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Calcilytics for asthma relief:

A promiscuous calcium receptor holds promise as a therapeutic target for asthma

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For decades, patients suffering from allergic asthma—the symptoms of which range from wheezing and shortness of breath to extreme difficulty in breathing—generally have been treated with agents that reduce airway inflammation, such as corticosteroids, or reverse airway constriction, such as beta2-adrenergic receptor agonists. Unfortunately, up to 55% of asthmatics have suboptimal control with these drugs (1). Moreover, safety concerns regarding the use of beta2 agonists have resulted in more stringent guidelines for their clinical use (2). Thus, there is pressing need to develop new and safe therapies. A study by Yarova *et al.* (3) points to a protein that controls the constriction and proliferation of smooth muscle cells lining the bronchial airway. Moreover, there is already a drug that inhibits this protein.

The calcium-sensing receptor (CaSR) is best known for its role in regulating calcium homeostasis. Expressed in the parathyroid gland, it surveys the concentration of circulating calcium. Calcium binds to and activates the CaSR, triggering intracellular signals that suppress the release of parathyroid hormone. This reduces calcium release from stores such as bone. However, the CaSR is promiscuous in its activation by other molecules, including polyvalent cations, amino acids, and virus elements. Indeed, Yarova *et al.* show that the CaSR uses this robust sensing ability to control airway hyperresponsiveness and inflammation in asthma. Importantly, inhibitory small molecules previously developed to antagonize the CaSR and treat hypocalcemia mitigate key features of allergic asthma.

Yarova *et al.* examined bronchial airway tissues and cells from a mouse model of asthma and biopsies from asthma patients, and demonstrate that calcium, as well as various agents (including eosinophilic cationic protein and l-arginine-derived polyamines) whose concentrations are elevated in the bronchial airway of asthma patients during allergic inflammation, can stimulate CaSR. In bronchial airway tissue excised from the mouse asthma model, as well as in the intact animal, this stimulation resulted in airway smooth muscle contraction, and enhanced the contractile effect of bronchoconstrictors such as acetylcholine or histamine. The authors confirmed the CaSR-dependent nature of these effects in both human bronchial airway smooth muscle cells with reduced expression of CaSR and in bronchial airway tissue and cells isolated from genetically modified mice lacking CaSR. In addition, when mice with allergic lung inflammation inhaled CaSR antagonists (calcilytics), the asthma phenotype was reversed. Calcilytics blocked the CaSR, prevented airway hyperresponsiveness and, surprisingly, inflammation. The latter effect

could be due to expression of the CaSR not only in resident lung cells (airway smooth muscle and epithelia) but also in invading inflammatory cells (eosinophils, macrophages).

Interestingly, Yarova *et al.* show that inflammation increases CaSR expression in human and mouse. That is consistent with the findings that show a prominent role of the CaSR in affecting airway contractility under asthmatic conditions.

Thus, the CaSR emerges as an exciting potential asthma therapeutic target. Recently, both bitter tastant receptors and chloride channels have been proposed as drug targets in asthma (4). Activated bitter tastant receptors relax airway smooth muscle and dilate the airway in human and mouse, but the mechanism is not yet clear (5). Chloride channel blockers also act on airway smooth muscle and limit the ability of agonists such as acetylcholine to stimulate contraction (6). However, calcilytics have certain advantages that favor success as a therapy for asthma. They are small molecules that are readily deliverable by inhalation, thus limiting potential problematic systemic effects. Their efficacy is favored by the ability to target multiple cell types and mechanisms that contribute to the asthma phenotype. Perhaps most importantly, the safety of 3 different oral calcilytics as osteoporosis drugs is suggested in Phase I clinical studies (7, 8), and the calcilytic NPSP795 is currently in phase II clinical trials for the treatment of autosomal dominant hypocalcemia (9, 10). Results from these studies may help limit the regulatory hurdles that an inhaled calcilytic as an asthma therapy will ultimately face. The ability to assess the presence of CaSR activators in the lung could enable identification of those asthmatics most likely to respond to calcilytics, in line with the goal of personalized asthma treatment (11).

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During asthma symptoms

Normal airway restored

Figure.

Asthma relief. Numerous agents activate the CaSR expressed on airway smooth muscle, as well as on certain inflammatory cells and airway epithelia (not shown). CaSR activation in airway smooth muscle promotes contractile hyperresponsiveness and possibly airway remodeling. CaSR activity also facilitates inflammatory cell infiltration into the lung (not shown). Calcilytics block the CaSR, and may represent an inhalable agent to treat asthma. IP₃, inositol 1,4,5-trisphosphate; ERK, extracellular signal-regulated kinase; PI3K, phosphatidylinositol 3-kinase.