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LETTER TO THE EDITOR

Lipophilicity and bitter taste

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In a recent communication, Schober, Bowers & Smith (1978) commented on the 'Low stereospecificity of quinine taste receptors'. In the light of their observations I would like to raise a number of points which may be of significance in the perception of a bitter taste and, perhaps, of flavours in general.

The range of compound types which induce the perception of bitterness in man is wide and includes alkaloids (Schober & others, 1978), amino acids and peptides (reviewed by Guigoz & Solms, 1976), polyphenolic compounds (Horowitz & Gentili, 1969; Esaki, Kamiya & Konishi, 1977), various compounds and their analogues, derived from *Humulus lupulus* L. (Whitear, 1969; Molyneux & Eggling, 1969; Gienapp & Schroder, 1975) and terpenes (Kubota & Kubo, 1969). The physical processes occurring when man perceives a given taste (or odour) are largely unknown, but, in general terms, some interaction between the tastant and a receptor-site seems likely. Although a 'bitter-sensitive' protein has been isolated from porcine tongues (Dastoli, Lopiekes & Doig, 1968), the view that it is a taste recognition molecule has now been abandoned (Price & Desimone, 1977). As an alternative to a protein it has been suggested (Kurihara, 1973) that membrane lipids are the bitter receptor sites.

Thus the nature of the receptor-site responsible for perception of bitterness is undecided and the structural features which make a given compound bitter unknown. However, Kubota & Kubo (1969) studying a series of diterpenes, found that a necessary prerequisite for these compounds to be bitter was the presence of a proton-donor group and a proton-acceptor group 'within a distance of about 1·5 Å making it possible to form an *intra*-molecular hydrogen bond'. They referred to this donor-receptor pair as the 'bitterness unit' and suggested that it interacted with the active site on the receptor, thus fixing the bonding units of the site at about 1·5 Å apart. However, the work of Schober & others (1978) is at variance with this conclusion. Thus although the quinines studied have appropriate acceptor and donor groups (quinuclidine N and C9 hydroxyl), they are further apart than the model proposes. Observations on the structures of bitter sugar analogues (Birch & Lee, 1976) also do not support the Kubota & Kubo (1969) model. One explanation for this difference lies in the possibility that there is more than one type of receptor. The fact that many people cannot taste phenylthiocarbamide, but can taste other bitter compounds, does imply the existence of at least two bitter receptor sites (Price & Desimone, 1977).

Even if there are a number of different receptor sites, the observation (Kubota & Kubo, 1969) that the presence of an *intra*-molecular hydrogen bond correlates with bitterness is puzzling from the structural point of view; i.e. such a bond has to be broken for interaction with the receptor site. The energies involved are not great, but it is known (Schallenberger, 1963) that hydrogen-bonding between hydroxyl groups in sugars restricts their sweetness. I would suggest that the correlation between an *intra*-molecular hydrogen bond and bitterness, in the terpenes, can be explained in terms of the effect of this feature on the physical properties of these compounds. Thus any *intra*-molecular hydrogen bonding in a molecule will effectively increase its lipophilicity compared with similar structures where *inter*-molecular hydrogen bonding occurs. Since bitter molecules probably have to penetrate cells (or at least cell walls) of the tongue to elicit a bitter response (Price & Desimone, 1977), *intra*-molecularly hydrogen bonded terpenes are more likely to reach the site of action than those bonded *inter*-molecularly.

The significance of lipophilicity to the perception of bitterness is illustrated by many observations:

1. The bitterness of a series of bitter compounds

correlates significantly with their interaction with monolayers of lipids from bovine papillae (Koyama & Kurihara, 1972).

2. The bitterness of a series of hupulone analogues (5,5-dialkyl (or diacyl)-3-acyl-cyclopentane-1,2,4-triones) has been found to increase with extension of either the alkyl, or acyl, side chain (Gienapp & Schroder, 1975).
3. The threshold concentrations of bitterness perception in the hulupones correlates significantly (Gardner, in preparation) with their log P (octanol/water partition coefficient) calculated using the π-values of Hansch (1971).
4. Reduction of olefinic double bonds in the side chains of various bitter compounds, which will increase the lipophilicity, causes an increase in bitterness, e.g. this has been observed in the α-*iso*-acids (Todd, Johnson & Worden, 1972) and quinine (Schober & others, 1978). Conversely, introduction of an olefinic double bond into the alkylic side chain of hulupones reduces the bitterness (Gienapp & Schroder, 1975).
5. Although many bitter peptides are known, there is no simple correlation between the sequence or configuration of their constituent amino acids and bitterness (Guigoz & Solms, 1976). However, peptides of average 'hydrophobicity' (Ney, 1971, 1972) greater than 1300 calories per amino acid residue are generally bitter. ('Hydrophobicity' is derived from the free energy of transfer of the amino acid from water to ethanol (Tanford, 1962) and is thus related to the partitioning properties of the molecules.)
6. Increasing the lipophilic character of dihydrochalcone sweetners can make them bitter (DuBois, Crosby & others, 1977).
7. Whenever a sugar molecule is chemically modified to increase it's lipophilicity it begins to exhibit bitterness (Birch & Lee, 1976).

The above comments emphasize the fact that a bitter tastant, like any other biologically active molecule, must reach the site of action to produce its effect. This factor has been largely overlooked in the development of models for the bitter taste response.

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