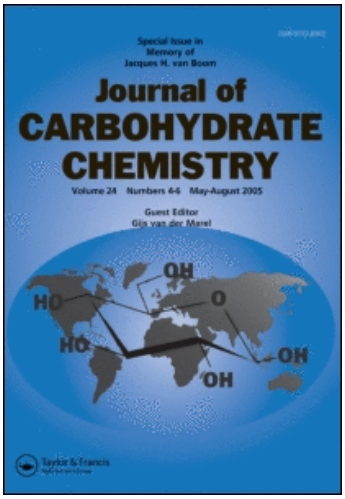

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MOLECULAR MECHANISMS OF SWEET TASTE 1: SWEET AND NON-SWEET TASTING AMINO ACIDS

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ABSTRACT

A novel mechanism is proposed for the AH/B interaction of sweet molecules, such as D-α-amino acids with the L-asparagine unit at the N-terminus of a receptor protein which has a right-handed α-helical conformation. The lipophilic, dispersive bonding occurs between the side chain of the fifth amino acid residue, from the N-terminus, and either the side chain of the α-amino acid or its methine group at the carbon 2. The sequence of AH, B and X groups on the sweet amino acids occurs in a clockwise orientation, when viewed from the receptor.

INTRODUCTION

A common molecular feature of all sweet organic compounds has been recognized as a bifunctional entity of AH and B components.[1,2] The AH, a proton donor, and the B, a proton acceptor, are separated by 2.5-4.0 Å.

In order to account for the observation that some D-amino acids are sweet whilst the L-isomers are not, a third hydrophobic component (X) was proposed by Kier,[3] which is consistent with a stereoselective receptor site with three binding components. The X site is located approximately 3.5 Å apart from the AH component and 5.5 Å from the B unit in α-amino acids. The lipophilic component X is attracted to a hydrophobic

site on the receptor, and the strength of this attachment appears to play an essential role in the enhancement of sweetness, for example making D-tryptophane 35 times sweeter than glycine.[4,5]

It has been suggested that the AH/B components of the sweet molecule then combine with a similar bifunctional system on a receptor protein of the taste bud in counterwise fashion with the formation of two intermolecular hydrogen bonds which initiate the sweet sensation (Figure 1).

Little is known concerning on the receptor itself, but there have been a few preliminary attempts to isolate from the tongue a sweet-sensitive protein that specifically responds to a sweet compound.[6-9] Whilst no correlative results have been obtained,[10-14] there is increasing evidence that the receptor is proteinaceous in character.[4] Some models of the receptor have been proposed to illustrate a relationship between structures of sweet compounds, such as amino acids,[15] aspartame,[16] and dihydrochalcone.[17] Thus, Fischer[18] suggested that the initial step of sweetness stimulation is due to an affinity of a sweet molecule to an α-helical region of a receptor protein, and Kier[5] favored a L-tryptophane unit of the protein as a possible lipophilic site (X) in his study on sweet 2-substituted-5-nitroanilines.

Recently, it has been speculated that a N-terminal amino acid residue of an α-helical protein, having a side chain capable of forming a hydrogen bond, such as a L-serine or L-threonine residue, could serve as a theoretical model for the receptor.[19] There is an AH/B/X triad at and near the N-terminus of the proposed receptor protein where the AH and B functions are NH_3^+ and OH groups of the N-terminal amino acid residue, respectively, and the X component is located on the lipophilic side chain of the fourth amino acid residue of the helical protein.

When the AH and B functions of a sweet molecule bind to the B and AH components of the receptor protein and the two hydrophobic X sites are linked by dispersion bonding (Van der Waals attractive forces), the sweet sensation is stimulated.

RESULTS AND DISCUSSION

In the present article, a new model of the receptor protein is postulated leading to a detailed mechanism of sweet taste which accounts

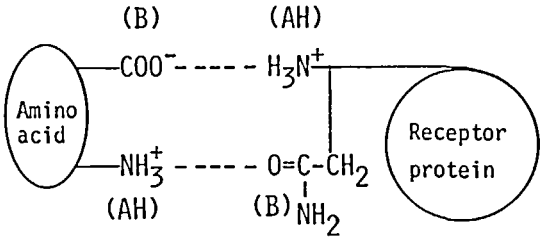
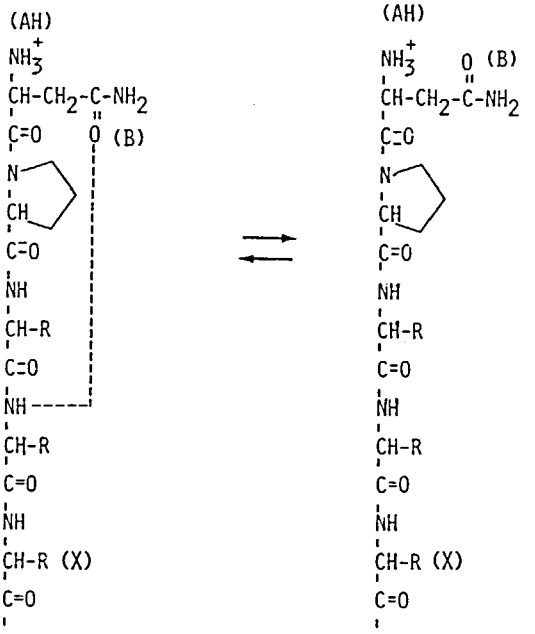


Figure 1. Interaction between α-amino acids and the receptor.



Recessed state (Resting form) Activated state (Active form)

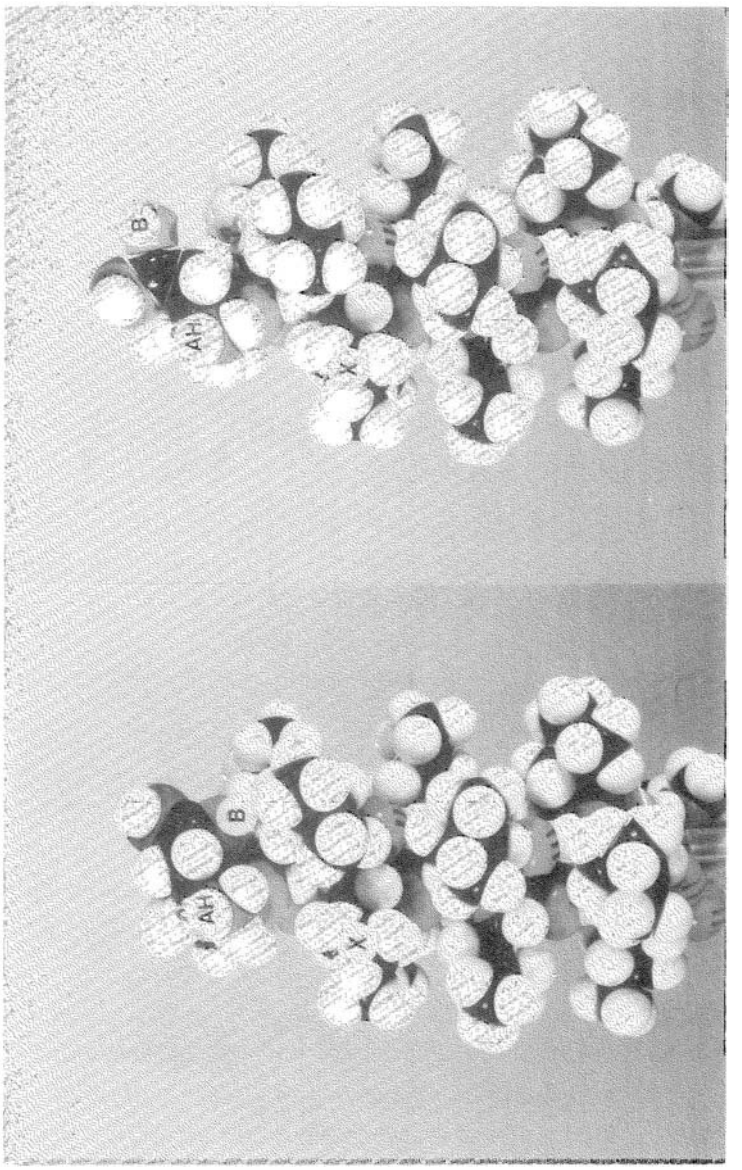
Figure 2. Interconvertible forms of the receptor.

for those molecular features which determine whether or not an amino acid is sweet. This new receptor model arises from recent findings[20,21] on the necessary peptide sequences for a formation of α-helices, which highlight the increased likelihood for L-asparagine to occur at the N-terminal of the helix and joined to L-proline as the penultimate residue. Thus, a right-handed α-helical protein, having L-asparagine at the N-termination linked to L-proline, is proposed as the receptor for the AH/B of the sweet molecules. The AH and B functions on the receptor are ascribed to the NH_3^+ and the C=O ($CH_2\underline{CO}\underline{N}H_2$) groups of the asparagine residue, respectively. The X site on the receptor is attributed to a lipophilic side chain of the fifth amino acid residue from the N-terminus, instead of the fourth one in the previous assumption,[19] because it has been described that there is a strong peak of preference for hydrophobic amino acids in the fifth position from the N-terminus of helices.[21]

There are two interconvertible conformations of the receptor: one corresponds to a recessed state (a resting form), whilst the other represents an active state (an active form). In the former conformation, the B component is intramolecularly bound to an unpaired amide group of the fourth amino acid residue of the helix by a hydrogen bond. In the active conformation, a stimulus molecule is adsorbed to the receptor, the intramolecular bond is cleaved and a new hydrogen bond is formed between the AH site of the sweet molecule and the B component of the receptor, resulting in the movement of the AH/B/X groups on the receptor into the correct geometry for binding to these sites on the sweet molecule (Figure 2). Thus, the conformational change of the receptor from the recessed to the active form is obtained. Desorption of the sweet molecule then permits a reversal of this transformation back to the initial resting form (Figures 2 and 3).

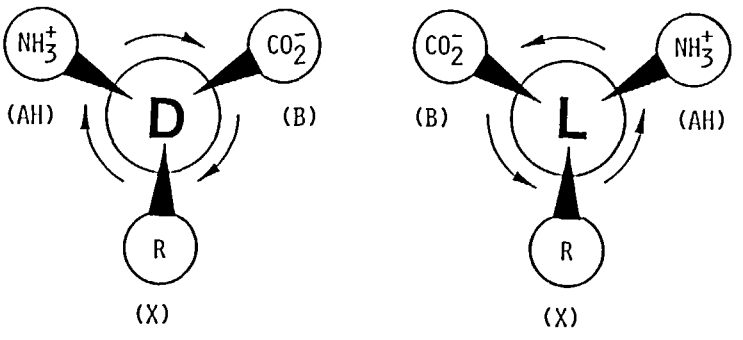
D-Tryptophane, D-phenylalanine, D-histidine, D-tyrosine and D-leucine are all sweeter than sucrose,[3,22] with NH_3^+ groups acting as the AH component, COO^- groups as the B function and the hydrophobic side chains as the X component. On the other hand, the isomeric L-amino acids are bitter, not sweet, due to the difference in stereochemistry of the chiral carbon atom.

In a case of the sweet tasting D-leucine,[23,24] the initial interaction between the amino acid and the receptor probably involves an



Recessed state (Resting form) Activated state (Active form)

Figure 3. CPK Molecular models of the receptor.



Clockwise order of AH/B/X (sweet)

Counterclockwise order of AH/B/X (non-sweet)

Figure 4. AH/B/X Arrangements of amino acids.

attraction between the isobutyl side chain (X) of D-leucine with the alkyl side chain (X) of the fifth amino acid residue of the helical receptor protein, and the formation of a linkage of the COO^- group (B) of D-leucine with the terminal NH_3^+ group (AH) of the receptor. At this stage, the disposition of the X and B sites of D-leucine has been fixed on to the receptor.

The second step of the interaction is the scission of the existing intramolecular hydrogen bond by an approach of the NH_3^+ group (AH) of D-leucine to generate a new intermolecular hydrogen bond, and thus to complete the binding of the tripartite, AH/B/X glucophore, of D-leucine on to the receptor protein with the concommitant conformational change of the receptor helix at the terminus.

Since the receptor protein is assumed to be a right-handed helix, the orientation of the bound AH/B/X components of a D-amino acid is the clockwise arrangement, when looked at from the position of the receptor (Figure 4). This is coincident with a suggestion described by Hough et al.[25] on glucophores of sucrose.

On the other hand, the orientation of the AH/B/X tripartite of the bitter L-leucine is the counterclockwise configuration, and the NH_3^+

D-Leucine L-Leucine

Figure 5. Interactions between leucines and the receptor with CPK molecular models.

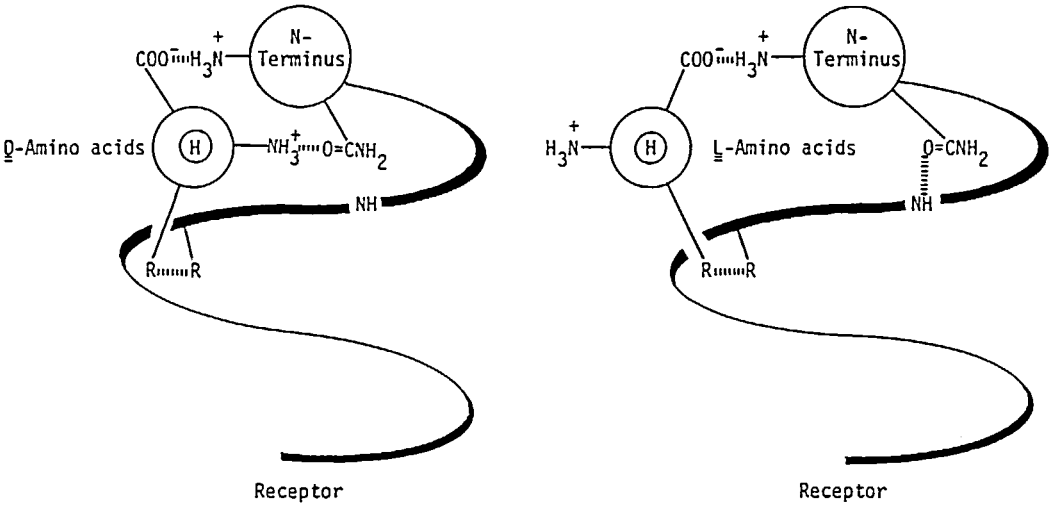


Figure 6. Diagrams of interactions between amino acids and the receptor.

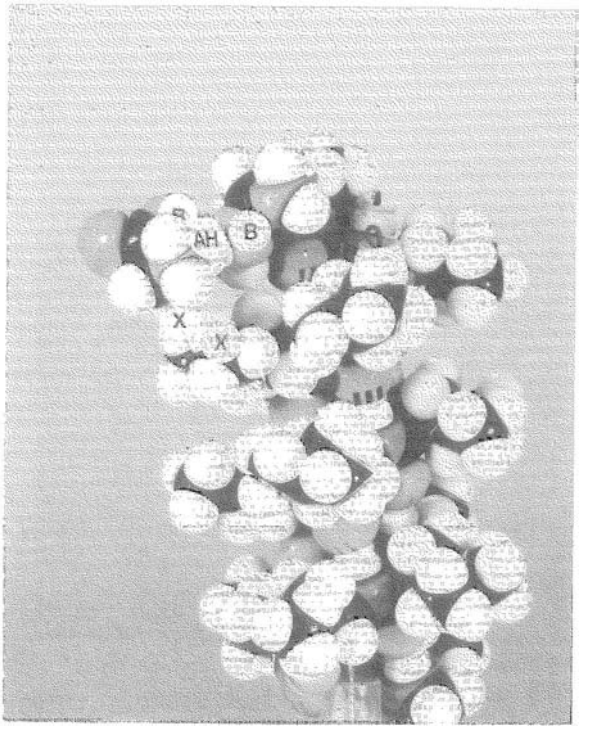


Figure 7. Interaction between glycine and the receptor with CPK molecular models.

group (AH) of this amino acid can not approach the potential site of the receptor. Hence, the second step can not occur with L-leucine, and this is true of almost all L-α-amino acids (Figures 5 and 6).

The anomalous sweet character of both L-alanine and L-2-aminobutanoic acid has been reported.[23,24,26] The lowest member of the α-amino acid series, glycine, is sweet,[27,28] and only the methylene group can act as the dispersive function (X) to complete the three point clockwise coupling with the receptor to elicit sweetness (Figure 7). Hence, by analogy with glycine, the methyl and ethyl side chains of L-alanine and L-2-aminobutanoic acid, respectively, do not appear to play a lipophilic role, due to the alternative participation of the methine groups as the dispersive function, which then allows the transformation of the AH/B/X orientations from the counterclockwise (non-sweet) to the clockwise (sweet). The side chains of these small amino acids are sufficiently remote from the receptor helix to allow this interaction, whereas in the cases of the larger amino acids, there is a steric hindrance.

CONCLUSION

The tripartite AH/B/X components of sweet tasting D-amino acids are in the clockwise order, when they are viewed from the receptor side, which enables a completion of the three point coupling with the similar AH/B/X sites of the proteinaceous receptor helix around the N-terminus. On the other hand, the AH/B/X of the non-sweet L-amino acids are in the counterclockwise order, which prevents the necessary three point coupling with the receptor, with the exception of L-alanine and L-2-aminobutanoic acid where the methine group acts as the hydrophobic group (X) and not the side chains.

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