonia. This pH profile can be changed by surgical interventions and in inflammatory bowel disease (Nugent et al. 2001; Holzer 2007).

3.2.2 Acid sensing as a feedback in the control of foregut homeostasis—The secretion of gastric acid at highly toxic concentrations requires a tight control of its production according to need. The major inhibitory regulator is an increase in intragastric acidity, given that a decrease of luminal pH below 3 has a concentration-dependent inhibitory influence on HCl and gastrin secretion, and at pH 1 further acid output is abolished (Shulkes et al. 2006). The major mediator of this feedback inhibition is somatostatin which via paracrine and endocrine pathways inhibits parietal cell function both directly and indirectly via reduction of gastrin secretion. The activity of D cells is in part regulated by acid-sensitive primary afferent neurons in the gastric mucosa which following

luminal acidification release CGRP to stimulate D cells (Manela et al. 1995; Holzer 1998). The acid sensors of the somatostatin-releasing D cells and of other endocrine cells in the gastrointestinal mucosa await to be explored. Excess acid causes release of 5-hydroxytryptamine from enterochromaffin cells in the rat gastric mucosa (Wachter et al. 1998). Enterochromaffin cells are often called the “taste buds” of the gut, but whether they monitor intraluminal pH is not known.

Exposure of the oesophageal, gastric and duodenal mucosa to excess acid elicits protective mechanisms including an increase in mucus gel thickness, HCO_3^- secretion and mucosal blood flow (Holzer 1998; Aihara et al. 2005; Akiba et al. 2006b; Montrose et al. 2006). These reactions are initiated in part by epithelial cells and their acid sensing mechanisms and in part by capsaicin-sensitive afferent nerve fibres. Since these nerve fibres reside in the lamina propria behind the epithelium, the mucosal acid signal must be transduced across the epithelium. In the duodenum, this seems to be achieved by diffusion of CO_2 into the epithelial cells, hydration to H^+ and HCO_3^-, intracellular acidification and exit of H^+ via the basolateral sodium-proton exchanger of type 1 (Akiba et al. 2006b; Montrose et al. 2006). As a result, interstitial pH is lowered, which activates sensory nerve terminals that release the vasodilator peptide CGRP (Akiba et al. 2006b). TRPV1 is involved in the duodenal hyperaemia due to luminal acid exposure, since it is attenuated by the TRPV1 blocker capsazepine (Akiba et al. 2006b), whereas the gastric hyperaemia is left unaltered by capsazepine (Tashima et al. 2002). The acid-evoked secretion of gastric and duodenal HCO_3^- also remains unchanged by capsazepine (Kagawa et al. 2003; Aihara et al. 2005).

The injurious potential of gastric acid is, in addition, kept in check by compartmentalization of the oesophago-gastro-duodenal region. This strategy is to restrict the presence of high acid concentrations to the stomach, the mucosa of which is most resistant to intrusion by H^+, and to precisely control H^+ passage from the stomach to the duodenum through coordinated activity of the lower oesophageal and pyloric sphincters. Both sphincters are under the control of neural reflexes involving acid-sensitive neurons which adjust the tone of these sphincters to balance the levels of acid present in the oesophagus, stomach and duodenum with the mucosal defence mechanisms in these compartments (Forster et al. 1990; Lu and Owyang 1999; Holzer et al. 2003; Holzer 2007). The molecular acid sensors and sensory neurons involved in the control of oesophago-gastro-duodenal motor activity await full exploration (Holzer 2007). Apart from extrinsic sensory neurons, it is likely that intrinsic primary afferent neurons of the enteric nervous system are involved, given that they have been found to respond to acidosis (Bertrand et al. 1997; Schicho et al. 2003).

Paradoxically, knockout of TRPV1 has been reported to ameliorate acid-induced injury in the oesophagus and stomach (Akiba et al. 2006a; Fujino et al. 2006). Analysis of this unexpected observation in the stomach has revealed that disruption of the TRPV1 gene causes a compensatory upregulation of other protective mechanisms in the gastric mucosa (Akiba et al. 2006a). Thus, experiments with selective TRPV1 blockers are needed to unveil the precise role of TRPV1 in acid-induced mucosal injury in the foregut.

3.2.3 Acid as a factor in abdominal pain—Acid is not only a factor in gastrointestinal tissue injury but also in gastrointestinal pain, contributing to the symptoms of gastro-

oesophageal reflux disease and peptic ulcer (Kang and Yap 1991). Whether acid also plays a role in the pain associated with functional gastrointestinal disorders such as non-cardiac chest pain, functional dyspepsia, irritable bowel syndrome and functional abdominal pain syndrome is less well understood (Holzer 2007). Whole-cell voltage-clamp recordings from DRG and nodose ganglion neurons innervating the rat stomach and mouse colon have shown that acidosis induces currents that can to a variable degree be attributed to the gating of ASICs and TRPV1 (Sugiura et al. 2005; Sugiura et al. 2007). The pH sensitivity and kinetics of these currents are distinctly altered after experimental induction of gastric ulcers (Sugiura et al. 2005).

Intramucosal acidosis induced by exposure of the rat or mouse gastric lumen to supraphysiological HCl concentrations (> 0.15 M) elicits a visceromotor response indicative of pain (Lamb et al. 2003) and causes many neurons in the nucleus of the solitary tract in the brainstem to express c-Fos, a marker of neuronal excitation (Schuligoi et al. 1998; Danzer et al. 2004; Wultsch et al. 2008). The gastric HCl-evoked visceromotor reaction and medullary c-Fos response are suppressed by vagotomy, but not transection of the sympathetic nerve supply to the stomach, which indicates that gastric HCl-evoked nociception depends critically on the integrity of the vagal afferent innervation (Schuligoi et al. 1998; Lamb et al. 2003). Apart from eliciting pain, acid causes sensitization of mechanosensitive afferent pathways from the oesophagus, stomach and colon (Coffin et al. 2001; Medda et al. 2005). Experimentally induced gastritis and gastric ulceration enhance the gastric HCl-evoked visceromotor reaction and medullary c-Fos response (Lamb et al. 2003; Holzer et al. 2007; Wultsch et al. 2008).

The gastric HCl-evoked visceromotor reaction is inhibited by pretreatment of rats with a neurotoxic dose of capsaicin (Lamb et al. 2003). In contrast, the medullary c-Fos response to gastric acid challenge is neither altered by pretreatment with capsaicin (Schuligoi et al. 1998) nor by deletion of the TRPV1 gene (Peter Holzer, Thomas Wultsch and Peter W. Reeh, unpublished observation). While afferent acid signalling from the normal stomach to the brainstem is preserved in ASIC3 knockout mice, the effect of gastritis to enhance the gastric acid-evoked expression of c-Fos in the brainstem is abolished by disruption of the ASIC3 gene (Wultsch et al. 2008). ASIC3 thus seems to play a major role in the inflammatory hyperresponsiveness of the vagal afferent - brainstem axis to gastric acid. Conversely, ASIC2 gene knockout does not alter inflammatory hyperresponsiveness but enhances the medullary c-Fos response to gastric acid challenge of the normal stomach (Wultsch et al. 2008). Although this finding suggests that ASIC2 may normally dampen acid-induced afferent input, it must not be forgotten that compensatory changes in germline knockout mice may obscure the functional implication of the disrupted gene.

Activation of TRPV1 on abdominal afferent neurons by capsaicin elicits visceral pain in animals and humans (Drewes et al. 2003; Holzer 2004a; Schmidt et al. 2004). The stimulant effect of luminal acidification on gastric and oesophageal vagal afferent nerve fibres is ablated in both TRPV1 null and ASIC3 null mice (Bielefeldt and Davis 2007). Similarly, disruption of the TRPV1 gene and blockade of TRPV1 by capsazepine depress the acid-evoked stimulation of afferent nerve fibres supplying the mouse jejunum (Rong et al. 2004) and the acid-evoked currents in thoracolumbar and lumbosacral DRG neurons innervating

the mouse colon (Sugiura et al. 2007). Experimental colitis induced by trinitrobenzene sulfonic acid is associated with an increase in TRPV1 expression in thoracolumbar and lumbosacral DRG neurons and in the visceromotor response to intracolonic acid administration (Miranda et al. 2007). The effects of trinitrobenzene sulfonic acid to induce colitis, TRPV1 overexpression and hyperalgesia in response to acid challenge are counteracted by the TRPV1 blocker JYL1421 (Miranda et al. 2007).

Pharmacological blockade of TRPV1 with SDZ 249-665, a vanilloid compound causing desensitization of sensory neurons to capsaicin, attenuates the behavioural pain response to intraperitoneal administration of acetic acid in rats (Urban et al. 2000). This pain reaction may indeed reflect a response to acidosis because the writhing response to intraperitoneal injection of acetic, lactic and propionic acid is attenuated by capsazepine, whereas that to phenylbenzoquinone is not (Ikeda et al. 2001). An involvement of TRPV1 in acetic acid-induced writhing is further corroborated by the ability of various TRPV1 blockers to reduce the abdominal contractions caused by intraperitoneal injection of acetic acid (Rigoni et al. 2003; Tang et al. 2007). Likewise, mice lacking TRPV4 are hyporesponsive to intraperitoneal injection of acetic acid (Suzuki et al. 2003a). Overexpression of a dominant-negative ASIC3 subunit has been found to increase the writhing response to intraperitoneal acetic acid (Mogil et al. 2005), a change that paradoxically is also seen in ASIC3 null mice (Chen et al. 2002). Whether this finding is the result of a change in the kinetics of ASIC1 and ASIC2 after knockout of ASIC3 (Kress and Waldmann 2006) or of a compensatory upregulation of acid sensors other than ASIC3 is not known.

The available information points to a role of TRPV1 and ASIC3 in acid sensing within the gastrointestinal tract as well as in ulceration- and inflammation-evoked sensitization of afferent neurons (Figure 5). This inference is consistent with a number of findings that show that abdominal hyperalgesia is associated with an upregulation in acid sensor expression and/or function. For instance, acute exposure of the rat gastric mucosa to a noxious HCl concentration leads to a rise of TRPV1 immunoreactivity, but not TRPV1 mRNA, in DRG neurons innervating the stomach (Schicho et al. 2004). TRPV1 in vagal and spinal afferent neurons is upregulated in acid-evoked oesophagitis as well as in trinitrobenzene sulfonic acid-induced pancreatitis and colitis (Banerjee et al. 2007; Miranda et al. 2007; Xu et al. 2007). Similarly, the expression of TRPV1 and ASIC3, but not ASIC1 and ASIC2, is enhanced in the colonic mucosa of patients with inflammatory bowel disease (Yiangou et al. 2001b; Yiangou et al. 2001c). TRPV1-like immunoreactivity is likewise increased in oesophagitis (Matthews et al. 2004), non-erosive reflux disease (Bhat and Bielefeldt 2006), rectal hypersensitivity and faecal urgency (Chan et al. 2003).

There is some evidence that P2X receptors are involved in gastrointestinal sensation and pain related to acidosis. Protons potentiate the ATP-evoked stimulation of nodose and DRG ganglion cells (Li et al. 1996; Li et al. 1997; Dunn et al. 2001; Zhong et al. 2001). The writhing behaviour elicited by intraperitoneal injection of acetic acid is inhibited by trinitrophenyl-ATP (a $P2X_1$, $P2X_3$ and $P2X_{2/3}$ receptor blocker) and A-317491 (a $P2X_3$ and $P2X_{2/3}$ receptor antagonist), whereas the $P2X_1$ channel blocker diinosine pentaphosphate is ineffective (Honore et al. 2002; Jarvis et al. 2002). Distension of the gut is thought to release ATP from the intestinal mucosa which subsequently excites afferent neurons expressing

P2X receptors. This mode of mechanosensory transduction via $P2X_3$ receptors is enhanced by experimental colitis in the rat (Wynn et al. 2004) and may, conceivably, involve inflammation-associated acidosis and/or upregulation of $P2X_3$ purinoceptors as has been observed in the colonic mucosa of patients with inflammatory bowel disease (Yiangou et al. 2001a).

3.3 Acidosis in the urogenital tract

The sensory innervation of the urogenital tract is of paramount relevance to the regulation of urine storage and voiding. Given that the urine is usually acidic and hyperosmotic, nerve endings behind the urotheliun are likely to be exposed to excess acid if the urothelial barrier is disrupted (Chuang et al. 2003). This scenario is likely to occur under the conditions of irritable bladder and cystitis in which there is evidence for sensitization of afferent neurons, at least to mechanical stimuli. As a result, bladder hyperactivity, bladder hyperreflexia and pain may occur. The plausibility of this concept receives support from the finding that both populations of afferent neurons innervating the bladder, thoracolumbar and lumbosacral DRG neurons, are excited by acidification and exhibit proton-evoked currents with different inactivation kinetics (Dang et al. 2005; Daly et al. 2007). Furthermore, there is emerging evidence that acid sensors on afferent neurons such as TRPV1 play an appreciable role in pathologies of the urogenital tract (Figure 5).

An implication of TRPV1 in bladder overactivity and pain has been proved both by experimental and clinical evidence. Thus, chronic intravesical administration of capsaicin or resiniferatoxin to desensitize the sensory innervation of the bladder is beneficial in patients with urinary bladder pain and hyperreflexia (Bley 2004; Brady et al. 2004; Avelino and Cruz 2006; Cruz and Dinis 2007). This finding is consistent with the finding that TRPV1-like immunoreactivity is upregulated in neurogenic bladder overactivity (Brady et al. 2004). The symptoms of women with sensory urgency, but not idiopathic detrusor overactivity, have been associated with increased expression of TRPV1 mRNA in the trigonal mucosa (Liu et al. 2007). A contribution of TRPV1 to bladder function has been confirmed experimentally by genetic and pharmacological studies. Knockout of the TRPV1 gene blunts the responsiveness of bladder afferent neurons to intravesical administration of hydrochloric acid and capsaicin as well as to bladder distension and impairs the function of low-threshold afferents (Birder et al. 2002; Daly et al. 2007).

There is ample evidence that $P2X_2$ and $P2X_3$ purinoceptors are involved in the physiology and pathophysiology of urinary bladder voiding (Cockayne et al. 2000; Cockayne et al. 2005; Burnstock 2007), but it is not known whether they contribute to acid sensing in the urogenital tract.

3.4 Acidosis in the pulmonary system

DRG and nodose ganglion neurons projecting to the lung and pleura express TRPV1 and ASICs (Groth et al. 2006; Jia and Lee 2007; Kollarik et al. 2007). Accordingly, vagal afferent neurons supplying the rat and guinea-pig lung display proton-induced currents with rapid and slow inactivation currents that appear to be carried by ASICs and TRPV1 as they are inhibited by amiloride and capsazepine, respectively (Kollarik and Undem 2002; Gu and

Lee 2006). Acidosis in the aiways can be the result of several processes including inflammation, ischaemia or aspiration of refluxing gastric contents, and exhaled breath condensate studies indicate that acidosis is associated with obstructive airway diseases such as asthma (Ricciardolo et al. 2004; Hunt 2006). The functional implications of acidosis in the airways are manyfold and comprise local effects on airway muscle tone and inflammatory processes as well as effects involving the central nervous system: cough, discomfort and pain (Jia and Lee 2007). In the guinea-pig isolated trachea acidosis has a differential effect on basal airway muscle tone and muscle responsiveness to contractile stimuli (Faisy et al. 2007). The acid-induced airway relaxation seems to be independent of sensory neurons and mediated by ASICs on smooth muscle cells, whereas the acid-evoked muscle hyperresponsiveness to acetylcholine involves sensory neurons expressing ASICs and TRPV1 (Faisy et al. 2007).

There is increasing evidence that acid is an important mediator in the pathogenesis of cough, given that inhalation of exogenous acid triggers cough, and acidosis accompanies a variety of respiratory diseases (Jia and Lee 2007; Kollarik et al. 2007). Following local generation, inhalation or aspiration, acid can directly stimulate vagal bronchopulmonary sensory nerve fibres involved in the cough reflex, Aα-fibre nociceptors in the large airways being most efficiently stimulated by rapid acidification (Kollarik et al. 2007). In contrast, C-fibre nociceptors expressing TRPV1 are able to continuously monitor the pH in the tracheopulmonary tissue and thus to react to persistent acidosis as it occurs in inflammation. In addition, acid is the single most important mediator of cough due to gastro-oesophageal reflux, given that acid-sensitive oesophageal afferent neurons sensitize the neural pathways underlying the cough reflex (Kollarik et al. 2007).

The sensors of vagal afferent neurons involved in acid surveillance and the cough reflex include TRPV1 and other probes (Figure 5). Accordingly, the TRPV1 blockers iodo-resiniferatoxin, JNJ17203212 and V112220 are able to attenuate cough induced by citric acid inhalation in guinea-pigs (Trevisani et al. 2004; Bhattacharya et al. 2007; Leung et al. 2007). It is not yet known whether ASICs account in full for the TRPV1-independent mechanisms of acid sensing in the airways (Canning et al. 2006; Kollarik et al. 2007; Leung et al. 2007). There is evidence that a TREK-like K_{2P} channel, which is sensitive to intracellular pH changes, could contribute to the function of intrapulmonary chemoreceptors (Bina and Hempleman 2007).

3.5 Acidosis in the skin

DRG neurons innervating the skin express many of the known acid-sensitive ion channels including TRPV1, ASICs and P2X. ASICs, for instance, are expressed by nociceptive and non-nociceptive afferent neurons innervating glabrous and hairy skin (Jiang et al. 2006). While intracutaneous perfusion of acid in human volunteers induces long-lasting non-adapting pain (Steen and Reeh 1993; Steen et al. 1995), transdermal iontophoresis of protons elicits transient pain that subsides within 5 min despite extended acid application (Jones et al. 2004; Cadiou et al. 2007). Intracutaneous injection of protons evokes an even shorter pain sensation that declines within 100 s (Rukwied et al. 2007). The route-dependent time course of proton-evoked cutaneous pain is probably due to differences in the kinetics of acid

exposure as well as in the activation/inactivation kinetics of the acid-sensitive ion channels involved (Kress and Waldmann 2006).

Intracutaneous co-injection of prostaglandin E_2 and acid has enabled Rukwied et al. (2007) to differentiate an early and late phase of proton-evoked pain. The late phase is thought to be mediated by TRPV1, because it is selectively potentiated by prostaglandin E_2 (Rukwied et al. 2007). Indeed, disruption of the TRPV1 gene prevents acid from stimulating unmyelinated afferent nerve fibres in a mouse skin-nerve preparation, whereas the proton-induced excitation of thinly myelinated nerve fibres persists (Caterina et al. 2000). Similarly, the effect of strong acidosis (pH 5.2) to cause release of CGRP from rat sciatic nerve axons is attenuated by capsazepine, whereas the peptide release evoked by mild acidosis (pH 6.1) is left unaltered (Fischer et al. 2003). Inflammation leads to upregulation of TRPV1 expression and function in afferent neurons supplying the skin and to an increase in the proton sensitivity of isolectin B_4-positive C-fibres (Carlton and Coggeshall 2001; Ji et al. 2002; Breese et al. 2005).

Other studies attribute ASICs an important role (Figure 5). Nitric oxide donors potentiate acid-induced currents in ASIC1, ASIC2 and ASIC3 homomeric channels and increase acid-evoked pain in the human skin (Cadiou et al. 2007). Acid-evoked pain is attenuated by nonsteroidal anti-inflammatory drugs (NSAIDs), which are known to interfere with ASIC expression and function, but left unaffected by the TRPV1 blocker capsazepine or desensitization to capsaicin (Steen et al. 1995; Voilley et al. 2001; Ugawa et al. 2002; Jones et al. 2004). These findings suggest that part of the analgesic effect of NSAIDs could be due to interference with ASICs, a conjecture that is consistent with the upregulation of ASICs in DRG neurons by cutaneous inflammation due to Freund's adjuvant (Voilley et al. 2001). An implication of ASICs is further supported by the ability of amiloride to reduce acid-induced pain in the skin but to spare capsaicin-induced pain (Ugawa et al. 2002; Jones et al. 2004). Post-operative pain due to skin incision in rats is attenuated by A-317567, a blocker of ASIC1, ASIC2 and ASIC3 subunits (Dubé et al. 2005).

Studies with ASIC knockout mice have yielded ambiguous results, which is not totally unexpected in view of the redundancy of acid sensors present on sensory neurons and the likelihood of compensatory changes that occur during the development of ASIC null mice. In the isolated skin-nerve preparation, the response of mechanoheat-sensitive C-fibres to acid is reduced in ASIC3 null mice (Price et al. 2001). Paradoxically, however, the behavioural licking response to acetic acid injection into the paw is preserved in ASIC3 knockout animals (Price et al. 2001). It awaits to be explored whether other acid sensors, e.g. K_{2P} channels and P2X purinoceptors, contribute to acidosis-evoked pain in the skin.

3.6 Acid sensors in the carotid body

Detection of blood pH and systemic acidosis is important for feedback regulation of respiration and cardiovascular function. To this end, O_2-, CO_2- and pH-sensitive chemoreceptors are present both in the carotid bodies and in the brain (López-López and Pérez-Garcia 2007). The acid sensors operating in the chemoreceptor (glomus type I) cells of the carotid body (Figure 5) comprise inward rectifier K^+ channels (Putnam et al. 2004), K_{2P} channels containing the TASK-1, TASK-3 and/or TASK-5 subunits (Buckler 2007;

Duprat et al. 2007), inwardly rectifying Cl^- channels (Petheo et al. 2001) and ASIC channels made up of ASIC1 and ASIC 3 (Tan et al. 2007). It is thus emerging that there is a parallel processing of O_2, CO_2 and pH signals in carotid body chemoreceptor cells, the resulting depolarization causing release of transmitters (ATP, acetylcholine and dopamine) from the chemoreceptor cells and subsequent excitation of afferent nerve endings (Rong et al. 2003; Zhang and Nurse 2004; López-López and Pérez-Garcia 2007; Tan et al. 2007).

Apart from acting on glomus type I cells, acidosis could also directly modify sensory neurons in the glossopharyngeal nerve, given that these neurons display a background K^+ conductance resembling THIK-1 which is weakly inhibited by extracellular acidosis (Campanucci et al. 2003). Acidosis enhances the ATP-induced whole cell current of petrosal ganglion afferents, which suggests that increased sensitivity of P2X receptors on afferent nerve fibres contributes to the transmission of acidosis in the carotid body (Zhang and Nurse 2004). Genetic disruption of the $P2X_2$ gene blunts the hyperventilatory response to hypoxia, which is consistent with the release of ATP from the glomus cells and the expression of P2X purinoceptors containing the acid-sensitive $P2X_2$ subunit by afferent neurons in the carotid sinus nerves (Rong et al. 2003). The ability of compounds such as halothane and isoflurane to activate TASK-3 channels in the carotid body is likely to have a direct bearing on their property to depress the hypoxic ventilatory drive when used for anaesthesia (Buckler 2007; Duprat et al. 2007).

3.7 Acidosis due to myocardial ischaemia

There is emerging evidence that ASICs account for the anginal pain associated with myocardial ischaemia, with lactate as a factor involved in channel activation. ASIC3 is highly expressed by sensory neurons innervating the rat heart (Benson et al. 1999; Sutherland et al. 2001; Yagi et al. 2006). Patch-clamp analysis of rat ASIC3 homomers and ASIC2a/ASIC3 heteromers shows that both channel complexes generate persistent inward currents at the modest extracellular pH changes typical of muscle ischaemia, the currents produced by the ASIC2a/ASIC3 heteromers being much larger than those produced by ASIC3 homomers (Yagi et al. 2006). The sustained current is caused by a region of pH where there is overlap between inactivation and activation of the channel (Yagi et al. 2006). Lactate causes the current to activate at slightly more basic pH values. The currents produced by the heterologously expressed ASIC3 and ASIC2a/ASIC3 complexes are in keeping with the sustained currents that changes of pH from 7.4 to 7.0 produce in somata of DRG neurons innervating the rat heart (Yagi et al. 2006). These observations indicate that ASIC3 homo- and heteromers may play a major role in detecting sustained myocardial ischaemia and in mediating prolonged anginal pain (Figure 5).

In contrast, the acidosis-evoked release of CGRP from sensory nerve fibres within the mouse heart appears to be mediated by TRPV1, since the response is absent in TRPV1 null mice but left unaltered in ASIC3 knockout animals (Strecker et al. 2005). Given that the neuropeptides (CGRP and substance P) released from afferent nerve fibres in the tissue are potent vasodilators, the TRPV1-mediated release of these peptides in myocardial ischaemia is likely to have a local cardioprotective effect (Wang and Wang 2005; Zhong and Wang 2007). This concept is supported by the finding that the recovery of cardiac function after

exposure to ischaemia/reperfusion is impaired by capsazepine and disruption of the TRPV1 gene (Wang and Wang 2005). The beneficial effect of preconditioning against cardiac injury induced by ischaemia/reperfusion is likewise attenuated in TRPV1 null mice (Zhong and Wang 2007).

3.8. Acidosis in the skeletal muscle

Unmyelinated afferent neurons innervating the skeletal muscle are excited by acidosis (Hoheisel et al. 2004), and injection of acid into the anterior tibial muscle of humans elicits a biphasic but short-lasting pain response (Rukwied et al. 2007). The second phase is suggested to involve TRPV1, because it is selectively potentiated by prostaglandin E_2 (Rukwied et al. 2007). Other studies provide evidence that ASIC3 is relevant to sensing acidosis in skeletal muscle. Thus, repeated intramuscular injection of acidic saline induces mechanical hyperalgesia, a response that is blunted by amiloride and knockout of the ASIC3 gene (Figure 5), but not by deletion of ASIC1a (Price et al. 2001; Sluka et al. 2003). Furthermore, ASIC3 is involved in the mechanical hyperalgesia that is associated with muscle inflammation (Sluka et al. 2007). Thus, ASIC3-deficient mice fail to develop mechanical hyperalgesia following experimental inflammation by injection of carrageenan into the muscle, whereas injection of a recombinant herpes virus vector to express ASIC3 in the muscle of ASIC3 knockout mice rescues the hyperalgesia phenotype (Sluka et al. 2007).

Analogously to the situation in the myocardium (Benson et al. 1999; Sutherland et al. 2001; Yagi et al. 2006) there is good reason to assume that lactic acid is a factor relevant to acidosis-evoked muscle pain. Lactate is formed under limited oxygen availability in the muscle and causes acidification of the extracellular space. In addition, lactate is able to sensitize ASIC3 to acid by decreasing the extracellular concentration of Ca^{2+} (Immke and McCleskey 2001). Lactic acid accumulation and activation of acid-sensitive afferent neurons in skeletal muscle contribute to the reflex hypertension and tachycardia that is evoked by exercise. A participation of ASICs is deduced from the ability of a low dose of amiloride ($0.5 \cdot^{00}$g/kg) to selectively block the hypertensive response to muscle exercise (Figure 5), whereas the response to capsaicin or muscle stretch is spared (Li et al. 2004; Hayes et al. 2007). In addition, P2X receptors and - at more pronounced acidity - TRPV1 also come into play (Gao Z et al. 2007). Another factor contributing to the muscle pressor reflex is thought to be diprotonated phosphate ($H_2PO_4^-$) whose excitatory action on afferent neurons involves both TRPV1 and ASICs as deduced from the inhibitory effects of capsazepine and amiloride, respectively (Gao et al. 2006).

3.9 Acidosis in the skeleton

ASICs are expressed not only by sensory neurons innervating bone but also by cells of the skeleton. Thus, ASIC1, ASIC2 and ASIC3 are found in the skeleton, with ASIC1 prevailing in chondrocytes, and ASIC2 and ASIC3 predominating in osteoclasts and osteoblasts (Jahr et al. 2005). These findings carry two important perspectives, because osteoclasts actively secrete acid when they resorb bone and because bone disorders with increased bone resorption by osteoclasts are frequently associated with pain. Osteoclasts degrade bone by secreting protons through a vacuolar H^+-ATPase, thereby creating an acidic microenvironment. Inflammation-induced mineral resorption in metatarsal bones of the rat is

associated with hyperalgesia, increased expression of ASIC1a, ASIC1b and ASIC3 in DRG neurons and enhanced c-Fos expression in the dorsal horn of the spinal cord (Nagae et al. 2006). The inflammation-induced hyperalgesia and upregulation of ASICs are reversed by the bisphosphonate zoledronic acid, which inhibits osteoclastic bone resoption, and by bafilomycin A1, an inhibitor of vacuolar H^+-ATPase (Nagae et al. 2006). Since amiloride is also beneficial (Nagae et al. 2006), it would seem that ASICs play a role in bone pain associated with osteoclastic mineral resorption (Figure 5).

Bone pain is one of the most common complications in cancer patients with bone metastases. Experimental evidence indicates that this type of bone pain is also related to bone degradation by osteoclasts and the acidic microenvironment that afferent neurons in the bone matrix are exposed to (Honore et al. 2000; Luger et al. 2001). Afferent neurons expressing TRPV1 innervate the mouse femur, and both genetic and pharmacological studies indicate that TRPV1 contributes to the hyperalgesia associated with an in vivo bone cancer model (Figure 5), given that disruption of the TRPV1 gene or treatment with the TRPV1 blocker capsazepine attenuates both ongoing and movement-evoked nocifensive behaviours (Ghilardi et al. 2005). In a model of bone cancer pain in the rat tibia, hyperalgesia is associated with an upregulation of mRNA for ASIC1a and ASIC1b, but not ASIC3 and TRPV1, in DRG neurons (Nagae et al. 2007). Although the findings in the rat and mouse have not yet been reconciled with each other, it is envisaged that both TRPV1 and ASICs participate in bone cancer pain.

Another line of investigation ascribes ASICs a role in the pain arising from vertebral disc herniation. The vertebral discs are innervated by primary afferent neurons (Ohtori et al. 2007), and an experimental model of lumbar disc herniation produced by application of nucleus pulposus to, and pinching of, L5 nerve roots is associated with mechanical allodynia and an upregulation of ASIC3 in the respective DRG (Ohtori et al. 2006). Local administration of lidocaine has been found to reverse both mechanical allodynia and ASIC3 upregulation (Ohtori et al. 2006), which makes a case for ASIC3 being involved in radicular pain. In this context it need be considered that ASIC3 is present on nucleus pulposus cells of the intervertebral discs and that ASIC3 expression by these cells is under the control of nerve growth factor (Uchiyama et al. 2007). In a functional perspective it would seem that ASIC3 is required for adaptation of nucleus pulposus cells to the acidic and hyperosmotic microenvironment of the intervertebral disc (Uchiyama et al. 2007).

4. PHARMACOLOGICAL INTERFERENCE WITH ACID SENSORS

From the pertinent studies it is clear that no single molecular sensor alone accounts for the acid sensitivity of afferent neurons. Neuroanatomical analyses and recordings from DRG and nodose ganglion neurons have shown that acidosis induces currents that can to a variable degree be attributed to the gating of ASICs, TRPV1 and other acid sensors, because these probes are differentially expressed by different subpopulations of sensory neurons (Liu et al. 2004; Dang et al. 2005; Sugiura et al. 2005; Ugawa et al. 2005; Leffler et al. 2006; Poirot et al. 2006; Smith et al. 2007; Sugiura et al. 2007). Although ASICs and TRPV1 survey different spectra of acidic pH, it is obvious that there is a redundancy of molecular

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acid sensors, which signifies that early detection of acidosis is physiologically so important that multiple mechanisms of acid sensing have evolved.

Acid sensors can be considered as drug targets in more than one respect. Many of the acid-sensitive ion channels are highly regulated by a number of endogenous factors as well as pharmacological agents. This is true, e.g., for NSAIDs regulating the expression and function of ASICs, pro-inflammatory mediators causing sensitization of TRPV1, and anaesthetics and other neuroactive drugs controlling the activity of K_{2P} channels. A number of acid-sensitive ion channels and receptors including ASICs, TRPV1 and P2X is upregulated by inflammation and nerve injury and appears to contribute to the hyperalgesia associated with these conditions. If so, drugs targeting peripheral acid sensors may evolve as novel therapies of chronic inflammation and pain. This concept is attractive for a number of reasons, particularly because it offers the opportunity to develop antinociceptive drugs with a peripherally restricted site of action, avoiding unwanted effects on the central nervous system. However, interfering with molecular probes that are physiologically so important poses a serious threat to homeostasis unless selective inhibition of “excess” acid sensors can be achieved while their physiological function is preserved.

With these considerations in mind, some of the attempts and developments to pharmacologically modulate acid sensors are discussed in the following sections, along with the rationale behind their design and emerging information on their utility and limitations.

4.1 ASICs

There is emerging evidence that ASIC expression is altered following inflammation and nerve injury (Voilley et al. 2001; Yiangou et al. 2001c; Mamet et al. 2002; Ohtori et al. 2006; Poirot et al. 2006; Nagae et al. 2007). These pathological implications of ASICs in pain and hyperalgesia suggest that ASIC blockade could be a novel avenue in pain therapy.

The pharmacology of specific ASIC-targeting drugs is just emerging. Most ASIC currents are blocked by the diuretic drug amiloride and its derivatives (e.g., benzamil) which, at the concentrations needed to inhibit ASIC activity, also suppress other ion channels and ion exchangers (Kress and Waldmann 2006; Page et al. 2007). As a consequence, the use of amiloride as a probe for the functional implications of ASICs is a pharmacological approach with limited specificity. In contrast, the peptide psalmotoxin 1 (PcTx1) isolated from the venom of the South American tarantula *Psalmopoeus cambridgei* is a highly selective ASIC blocker as it inhibits ASIC1a homomers with an affinity of 0.7 nM (IC50) but does not affect ASIC1a-containing heteromers (Escoubas et al. 2000). It modifies ASIC1a gating by shifting the channel from the resting to an inactivated state (Escoubas et al. 2000; Diochot et al. 2007; Mazzuca et al. 2007). Another selective ASIC blocker, APETx2, has been isolated from the venom of the sea anemone *Anthopleura elegantissima*. This peptide toxin inhibits several ASIC3-containing channels with IC_{50} values between 63 nM and $2{\cdot}^{00}$M, while its mode of action awaits to be elucidated (Diochot et al. 2004; Diochot et al. 2007). The first synthetic ASIC inhibitor different from amiloride is A-317567, a compound that blocks proton-evoked currents through ASIC1, ASIC2 and ASIC3 channels as well as the sustained phase of the ASIC3-like current in DRG neurons (Dubé et al. 2005).

A number of drugs interferes with ASIC function in a nonselective manner. This is in particular true for NSAIDs which counteract the upregulation of ASICs caused by experimental inflammation and inhibit proton-evoked ASIC currents in afferent neurons (Voilley et al. 2001; Mamet et al. 2002). Ibuprofen and flurbiprofen inhibit homomultimeric ASIC1a channels, whereas salicylic acid, aspirin and diclofenac block the sustained currents of ASIC3 and ASIC2b/ASIC3 channels (Voilley et al. 2001). Although it remains to be established whether the effects of NSAIDs on ASICs are relevant to their anti-inflammatory and analgesic action, it appears conceivable that ASICs participate in inflammatory hyperalgesia. This inference is supported by the ability of proinflammatory mediators such as nerve growth factor, 5-hydroxytryptamine, interleukin-1 and bradykinin to promote the transcription of ASIC3 in sensory neurons, 5-HT and NGF interacting directly with the promoter region of the ASIC3 gene (Mamet et al. 2002). Another proinflammatory mediator, arachidonic acid, is able to potentiate proton-evoked currents in heterologously expressed ASIC1a, ASIC2a and ASIC3 by a direct action on the channel protein (Smith et al. 2007).

Peripheral inflammation causes upregulation of FMRFamide-like peptides including neuropeptide FF and NPFF-R2 in DRG neurons and the spinal cord, and both neuropeptide FF and FMRFamide are able to potentiate H^+-gated currents in cultured sensory neurons and heterologously expressed ASIC1 and ASIC3 channels (Askwith et al. 2000; Catarsi et al. 2001; Deval et al. 2003; Yang et al. 2008). This action appears to result from a delay in current inactivation or from enhancement of a sustained and slowly inactivating current. ASICs are modulated by a number of other factors, some of which may be generated or released during inflammation and acidosis. Nitric oxide, for instance, is able to potentiate acid-induced currents in ASIC1, ASIC2 and ASIC3 homomeric channels (Cadiou et al. 2007). Serine proteases modulate the pH sensitivity of ASIC1a and ASIC1b, probably by proteolytic cleavage of the long extracellular loop (Poirot et al. 2004).

An approach to reduce excess ASIC expression and function could be the interference with ASIC translocation to the cell membrane, integration in the cell membrane, and phosphorylation. As other membrane proteins, ASICs appear to form macromolecular complexes with other proteins that may control the trafficking, function and turnover of ASIC subunits (Kress and Waldmann 2006; Wemmie et al. 2006) and be future targets for pharmacological intervention.

ASICs do not only play a role in pain owing to their peripheral nocisensor function but also in the spinal transmission of pain impulses. ASIC1a is prominently expressed by neurons in the dorsal horn of the spinal cord, and downregulation of these ASIC1a channels by antisense oligonucleotides attenuates thermal and mechanical hypersensitivity induced by peripheral administration of complete Freund’s adjuvant (Duan et al. 2007). ASIC1a participates in two forms of central sensitization in the spinal cord: C-fibre-induced “wind-up” and inflammation-evoked hypersensitivity of dorsal horn neurons (Duan et al. 1997). Based on these observations it has been proposed that specific blockade of Ca^{2+}-permeable ASIC1a channels may have an antinociceptive effect by reducing or preventing the development of central sensitization due to inflammation (Duan et al. 2007). ASIC1a in the brain emerges as being involved in cell damage after ischaemic stroke (Wemmie et al. 2006;

Friese et al. 2007), and blockade of this Ca^{2+}-permeable channel has been proposed to offer a 5 h therapeutic time window following a cerebral vascular insult (Xiong et al. 2006).

4.2 TRPV channels

Recognition of TRPV1 as a multimodal nocisensor, its sensitization by a number of proalgesic pathways and its upregulation under conditions of hyperalgesia have made this ion channel an attractive target for novel antinociceptive drugs. TRPV1 function can be counteracted both by desensitizing TRPV1 agonists as well as TRPV1 antagonists, and the current patent literature discloses more than 1,000 natural and synthetic compounds as TRPV1 activators or blockers (Gharat and Szallasi, 2008). It is important to consider that TRPV1 agonists and antagonists are not equivalent approaches (Holzer 1991; Szallasi et al. 2007). Capsaicin-sensitive afferent neurons express a plethora of different nocisensors, and desensitizing TRPV1 agonists do not only inactivate this nocisensor alone but defunctionalize the whole afferent neuron expressing TRPV1. In contrast, TRPV1 blockers selectively target this nocisensor and prevent its function. Resiniferatoxin and other compounds such as SDZ 249-665 are examples of TRPV1 agonists whose action manifests itself primarily in a defunctionalization of nociceptive neurons. Intravesical resiniferatoxin has been shown to be beneficial in patients with neurogenic bladder disorders (Avelino and Cruz 2006; Cruz and Dinis 2007) in which activation of afferent neurons by acidic urine penetrating through a leaky urothelium may play a role. SDZ 249-665 is able to attenuate acid-induced nociception arising from the peritoneal cavity of rats (Urban et al. 2000).

Most efforts have been directed at developing compounds that block TRPV1 activation in a competitive or noncompetitive manner. The first of this kind, capsazepine, has been extensively used in the exploration of the pathophysiological implications of TRPV1. However, the results obtained with this compound need to be judged with caution because the selectivity of capsazepine as a TRPV1 blocker is limited by its inhibitory action on nicotinic acetylcholine receptors, voltage-activated Ca^{2+} channels and other TRP channels such as TRPM8 (Docherty et al. 1997; Liu and Simon 1997; Behrendt et al. 2004). Since TRPV1 is activated by multiple stimuli that interact with different domains of the channel protein, not all TRPV1 blockers prevent acid from gating TRPV1 (Gavva et al. 2005a). For instance, AMG-0610 and SB-366791 inhibit the activation of rat TRPV1 by capsaicin but not acid, whereas iodo-resiniferatoxin, BCTC, AMG-6880, AMG-7472, AMG-9810 and A-425619 are TRPV1 antagonists that do not differentiate between capsaicin and protons (Seabrook et al. 2002; Gavva et al. 2004; Gavva et al. 2005a; Gavva et al. 2005b; Neelands et al. 2005). In addition, there are species differences in the stimulus selectivity of TRPV1 blockers as, e.g., capsazepine and SB-366791 are more effective in blocking proton-induced gating of human TRPV1 than of rat TRPV1 (Gunthorpe et al. 2004; Gavva et al. 2005a).

While the vast list of emerging TRPV1 blockers attests to the antinociceptive potential that is attributed to this class of pharmacological agent, it is important to be aware of the likely drawbacks these compounds may have. It has repeatedly been argued that TRPV1 subserves important homeostatic functions, and that the challenge for an effective and safe therapy with TRPV1 blockers will be to suppress the pathological contribution of “excess” TRPV1 while preserving its physiological role (Holzer 2004b; Hicks 2006; Szallasi et al. 2007).

TRPV1 is emerging as an important heat sensor involved in thermoregulation, given that most TRPV1 blockers cause hyperthermia in rats, dogs, monkeys and humans by a peripheral site of action (Gavva et al. 2007; Gava et al. 2008; Lehto et al. 2008). This hyperthermic action is unrelated to the ability of TRPV1 antagonists to block proton-induced activation of TRPV1 (Gavva et al. 2007). Hyperthermia is a serious adverse effect of TRPV1 blockade that went unnoticed after disruption of the TRPV1 gene (Szelényi et al. 2004; Woodbury et al. 2004), most probably because of developmental compensations in heat sensing.

One possible approach to differentiate between the pathological and physiological implications of TRPV1 is the development of uncompetitive blockers that preferentially bind to the active, open state of the channel and therefore will predominantly silence overactive TRPV1 (García-Martínez et al. 2006). Another approach that appears increasingly feasible is interference with the intracellular trafficking of TRPV1 to the cell membrane, which will result in a reduction of TRPV1 channels on the cell surface (Morenilla-Palao et al. 2004; Planells-Cases et al. 2005). Sensitization of TRPV1 is due not only to an enhancement of channel currents but also to a rapid translocation of TRPV1 from the cytosol to the plasma membrane (Morenilla-Palao et al. 2004; Van Buren et al. 2005; Zhang et al. 2005). The trafficking of TRPV1 (and other channels) to the cell surface is blocked by botulinum neurotoxin A (Morenilla-Palao et al. 2004), which may explain why intra-detrusor injection of botulinum neurotoxin A in patients with urinary bladder overactivity reduces TRPV1- and $P2X_3$-like immunoreactivity in the detrusor muscle and causes improvement of clinical and urodynamic parameters (Apostolidis et al. 2005). Intravesical administration of botulinum toxin likewise counteracts acetic acid-evoked bladder overactivity in rats (Chuang et al. 2004).

4.3 K_{2P} channels

Blockade of K_{2P} channels contributes to proton-evoked depolarization of DRG neurons from humans with neuropathic pain (Baumann et al. 2004), which makes it worthwile to elucidate the role of these background channels in health and disease. Apart from the targeted design of drugs specifically acting at K_{2P} channels, it is important to realize that many endogenous and exogenous factors modify and regulate the activity of these channels (Duprat et al. 2007; Mathie 2007). For instance, K_{2P} channels of the TASK subfamily are regulated by a number of different G protein-coupled receptor pathways (Duprat et al. 2007; Mathie 2007). Along these lines, TASK-1 and TASK-3 are inhibited by the endocannabinoid anandamide (Maingret et al. 2001; Duprat et al. 2007). Another interaction that is of clinical relevance relates to the effect of anaesthetics on K_{2P} channels. TASK-1 activity is stimulated by halothane and partially inhibited by isoflurane, whereas TASK-3 channel activity is enhanced by halothane as well as isoflurane (Duprat et al. 2007). In addition, the activity of both TASK-1 and TASK-3 is inhibited by bupivacaine (Duprat et al. 2007).

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5. CONCLUSIONS

Acidosis is a noxious condition associated with many pathological changes such as inflammation, ischaemia or mucosal defects in the upper gastrointestinal tract. To monitor these challenges of homeostasis, chemonociceptive afferent neurons express several acid sensors with distinct and overlapping properties. ASICs and TRPV1 have been most thoroughly studied, given that their proton sensitivities cover a complementary range of pH aberrations. While ASICs survey moderate decreases in extracellular pH, TRPV1 is activated only by severe acidosis resulting in pH values below 6. Acidosis, however, can sensitize TRPV1 to stimuli that are known to participate in inflammatory hyperalgesia. Emerging evidence indicates that other TRP channels such asTRPV4, TRPC4, TRPC5 and TRPP2, P2X purinoceptors, K_{2P} channels, inward rectifier K^+ channels, voltage-activated K^+ channels, L-type Ca^{2+} channels, hyperpolarization-activated cyclic nucleotide-gated channels, gap junction channels, Cl^- channels and acid-sensitive G protein-coupled receptors also contribute to the acid sensitivity of afferent neurons. This redundancy of pH surveillance systems testifies that the maintenance of interstitial and intracellular pH within a narrow range is of paramount physiological importance. Since acid-sensitive ion channels and receptors have been found to be overactive and/or upregulated in chronic pain conditions and to play a role in chemonociception, they represent worthwile targets for novel analgesic drugs. The pharmacological challenge in pursuing this goal is to differentiate between the pathological implications of acid sensors, which should be suppressed, and their physiological functions which should be preserved.

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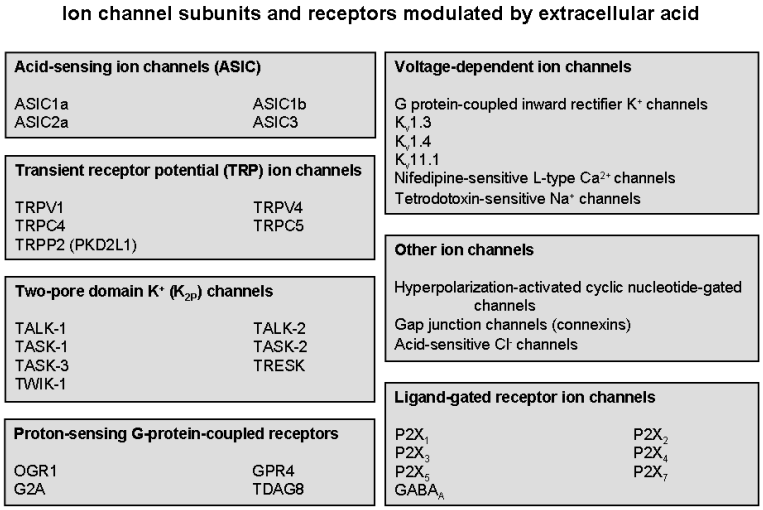

Figure 1.

Overview of ion channel subunits and receptors that are modulated by changes in the extracellular pH (acidification) and expressed by primary afferent neurons or their associated cells. For details see text.

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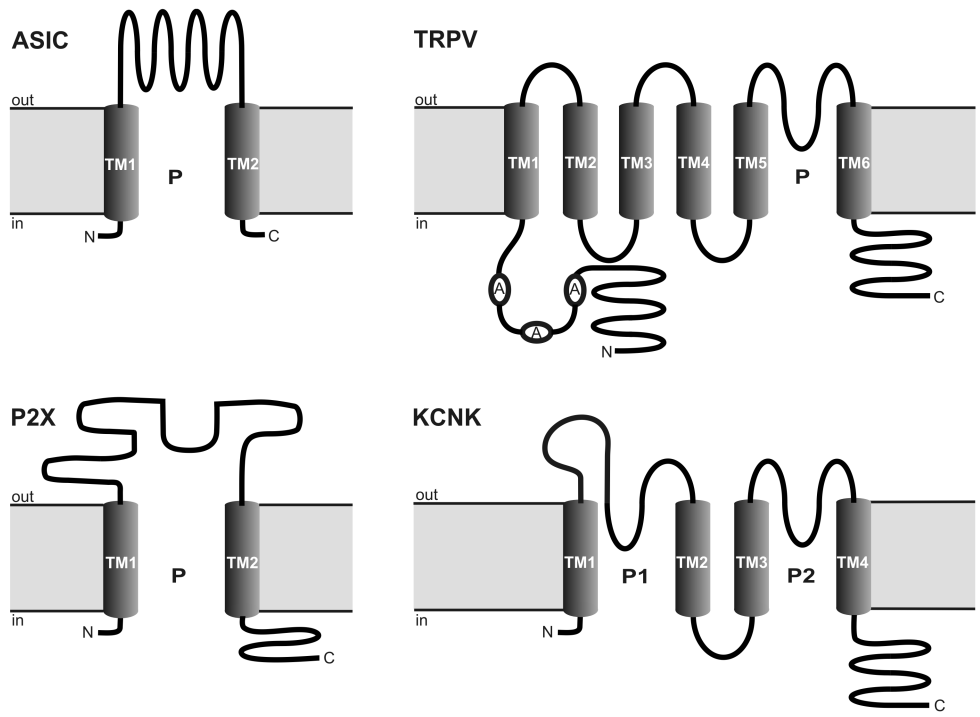

Figure 2.

Membrane topology of 4 classes of acid-sensitive ion channel subunits: ASIC (acid-sensing ion channel), TRPV (transient receptor potential ion channel of the vanilloid subtype), P2X (ionotropic purinoceptor) and KCNK (K_{2P} ion channel). A, ankyrin; C, COOH terminal; N, NH_2 terminal; P, pore; TM, transmembrane domain.

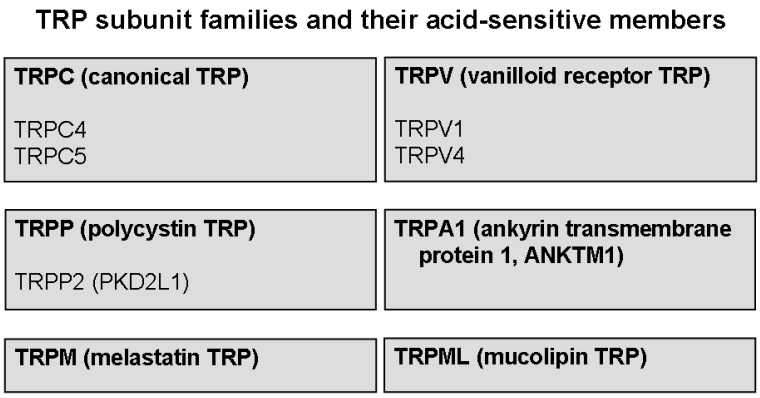

Figure 3.

Overview of the TRP channel subfamilies and of the acid-sensitive subunit members among the TRPC, TRPP and TRPV subfamilies. For details see text.

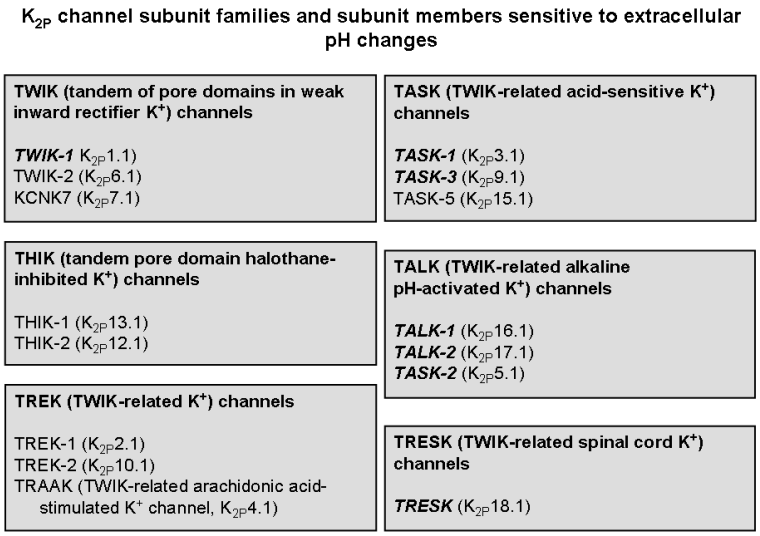

Figure 4.

Overview of the K_{2P} channel subunit families and of the subunit members (indicated in bold and italics) that are modulated by changes in the extracellular pH. For details see text.

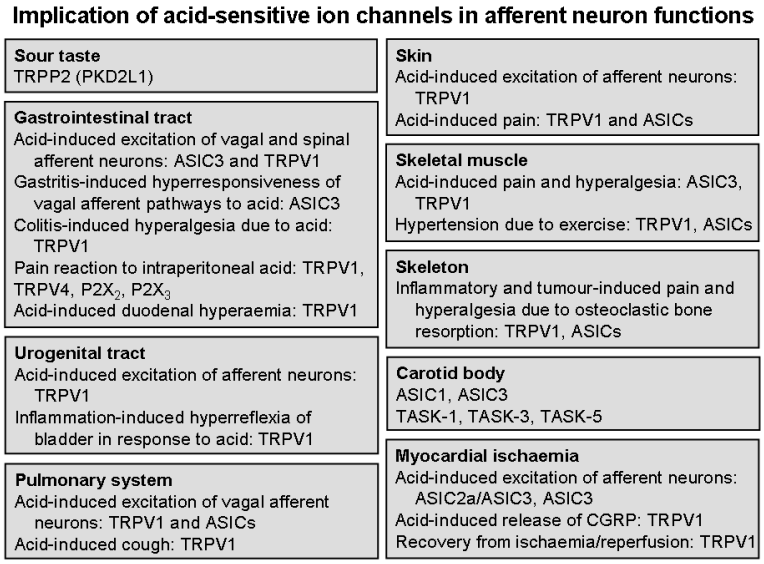

Figure 5.

Overview of the pathophysiological implications of acid-sensitive ion channels in afferent neuron function, based primarily on pharmacological antagonist and gene disruption studies. For details see text.