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Letter to Editor Open Access

Expression of Bitter Taste Receptors in the Human Skin *In Vitro*

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Letter to the Editor

Human bitter taste is mediated by the hTAS2R family of G-protein coupled receptors [1]. The main function of these receptors but to date never has been proved sufficiently is to protect the organism against ingestion of toxic substances [2]. A number of studies have been performed to the analyse *TAS2R* gene expression in gustatory and, more recently, in extragustatory tissues of rodents and humans [3]. Cells that express signalling components related to the TAS2R system have been found, among others in nasal respiratory epithelium, human airway smooth muscle, gastrointestinal tract and several other tissues [2,4-6]. TAS2Rs are present in some gastrointestinal endocrine cells, including those that secrete the peptide hormones (e.g. cholecystokinin, ghrelin and glucagons-like pepitide-1). Thus *TAS2Rs* may regulate metabolism, satiety, gastric empting, and the processing and absorption of ingested foods and pharmaceuticals [7]. Bitter tastants caused relaxation of isolated airway smooth muscle and dilation of airways that was threefold greater than elicited by beta-adrenergic receptor agonists [5]. Thereby providing new treatment strategies for asthma and COPD. Moreover transcriptome analysis revealed upregulation of bitter taste receptors in white blood cells in children with severe, therapy-resistant asthma [8]. *TAS2Rs* are also connected with the ability to detect and respond to gram-negative bacteria such as *Pseudomonas aeruginosa* in the upper respiratory tract [9]. Finally the *TAS2R* genetic polymorphisms seem to play a role in the human longevity [10]. An interesting hypothesis was presented by Clark et al. that could explain many off-target effects of diverse pharmaceuticals [11]. They proposed that any drug with a bitter taste could have unintended actions in the body through stimulation of extraoral TAS2Rs. New evidence strongly suggests that *TAS2R* system play a much broader role in human health and they are present in "barrier" tissues and organs. Thus the goal of our study was to examined the expression of *TAS2R* in the human skin of facial area of healthy donors who underwent elective surgery due to esthetic reasons.

We analyzed expression patterns of all twenty five *TAS2R* transcripts from facial skin biopsies from 15 healthy volunteers (10 women and 5 men, mean aged 58 ± 19.23). The Ethics Committee for Scientific Research at Nofer Institute approved the study protocol, and a written informed consent was obtained from each participant before taking part in the study. Each patient was given 1% Lidocaine for local infiltration anesthesia. The incision was carried down through the skin and dermis using the scalpel. The 1 cm^2 specimen was grasped using toothed forceps and was dissected out circumferentially and excised. All skin specimens were immediately stored in RNAlater reagent and then were stored at -80°C until mRNA PCR analysis. Total RNA was isolated with AllPrep DNA/RNA Mini Kit (Qiagen, Hilden, Germany) including DNase digestion during RNA purification.

Transcript levels in skin biopsy were determined by means of quantitative real-time PCR (qPCR). Primers for target genes were designed with Beacon Designer 7.0 (PREMIER Biosoft Int., Palo Alto, CA, USA) according to GenBank® genetic sequence database. The cDNA was synthesized on 500 ng RNA with Quantitect Kit (Qiagen, Hilden, Germany). PCR efficiencies were calculated using dilutions of three randomly selected pooled cDNA samples. All the samples were amplified in duplicate. Expression was quantified with FastStart SYBR Green Master (Roche, Basel, Switzerland) and using β-glucuronidase (GUSB) as the endogenous control. Data obtained from qPCR were evaluated by Pfaffl method [12] with reference gene-normalized relative quantification with efficiency correction using qbasePLUS software (Version: 2.3) (Biogazelle NV, Zwijnaarde, Belgium).

Human skin biopsies expression of the gene transcripts of twenty three TAS2Rs is summarized in Figure 1. *GUSB* reference gene presents stable expression in human skin specimens [13]. Gene expression was estimated according to Pfaffl method with qRT-PCR efficiency correction. All transcripts were found expressed in all patients, except *TAS2R7, 8, 9, 20, 38* and *39* which were found in specimens from 13/15, 9/15, 13/15, 11/15, 9/15 and 10/15 patients only. *TAS2R1* and *TAS2R16* showed lack of mRNA expression in human skin biopsies. Study on human keratinocyte cell line HaCaT revealed expression of *TAS2R1* and *TAS2R38* receptors at protein level, which is in conflict in our results [14]. To add *TAS2R1* and *TAS2R38* gene expression was also found in breast cancer epithelial cells [15]. In contrast human airway smooth muscle presented very low mRNA expression of *TAS2R1* and non-detectable expression of *TAS2R38* [5].

In summary we have demonstrated expression of *TAS2Rs* in the human skin and to our knowledge this is the first report of this expression. *TAS2Rs* expression pattern in skin biopsies was different than observed in human blood leukocytes, which may exclude blood contamination of skin specimens [16]. Surprisingly, *TAS2R31*-bitter taste receptor with the highest expression in skin among 25 known human *TAS2Rs* (Figure 1), revealed the highest relative RNA expression in various subpopulations of circulating leukocytes. It has been shown that *TAS2Rs* were differentially expressed in different cell types, and their expression was associated with the age [17] of analysed patients and also with undergoing pathologies [18]. Similarly in our

study the pattern of expression of *TAS2Rs* is different to the one observed in isolated mixed leukocytes, lymphocytes, monocytes and neutrophils in adult human asthmatics [8]. Specific pattern of *TAS2Rs* was also found in mammary epithelial cells with some *TAS2Rs* downregulated in breast cancer cells [15]. Additionally, we should consider that selective *TAS2Rs* expression in different specimens may indicate presence of gene variants [19]. Further studies on the expression of these receptors and their potential role in the maintenance of homeostasis, in health and disease including carcinogenesis, acute and chronic inflammation are warranted. The usefulness of the discovery of *TAS2R* expression in human skin in clinical practise is difficult to predict but it could be the novel therapy of IgE-mediated skin diseases by *TAS2R* antagonists [20].

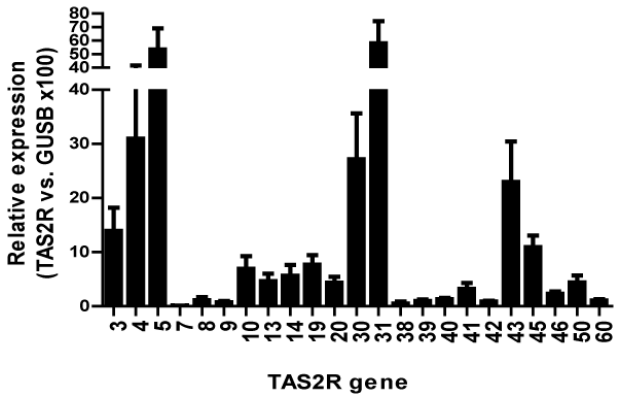

Figure 1: Relative expression of genes encoding for bitter taste receptors: *TAS2R3, 4, 5, 7, 8, 9, 10,14,19, 20, 30, 31, 38, 39, 40, 41, 42, 43, 45, 46, 50, 60* gene transcripts in human skin biopsies. Values are expressed as mean ± SEM.

Conflict of Interest

The authors state no conflict of interest.

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