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The nose of the matter

27/02/03 - One of our most powerful senses – that of smell – remains enigmatic. Of the five basic senses, the sense of smell is the least understood - up until now. Scientists in the US claim this week to have sniffed out potential clues to how olfactory receptors in the nose detect odours. And they suggest that these clues might explain why dietary zinc deficiencies lead to a loss of smell.

Olfactory receptors are proteins that bridge through the cell membrane. Professor Kenneth S. Suslick and co-workers at the University of Illinois have found that the structure of the protein changes dramatically when a zinc or copper ion binds to it.

As a result, they propose that the olfactory response to an odorant involves this change in structure that pushes and pulls part of the olfactory receptor protein into and out of the cell in a "shuttlecock" motion. This back-and-forth motion passes information through the cell membrane.

Astonishingly, the average human nose can detect nearly 10,000 distinct scents, a feat that requires about 1,000 olfactory genes, or roughly 3 per cent of the human genome.

"It seems surprising that such a large percentage of our genome is dedicated to the olfactory system," said Suslick, a William H. and Janet Lycan Professor of Chemistry at Illinois. *"Being visually oriented and olfactorily impaired, we tend to overlook our sense of smell. But other mammals, like dogs and rats, live or die by their sense of sr*

Knowing that molecules that bind strongly to metal ions usually smell strongly (and often badly), Suslick and his colleagues - chem professor Zaida A. Luthey-Schulten and doctoral student Jianguyun Wang - investigated the possibility that olfactory receptors are metalloproteins (proteins that contain a metal ion as part of their structure).

Inorganic chemists have long suspected that the olfactory system involved metal ions. Only recently, however, have the genes responsible for smell been identified. *"When we searched the genome data, we found an identical site in more than 75 per cent of olfactory receptors that looks like it can bind to metal ions very strongly,"* added Suslick.

The structure of these receptors is thought to be a protein that weaves in and out of the cell membrane seven times. Between the fourth and fifth helices, the scientists found an uncommonly long loop that they suspected contained the binding site for a metal ion

To test their theory, the researchers created synthetic peptide analogs of the potential binding site in the receptor protein. As predicted the scientists report that metal ions - particularly zinc and copper - were bound very strongly.

After this, the researchers used computer models to study the behaviour of olfactory receptors on odorant binding. *"Computer simulations initially put this big loop outside the cell membrane because the loop is negatively charged,"* Suslick said. *"When a positively charged metal ion binds to the site, however, the loop's charge is neutralised, so the computer places the loop in the membrane."*

When the long loop containing the metal ion slides into the cell membrane, a portion of the receptor protein's fourth helix is pushed outside the membrane, explained Suslick. When an odorant binds to the metal ion, the loop is ejected from the membrane, and the fourth helix is dragged back in, triggering a sequence of events leading to nerve cell activity. Then, when the odorant leaves the membrane, the process can start all over again.

This back and forth movement of the protein, which the researchers refer to as a shuttlecock motion, may be a new mechanism for passing information through cell membranes.

"Another piece to this puzzle is that one of the first symptoms of dietary zinc deficiency is loss of the sense of smell," said Suslick. *"That, too, is keeping with this idea that the olfactory receptors are metalloproteins."*



Note: to freeze animation, right-hand click on 'Play'.

The researchers have published their findings in the Proceedings of the National Academy of Sciences. A paper on the subject is currently on the 24 February PNAS Online Early Edition.

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