Bitter Taste Receptors: Taking a Bigger Bite of Airway Smooth Muscle Pathophysiology

Atypical sensory receptors in airway cells are no longer atypical. The study of G protein–coupled receptors in airway cells, particularly airway smooth muscle, has been a topic of interest for many decades. This is relevant because many endogenous ligands and exogenous therapeutics target classic signaling pathways coupled through G_s, G_i, and G_q proteins to regulate airway smooth muscle contractile tone and thus airway luminal diameter in bronchoconstrictive diseases. Although classical prorelaxant β_2-adrenoceptors and procontractile muscarinic, histamine, and leukotriene receptors have been known for a long time, only in the last decade has it been realized that receptors thought to be limited to other neuronal or sensory tissues can also modulate airway smooth muscle tone. Ligand-gated ion channels of the $GABA_A$ (γ-aminobutyric acid A receptor) (1), glycine (2), and NMDA (*N*-methyl-D-aspartate) (3) families were once thought to be limited to neuronal cells but have been shown to be functionally expressed in airway smooth muscle cells. In landmark research published in 2010, Deshpande and colleagues demonstrated the functional expression of bitter taste receptors on airway smooth muscle that served as a novel target for airway smooth muscle relaxation (4). This finding unleashed a flurry of investigations that identified at least six subtypes of the 25 known subtypes of bitter taste receptors (TAS2R) that are expressed in airway smooth muscle; these are functionally coupled to relaxation, and they relax airway smooth muscle even in the presence of β_2-adrenoceptor tachyphylaxis (5). TAS2R-mediated signaling in airway smooth muscle cells is maintained in cells obtain from human patients with asthma (6), appears to couple through $G\alpha_{i1,2,3}$ (7), and undergoes limited homologous desensitization (8).

In this issue of the *Journal* (pp. 532–540), Kim and colleagues further expand the functional understanding of the role of TAS2R in airway smooth muscle proliferation (9). Not only is acute contraction and relaxation of airway smooth muscle a determinant of airway caliber, but airway smooth muscle hypertrophy and hyperplasia also contribute to chronic airway narrowing. Kim and colleagues show that biased TAS2R chronic agonism inhibits airway smooth muscle growth by downregulating phosphorylated extracellular signal-regulated kinases 1/2 (ERK1/2). This suggests that TAS2R ligands could have complementary and synergistic beneficial effects on two pathophysiologic aspects of airway smooth muscle in bronchoconstrictive diseases: acute relaxation of contracted airway smooth muscle and chronic antiproliferative effects of smooth muscle mass in the airways.

Kim and colleagues demonstrate that three diverse ligands—papaverine, aloin, and famotidine—acutely increase intracellular calcium concentrations and induce phosphorylation of ERK1/2 in human airway smooth muscle cells. In contrast, only papaverine and aloin impaired cell growth measured over 3 days, which was quantified by measuring cell numbers and by visualizing monolayer expansion of cultured cells into a scraped area of a culture plate. Similarly, the authors demonstrate that chronic exposure of human airway smooth muscle cells to papaverine and aloin, but not famotidine, resulted in a decrease in phosphorylated ERK1/2 while not affecting levels of total ERK. These chronic effects of papaverine or aloin on phosphorylated ERK are in contrast to the absence of acute inhibitory effects of other TAS2R ligands on ERK1/2 phosphorylation (10). In earlier work, pretreatment with chloroquine, quinine, or saccharin, some of the earliest reported TAS2R ligands in airway smooth muscle (4), did not block the acute phosphorylation of ERK1/2 induced by platelet-derived growth factor or epidermal growth factor (10). However, the study by Kim and colleagues differs from the previous studies in at least two important ways that could account for the differences: *1*) The stimulus for phosphorylation of ERK was platelet-derived growth factor or epidermal growth factor in the earlier study, whereas serum was the stimulant in the study by Kim and colleagues; and *2*) in the earlier study, TAS2R ligands were given as a 15-minute pretreatment before ERK1/2 phosphorylation was measured 30 minutes later, whereas in the study by Kim and colleagues, inhibition of ERK1/2 phosphorylation by papaverine was demonstrated after 6, 12, and 24 hours of serum exposure. Thus, the differences in these studies are not necessarily incongruent but may be accounted for by different stimulants of ERK1/2 phosphorylation and different time courses.

Perhaps one of the more challenging areas of TAS2R signaling mechanisms is the diverse array of ligands that activate TAS2Rs. Virtually all of these ligands have other known receptor/cellular targets (11), which may confound the interpretation of cell signaling events. Fortunately, this concern is addressed in the study by Kim and colleagues by the siRNA knockdown of TAS2Rs. The combined knockdown of TAS2Rs 10, 14, and 31 eliminated the effects of papaverine on cell growth inhibition and acute phosphorylation of ERK1/2.

These findings expand on an emerging area of sensory signaling in airway biology (12) and add to the understanding of biased agonism of G protein–coupled receptors. Indeed, some TAS2R ligands may directly relax airway smooth muscle, whereas other ligands, acting through the same receptor but activating different or additional pathways, may have a synergistic effect in asthmatic airways by decreasing airway smooth muscle proliferation and improving chronic airway caliber. It will be important to determine whether many of these effects demonstrated in cultured cells or *ex vivo* tissues translate into physiologic effects *in vivo*, which is a requirement for their potential therapeutic use. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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