The Mechanism of Interaction of Sweet Proteins with their Receptor: Modelling the Complexes - (session: Other)

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Most sweet compounds, including all popular sweeteners, are small molecular weight compounds of widely different chemical nature, but a few sweet proteins are also known. Sweet tasting proteins have different molecular lengths (from the 54 residues of brazzein to the 202 residues of thaumatin), virtually no sequence homology and very little structural homology.
Why are sweet proteins sweet? From a very general point of view it is natural to think that glucophores, i.e., key groups responsible for the biological activity of sweet proteins similar to those of small molecular weight sweeteners, are localized on a protruding structural feature, i.e. a sweet finger that can probe the active site of the receptor.
Sweet molecules elicit their taste, in humans and other mammals, by interacting with the T1R2-T1R3 receptor. The sequence of this protein indicates that it is a metabopromic 7TM GPCR receptor with a high homology to the mGluR subtype 1 (Margolskee, 2002). The structure of the N-terminal part of the mGlu receptor, determined by X-ray diffraction (Kunishima et al., 2000), has been used as a template to build homodimeric (Margolskee, 2002) and heterodimeric (Temussi, 2002) models of the T1R3-T1R3 receptor. It is very likely that small molecular weight sweet molecules occupy a pocket analogous to the glutamate pockets in the mGlu receptor, possibly similar to the active site models predicted by indirect receptor mapping studies. However, the glucophores of sweet proteins have not yet been identified with certainty, even for sweet proteins of known structure. In addition, it is difficult to envisage the same type of interaction for sweet proteins.
Recently, an alternative explanation, based on the spread of key residues on a large surface area, has been suggested (Temussi, 2002). This new model of interaction hypothesizes that the site of interaction with the T1R2-T1R3 receptor is different for small molecular weight sweeteners and for sweet proteins. Sweet proteins should bind to the surface of form II of the ligand-free receptor stabilizing it. The complexes of brazzein, monellin and thaumatin with the heterodimeric model of the T1R2-T1R3 receptor show that all three proteins bind as wedges on a cavity of the receptor (Temussi, 2002). The crucial features of this model are that, by analogy to the mGlu receptor, free form II is the active form of the receptor and that a large interaction surface does not require identical glucophores for different sweet proteins.

Comparison of the structures of wild type monellin and G16A, a structural mutant, shows that the mutation does not affect the structure of potential glucophores but produces a distortion of the surface owing to the partial relative displacement of elements of secondary structure. This result shows conclusively that sweet proteins do not possess a sweet finger and strongly supports the hypothesis that the mechanism of interaction of sweet tasting proteins with the sweet receptor is different from that of low molecular weight sweeteners.

References
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