Coordinates of Agonist-bound TAS2R14 Structures

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Bitter taste receptors (TAS2Rs) consist of 25 human subtypes, many of which are expressed on the cell surface of cells that are not involved with sensing bitter tastes. For example, TAS2R10, 14, 31 and 5 are expressed on human airway smooth muscle (HASM) cells, and their activation by agonists causes relaxation of this muscle that surrounds the conducting airways (1,2). The relaxation is not cAMP dependent, which distinguishes it from the relaxation caused by agonists acting at HASM β_2-adrenergic receptors (β-agonists, such as albuterol). Thus, these receptors represent targets for a new class of bronchodilator for treating asthma and chronic obstructive lung disease.

TAS2Rs are G protein coupled receptors (GPCRs), but their positioning within this superfamily is not clear based on fingerprinting and homology. While originally thought to be “rhodopsin-like” and thus belonging to Class A, it has been suggested that they belong to a small clade that is split from Class A, perhaps including the frizzled receptors (3). Another feature of most TAS2Rs is their apparent activation by a large number of chemically diverse compounds. TAS2R14 appears to be one of the most broadly tuned of the TAS2Rs, being activated by hundreds of known agonists. For drug development, this raises the issue of how to design drugs with high affinity and efficacy, when the binding/activation requirements are atypical compared to most other GPCRs, where specificity and similarity of the structures of known agonists is generally apparent.

Of particular interest for TAS2R14 is whether there may be more than one binding pocket that accommodates these diverse agonists, or, if there is a single pocket that is sufficiently pliable to bind and subsequently activate these receptors by agonists within this diverse chemical space. To address this, we computationally derived the structures of TAS2R14 (in complex with G protein) bound to five diverse agonists (4). For these compounds, the Tanimoto maximal common substructure similarity scores ranged from 0.03 to 0.39. The agonists were:

diphenhydramine, flufenamic acid, papaverine, glycyrrhizic acid and rubusoside. Despite this diversity in chemical structures and potencies of activation, a single binding pocket was identified that accommodated all these agonists. Each agonist has certain features (interactions) which affect the apparent affinity for the receptor, but nevertheless have this core pocket in common. The spatial coordinates for these models are provided (see Supplemental Material), so that others can dock additional compounds or consider alternative orientations.

Supplemental Material

The coordinates are deposited here:

https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/G3MRKA

References:

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