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Review

Taste and smell GPCRs in the lung: Evidence for a previously unrecognized widespread chemosensory system

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ABSTRACT

Taste and smell receptor expression has been traditionally limited to the tongue and nose. We have identified bitter taste receptors (TAS2Rs) and olfactory receptors (ORs) on human airway smooth muscle (HASM) cells. TAS2Rs signal to PLCβ evoking an increase in $[Ca^{2+}]_i$ causing membrane hyperpolarization and marked HASM relaxation ascertained by single cell, ex vivo, and in vivo methods. The presence of TAS2Rs in the lung was unexpected, as was the bronchodilatory function which has been shown to be due to signaling within specific microdomains of the cell. Unlike β_2-adrenergic receptor-mediated bronchodilation, TAS2R function is not impaired in asthma and shows little tachyphylaxis. HASM ORs do not bronchodilate, but rather modulate cytoskeletal remodeling and hyperplasia, two cardinal features of asthma. We have shown that short chain fatty acids, byproducts of fermentation of polysaccharides by the gut microbiome, activate HASM ORs. This establishes a non-immune gut-lung mechanism that ties observations on gut microbial communities to asthma phenotypes. Subsequent studies by multiple investigators have revealed expression and specialized functions of TAS2Rs and ORs in multiple cell-types and organs throughout the body. Collectively, the data point towards a previously unrecognized chemosensory system which recognizes endogenous and exogenous agonists. These receptors and their ligands play roles in normal homeostatic functions, predisposition or adaptation to disease, and represent drug targets for novel therapeutics.

Contents

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1. Introduction

G-protein coupled receptors (GPCRs) are well known to be expressed throughout the body, and they represent the largest superfamily of signaling proteins in the genome. We have recently found "sensory GPCRs" of the bitter taste receptor (TAS2R) family [1], and the olfactory receptor (OR) family [2] expressed deep in the lung, on human airway smooth muscle (HASM) cells. These findings of receptors "in the wrong place" was initially met with skepticism because of the bias that such specialized receptors were only expressed on taste cells of the tongue and sensory neurons in the nose, responding to external ligands involved in taste and smell perceptions, respectively.

We have now extensively characterized these receptors on HASM [1–7], and it is now clear that TAS2Rs and ORs are expressed on other cell-types in different organs as well. They represent a previously unrecognized chemosensory system that is activated by endogenous and exogenous agonists, representing potential homeostatic/disease loci as well as novel targets for therapeutic intervention. At the molecular level, these receptors also appear to signal differently than was expected from the pharmacology in taste and smell perception, indicating a plasticity of receptor-activated events with these receptors that is cell-type dependent. Herein we review TAS2R and OR expression in HASM, the biochemistry of their cellular signaling, and their physiologic function, including development of enabling single-cell technologies for ascertaining mechanical effects of receptor activation and performing screening for new therapeutics.

2. TAS2Rs on HASM

2.1. Expression of TAS2Rs on HASM

There are 25 TAS2R subtypes in the human genome [8,9]. Quantitative RT-PCR was performed using 25 subtype-specific primers to determine mRNA levels in cultured HASM cells derived from subjects without lung disease. Six subtypes (TAS2R10, 14, 31, 5, 4, 19) were found at levels greater than the β_2-adrenergic receptor (β_2AR) (Fig. 1A) [1]. In taste cells, TAS2Rs couple to the G-protein gustducin, and the βγ subunits released from the heterotrimer activate phospholipase Cβ (PLCβ), resulting in an increase in inositol 1, 4, 5-triphosphate (IP_3). IP_3 activates the IP_3 receptor on the endoplasmic reticulum resulting in release of Ca^{2+} from this intracellular depot. Released $[Ca^{2+}]_i$ is thus readily assayed as a second messenger for activated TAS2Rs. In taste cells the increase in $[Ca^{2+}]_i$ activates a transient receptor potential (TRP) channel, depolarizing the membrane, with release of neurotransmitter and subsequent activation of the Type III cell which signals to the brain. A search of available expression databases and our own studies indicated expression of $G_{\alpha gust}$, PLCβ, IP_3 receptor, but not the classic TRP channel (TRPM5), in HASM. This suggested a deviation of signaling, if these receptors were functional, in HASM compared to taste cells. Because of their higher expression, most of our studies have been targeted to TAS2R10, 14, and 31.

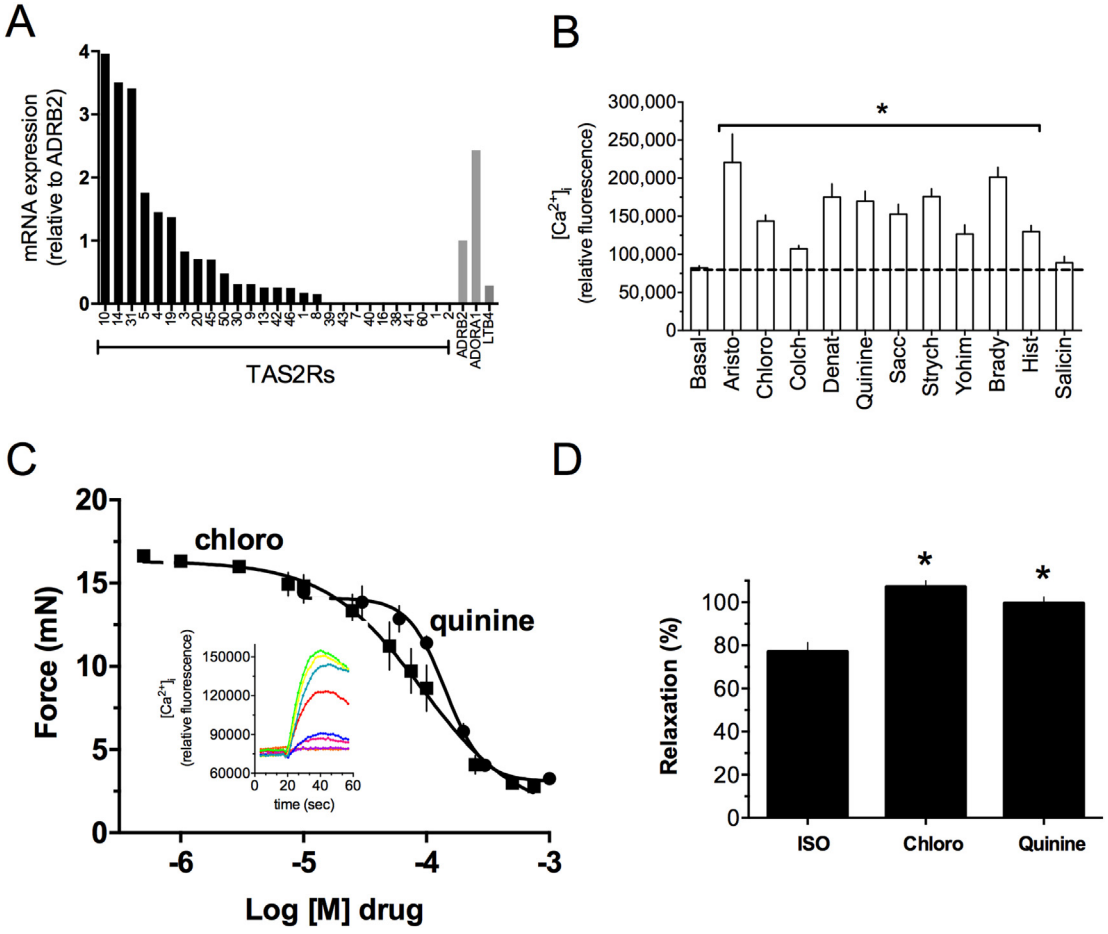

Fig. 1. TAS2R expression and function in human airway smooth muscle (HASM). (A) Relative expression of the 25 TAS2R subtypes in HASM as determined by quantitative RT-PCR. A high expressing (ADORA1) and low expressing (LTB4R) GPCR known to be expressed on HASM were controls. (B) $[Ca^{2+}]_i$ response to TAS2R agonists. Bradykinin and histamine, acting at Gq-coupled receptors, acted as positive controls. The bitter substance salicin is an agonist for TAS2R16 which is not expressed (see A), and showed no $[Ca^{2+}]_i$ response. Results are from 4 to 6 experiments. *$p < 0.05$ vs basal. (C) Relaxation of intact mouse airway by the TAS2R agonists quinine and chloroquine. Airways were precontracted with serotonin ($n = 4$ experiments). The inset shows $[Ca^{2+}]_i$ traces in HASM in response to increasing doses of chloroquine. (D) Maximal relaxation of intact human airways to the β-agonist isoproterenol and the TAS2R agonists quinine and chloroquine. *, $p < 0.05$ vs isoproterenol ($n = 5$).

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