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Bitter taste receptor agonists mediate vasodilation in human and guinea vascular smooth muscle that is independent of L-type calcium channel blockade

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Introduction: Taste-sensing type 2 receptors (TAS2Rs) are G-protein coupled receptors that recognize a wide range of bitter-tasting compounds with a relatively low affinity and specifity. TAS2Rs are suggested to have extraoral functions. Airway smooth muscle, which expresses TAS2Rs, can be relaxed by TAS2R agonists. Previous studies in guinea pig aorta demonstrated that TAS2R agonists also induce vasodilation[1]. The aim of this study was firstly to translate earlier findings to human vascular smooth muscle, and secondly to evaluate the proposal that L-type Ca^{2+} channels mediate TAS2R agonist-induced relaxations.

Methods: Macroscopically healthy human lung tissues were obtained from sixteen consenting patients (8 male, 8 female, mean age: 62.7±3.7 years) undergoing lobectomy. Pulmonary arteries (diameter of 1-2 mm) were dissected out based on their location and visual appearance and either stored in RNAlater® for expression studies or in Krebs-Henseleit buffer overnight at 4ºC for functional experiments. Real-time PCR was performed using commercially available TaqMan® primers. Human pulmonary arterial rings were mounted in organ baths containing Krebs-Henseleit buffer (37ºC) which was continuously bubbled with carbongas (5% CO_2 in O_2). Isometric smooth muscle force was detected using a force-displacement transducer. Rings were stretched during a one-hour equilibration phase. Viability of the segments was evaluated by two consecutive administrations of 60 mM potassium chloride, followed by evaluation of the endothelium function through administrations of acetylcholine (0.1-10μM) on phenylephrine induced contractions. Relaxations to the TAS2R agonists; chloroquine (TAS2R3), denatonium (TAS2R10, TAS2R39, TAS2R46 and TAS2R47), dextromethorphan (TAS2R1 and TAS2R10) and noscapine (TAS2R14) were assessed by cumulative administration (1-300μM) in human pulmonary arteries after pre-contractions with either 10μM phenylephrine or 30nM U-46619 in the presence of indomethacin.
Guinea pig denuded aorta rings were set-up according to described methodologies[1] and pre-contracted with 10 μM phenylephrine. The L-type channel blocker nifedipine (1-10μM) was administrated on top of pre-contractions before the administration of chloroquine, denatonium, dextromethorphan or noscapine.
Data are presented as percentage decrease of pre-contractions (Mean±SEM) with 4-6 observations for each sub- study. Statistical analysis was performed using One-Way ANOVA.

Results: Human pulmonary arteries expressed mRNA for TAS2R3, TAS2R10 and TAS2R14 with similar levels as the $\alpha 1_A$ adrenoceptor, but 3.5-9 folds lower expression than the endogenous control hypoxanthine-guanine phosphoribosyltransferase1 (in 6 patients). After pre-contractions with phenylephrine, chloroquine (64.0±10.6%), dextromethorphan (62.1±17.0%) and noscapine (82.7±11.0%) induced concentration-dependent relaxations of human pulmonary arteries (pEC_{50} mean-range: 4.3-5.0), whereas denatonium only had a transient effect with smaller efficacy (38.0±7.3% at 100μM). Chloroquine (41.3±10.9%) and noscapine (76.2±9.5%), also relaxed U-46619 mediated contractions, whereas relaxations to dextromethorphan (15.9±2.2%) were negligible in U-46619 pre-contracted preparations. When tested in phenylephrine pre-contracted guinea pig aortic rings, all TAS2R agonists were able to induce complete vasodilation in the presence of the L-type Ca^{2+} channel blocker nifedipine, which by itself induced small relaxations (19.2±2.7%).
Human vascular smooth muscle expressed TAS2Rs and purported TAS2R agonists caused vasodilation, suggesting that TAS2Rs might be a new target to achieve vasodilation by a yet undefined mechanism.

[1] Manson ML et al, Proceedings of the British Pharmacological Society 10:abstract154p, 2012