Protein Cell 2011, 2(6): 433–434
DOI 10.1007/s13238-011-1066-6

Protein & Cell

NEWS AND VIEWS

A "bitter" end to asthma revealed

Min-Sheng Zhu

The Model Animal Research Center, Nanjing University, Nanjing 210012, China
✉ Correspondence: zhums@nju.edu.cn

Speaking of asthma, one is immediately reminded of incessant coughing and wheezing, and the unsightly scene of phlegm-spitting. A wide range of remedies have been tried, ranging from ancient folklore belief of smelling honey to modern inhaling β2-adrenoceptor agonists, but none proves to have long-lasting effect for this common chronic pulmonary disease. As a Chinese proverb says, a good medicine always tastes bitter. Maybe the problem with those old remedies is that they are not bitter enough. Jokes aside, there may actually be some truth in this, as shown by a recent study from Stephen B. Liggett's laboratory in the University of Maryland (Deshpande et al, 2010). In a survey for G-protein coupled receptors (GPCR) in human airway smooth muscle (ASM), this group inadvertently identified several types of bitter taste receptors, which are members of the GPCR family. Even more surprisingly, they found that stimulation of these bitter taste receptors with agonists such as saccharin, chloroquine, and denatonium relaxed ASM to the extent that superseded three times the maximum relaxation induced by β2-adrenergic agonists. This finding may eventually open up new ways of relieving asthma symptoms with thousands of known synthetic or natural bitter tastants.

The difficult breathing symptom of asthma is primarily caused by constriction in the bronchial passage, which itself is the result of remodeling of the bronchial smooth muscle. As inflammation is known to enhance contractile responsiveness of airway to various irritants and to induce airway remodeling in asthma, inflammation was once considered the primary cause of asthma pathogenesis. However, clinical evidence indicated that anti-inflammation strategy offered little benefit to asthma patients (Zuyderduyn et al., 2008). A more direct approach aimed at relaxing smooth muscle contraction with β2-adrenergic receptor agonists was then widely adopted, but this strategy has its downfall in carrying unnecessary risk of excessive heart stimulation and its efficacy is also in question.

Smooth muscle contraction is initiated by phosphorylation of the regulatory myosin light chain (RLC), the level of which is determined by the balance between myosin light chain kinase (MLCK) and myosin light chain phosphatase (MLCP) activities. After several decades of investigation, many signals that evoke smooth muscle contraction by activating MLCK have been defined. These include membrane depolarization that activates MLCK by elevating cytosolic calcium concentration through opening the L-type calcium channel and muscarinic agonists that induce calcium release and MLCK activation through GPCRs. On the other hand, some agonists can relax contracting smooth muscle by binding to β2-adrenergic receptor (β2AR), which is coupled to the stimulatory G protein, Gs. The Gαs subunit then mediates the relaxant signaling cascades by activating K^+ channels and the cAMP–PKA axis. The currently approved therapeutics for relaxing asthmatic smooth muscle are agonists to β2AR, usually delivered in the form of an inhaling mist. However, according to a report from FDA, frequent use of β2 adrenergic agonists risks worsening wheezing and respiratory death by more than two-fold compared to placebo control, and at least half of patients in the cohort exhibited inadequate control of the disease. To improve the efficacy and reduce the side effect of existing asthma drugs, Liggett's group screened subtypes of GPCR hoping to find new drug targets. In airway smooth muscle, such agonists as histamine, leukotriene, prostaglandin and others acting at GPCRs caused enhanced bronchial hyper-responsiveness and airway constriction; some agonists appeared to oppose constriction or evoke relaxation. Liggett's group found that such contradictory or paradoxical responses of GPCR in airway smooth muscle are due to alternative splicing of GPCR and hence diversify the complement of receptors. Among these GPCRs, the cognate G proteins for bitter taste receptors have been identified in human airway smooth muscle. Receptors for bitter tastes on the tongue are thought to have evolved for the avoidance of plant-based toxins. What is their function in the airway? Liggett and his colleagues thought that existence of such bitter taste receptors on airway is a protective mechanism for avoidance of harmful inhalants by bronchoconstriction. This idea is supported by the fact that bitter taste receptors coupled to increase in cytosolic calcium in specialized taste cells, which are very similar to many agonists of GPCR

capable of inducing smooth muscle contraction. However, they found that the bitter taste receptor agonists cause marked relaxation of the airway. The bitter tastants, chloroquine, denatonium and quinine, caused dose-dependent relaxation, with a maximal response of > 90% loss of the contraction induced by acetylcholine or serotonin. Under the same experimental condition, beta-adrenergic receptor agonist isoproterenol caused about 30% reduction in active tension. These relaxant responses can also be observed in human airway smooth muscle. Surprisingly, they found that bitter taste receptor agonists had greater efficacy than any other known therapeutic reagents. In asthma animal model with allergic inflammation, these bitter tastants are able to reduce asthmatic bronchoconstriction effectively. Thus, the investigators propose that activation of this bitter pathway has therapeutic relevance in a diseased state of asthma. Because bitter taste receptors are specifically expressed in taste tissue and airway smooth muscle, and the effects of their agonists are powerful, we may expect a great decrease of side-effects of these agonists in future therapy. Yet, a powerful relaxation does not mean a perfect therapy for asthma. The relaxed smooth muscle will contract again very soon and restore the lung in disease state again, because the asthmatic smooth muscle will still keep an increased sensitivity to agents, such as acetylcholine and histamine.

Many studies suggest that the development and maintenance of this hyper-responsiveness depend on Th2 cytokines including IL-4 and IL-13, which are over-expressed in asthma lung. Blockade of IL-4 receptor with antagonists may improve the pulmonary function in human asthmatics. In fact, some anti-inflammation or anti-immunological therapeutics usually obtain more or less outcomes. Thus, the inflammatory response is usually believed to be an important target for asthma therapy. The question is whether the hyper-responsiveness of airway constriction is caused by altered contractile properties intrinsic of smooth muscle cell after inflammatory or immunological stimulation in asthma. If it is, the therapeutic target should be moved to inflammatory smooth muscle in airway. Finkelman's group of University of Cincinnati College of Medicine used IL-4R knockout mice and tissue-specific transgenic mice to examine the roles of IL-4R and IL-4 in asthmatic smooth muscle tissues. They found that direct smooth muscle activation by IL-4, IL-13, or allergen is sufficient but not necessary to induce hyper-responsiveness of airway, where contractility is also activated by IL-13 in smooth muscle *in vivo*. These observations strongly suggest that the altering properties of smooth muscle are the primary causes of asthma. Therefore, combination with direct smooth muscle relaxation particularly by bitter receptor agonists, and intervention for IL-4 or IL-13 response in smooth muscle cells may be a prospective therapeutic strategy to cure human asthma. However, this strategy requires further development. Either the bitter tastants or cytokines function through the receptors that work on the top of the signal cascades. Their responsiveness may be easily "modified" by signaling networks, and the side effects may be raised by ubiquitous expression of cytokine receptors. Thus, it is still necessary to continue our bitter search for new therapeutic strategies and new drug targets for human asthma, although the current bitter receptor pathway is promising.

REFERENCES

Deshpande, D.A., Wang, W.C.H., McIlmoyle, E.L., Robinett, K.S., Schillinger, R.M., An, S.S., Sham, J.S.K., and Liggett, S.B. (2010). Bitter taste receptors on airway smooth muscle bronchodilate by localized calcium signaling and reverse obstruction. Nat Med 16, 1299–1304.

Zuyderduyn, S., Sukkar, M.B., Fust, A., Dhaliwal, S., and Burgess, J. K. (2008). Treating asthma means treating airway smooth muscle cells. Eur Respir J 32, 265–274.

