UNDERSTANDING LIGAND SELECTIVITY IN BITTER TASTE RECEPTORS USING MULTISCALE MOLECULAR DYNAMICS SIMULATIONS.

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Bitter taste receptors (TAS2Rs) were initially identified in the tongue, where they are responsible for detecting bitter molecules present in food with either health benefits (such as salicin, long used as analgesic and antipyretic) or toxic effects (such as the cyanogenic glycosides in bitter almonds and apricot seeds). In addition, TAS2Rs have recently been shown to be expressed in other parts of the body and thus constitute novel targets for drug design. More than 100 ligands have been identified so far for bitter taste receptors, but the number of compounds recognized by each receptor varies significantly across the TAS2R family. A particularly intriguing case is TAS2R16, which is highly specialized in detecting "bitter sugars". All its ligands share a common sugar unit (typically glucose) attached to a variable aglycon that can largely vary in terms of size and hydrophobicity. This poses the question of how the binding cavity of a single receptor is capable to adapt to such wide range of ligands.

Here we tackle this problem using multiscale molecular dynamics simulations, in which the ligand and the surrounding protein residues and water molecules are described with molecular mechanics (MM), whereas the rest of the receptor is treated as coarse-grained (CG). Our MM/CG simulations show that bitter sugars interact with TAS2R16 through a previously unrecognized dual binding mode. Such mechanism may offer a seamless way to fit different aglycons inside the same binding cavity, while maintaining the sugar bound. Our prediction is fully consistent with mutagenesis data and also provides a rationale for the available structure-activity relationship data. Together with previous simulations for other TAS2Rs, this study paves the way to improve our overall understanding of the structural determinants of ligand specificity in bitter taste receptors.