

EDITORIAL

Clinical & Experimental Allergy

Acid-sensing ion channels in allergic rhinitis

This editorial discusses the findings of the paper in this issue by S. Khoo et al. [2], pp. 1028–1039.

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Eosinophilic inflammation is a hallmark of allergic inflammation. After allergen exposure, basophils and eosinophils are the first infiltrating effector cells, followed by dendritic cells and T cells in the nasal mucosa [1]. Eosinophils are a source of eosinophil peroxidase and arachidonic acids. Due to inflammation, tissue acidosis is an important feature that has several effects on inflammatory cells, neurological cells and, last but not least, structural cells like epithelial cells. Khoo et al. describe, in this issue of the CEA, the role of eosinophil peroxidase in the expression of acid-sensing ion channel-3 in allergic rhinitis (AR) [2]. Acid-sensing ion channel-3 is a member of the family of acid-sensing ion channels (ASICs), a family of ligand-gated cation channels known as epithelial Na⁺ channels (ENaCs). ASICs are transiently activated by a rapid drop in extracellular pH. Low extracellular pH results from ischaemia and inflammation, with the latter leading to the activation of ASICs in AR. ASICs are expressed in all kinds of structural cells, neurological cells and cells of the immune system.

The role of ASICs is to respond rapidly to a reduction in extracellular pH with an inward cation current that is quickly inactivated despite the continuous presence of protons in the medium. Analysis in heterologous systems shows that ASICs have different pH sensitivities and inactivation kinetics. The pH for half-maximal activation (pH 0.5) is in the range 5.9–6.5 for ASICs 1a, 1b and 3. ASICs respond directly to lower environmental pH, resulting in an effect on all kinds of inner-cell activities in neurogenic cells, immune cells and struc-

tural cells. ENaC and ASIC subunits are co-expressed in multiple tissues and cell types, sharing subunits. Combinations of ASIC1 with ENaC subunits exhibit novel electrophysiological properties [3]. ASIC1 can be cleaved by serine protease matriptase [4] and other serine proteases [5]. This also makes it possible for serine protease from mast cells and basophils and other inflammatory cells to act on ASICs, including ASIC3, which is sensitive to eosinophil peroxidase [2]. Cleavage of ASICs leads to a decrease in current response when ASICs are activated by a pH drop.

ASICs in respiratory tract

Khoo et al. show that intranasal lactic acid administration induces nasal secretion in healthy controls and AR patients. This effect was abrogated due to pre-treatment with amiloride, a specific ASIC inhibitor only in AR patients, suggesting that the secretion in AR is mediated by functional ASICs [2]. Another interesting population of rhinitis patients who suffer from rhinitis and nasal discharge are the non-allergic non-infectious perennial rhinitis (NANIPER) patients, a group of idiopathic rhinitis patients. The NANIPER patients are also highly sensitive and a response can be provoked with cold dry air [6] that has similarities to skier's nose in AR patients in the Alps. Complete desensitization with capsaicin is effective treatment for at least 1 year [7]. It would be interesting to study ASIC3 expression in the nasal mucosa of NANIPER patients. The expression of ASICs in the lower airways is illustrated by the presence of alpha-ENaC and cystic fibrosis transmembrane conductance regulator (CFTR) [8] in alveolar type I (ATI) and ATII cells. The functional role of sodium channels, including ENaCs and ASICs, in the lung is to maintain a relatively dry environment in the alveolar space to support gas exchange [9]. In viral infection, ASICs are unregulated and they contribute to a mechanism that supports this relatively dry environment, which could be disturbed by damage to epithelial cells and their capacity

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to 'dry' the airways. It is known that high levels of NO are present in the upper airway. These high levels of NO and/or other free radicals may contribute to tissue acidosis. The potentiation of ASIC activity by NO in the airways is likely to be of physiological relevance in pathologies [10].

Acid-sensing ion channels (ASICs) in nerves pass through current, ASIC1b and ASIC3 are restricted to peripheral sensory neurons and extracellular acidosis correlates with pain sensations. A blocker-like amiloride or non-steroidal anti-inflammatory drugs (NSAIDs) support ASIC function in acid-induced pain. When tissue pH falls below a certain threshold, ASICs act and, in the end, a sensation of pain results.

In the nasal mucosa, acidation occurs as a result of inflammation. Rhinosinusitis involves symptoms produced by two mechanisms. Local symptoms are caused by the generation of local inflammatory mediators, such as bradykinin, prostaglandins and histamine in the respiratory epithelium. Bradykinin is commonly induced by viral and bacterial inflammations and it causes pain-related symptoms, such as sore throat pain and sinus pain. This effect of bradykinin may be due to the inflammation-induced acidification of the tissue that triggers ASICs, resulting in the sensation of pain. The exact role of mediators of allergic inflammation on the sensitivity and reactivity of afferent neurons and these secretory reflexes remains unknown [11].

Allergic rhinitis (AR) and other diseases, like chronic sinusitis, are generally accompanied by pain in the diseased area [12]. In the first place, nerve endings are abundant in the nasal mucosa. It is one of the most innervated mucosal sites. When airborne particles or pathogens come into contact with the inner wall of the nasal mucosa, patients may sense them. Pain results due to pain mediators like neurotrophins (NGF, histamine, bradykinin), prostanoids (PGE₂, LTB₄) serotonin protons, cytokine IL-1, IL-6 peptides, substance P and free radicals. Nasal wash with isotonic fluid and neutral pH is used to reduce symptoms of facial pain by removing an acidic milieu. In inflammatory response to viruses, these pathogens induce all kinds of inflammatory responses, including a sensation of pain. Due to the innervation of C-fibres and other nerves expressing ASIC3, and because of the acidic milieu, patients may experience facial pain with moderate chronic course.

ASICs expressed by immune cells and the effect of acidosis on immune cells

Allergic inflammation is a complex interaction between all kinds of immune cells, including eosinophils, mast cells, basophils, T-cells and dendritic cells (DCs). These immune cells are present in the niches of airway epithelial cells.

In inflammatory disease, pH values are considered to be a hallmark of local inflammatory reactions when levels fall below pH 7. In exhaled breath condensation in asthmatic patients, pH values are lower than those in normal tissues [13]. These lower values could be due to more inflammation. In allergic inflammation cells like eosinophils, basophils, mast cells degranulate and proteins like EPO, MBP and ECP can be found in lavage fluids, reflecting active inflammation. In addition, mediators like arachidonic acid, leukotrienes and prostaglandins are released, influencing the microenvironment. Arachidonic acid potentiates the currents carried by ASIC1a and ASIC3 in rat dorsal root ganglion neurons [14]. This illustrates the functional reactivity of ASICs to these mediators. The next effect of all these inflammation-driven mediators is the sensitivity to changes in pH in the cells present in the airways. Structural cells like the epithelial cells are highly susceptible to pH. Inflammatory cells are also sensitive to changes in pH. Murine studies have shown that DCs express ASIC3 and treatment lowering the pH from 7.3 to 6.5 induces the activation of DC by the induction of MHCII, CD80 and CD86, all of which are important for the interaction with T-cells. These effects result in an enhanced proliferation index for T-cells, which could be inhibited by amiloride or NSAIDs [15]. In mice and humans, eosinophil viability is enhanced by acidic pH in a cAMP- and GPR65-dependent manner [16]. Acidosis has all kinds of effects on inflammatory cells: it promotes the MHC II expression of neutrophils, upregulates CD11c and MHCII and costimulatory molecules of DCs and the Ag-presenting ability of DCs via ASICs in mice. In humans, similar observations have been made and the incubation of DCs at pH 6.5 results in the activation of the PI3K/Akt and MAPK pathways and the induction of IL-12 [17]. It increases the acquisition of extracellular antigens for MHC class I-restricted presentation and the ability of antigen-pulsed DCs to induce both specific CD8⁺ CTL and B-cell responses [18]. NSAIDs can stop the effects of acidosis on DCs [15] and NSAIDs have no effect on human DCs in pH-neutral environments [19]. Acidosis not only affects epithelial cells; it also leads to general immune stimulation.

Acid-sensing ion channels (ASICs) may be therapeutic targets. Experiments with ASIC3^{-/-} mice and miRNA knock-down ASIC3 expression, to the extent that this is described by the reduction in pain in hyperalgesia models by the Sluka group [20]. ASICs are widely expressed in tissues and central and peripheral nerves, and so several treatment entities are used. Compounds like APTEx2 peptide and A-317567 have been used in muscle pain experiments [21]. Other compounds like agmatine or acraïne seem to be less suitable for clinical use because they need to be used in high concentrations. No data are available, yet indicating that this com-

pound can be used in rhinitis or that it has benefits for inflammation. These results indicate that it is possible to target ASIC3 and some benefits have already been found in pain models, suggesting that targeting ASIC3 in rhinitis may be a valid avenue for future investigation.

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