Scientists thought they knew how the nose 'knows,' but new research suggests otherwise

August 19 2022, by Lauren Hines

Credit: Pixabay/CC0 Public Domain

Johns Hopkins Medicine researchers say they have evidence to potentially overturn a prevailing belief in a type of important signaling within cells. The mainstream idea is that a single protein receptor

molecule—a kind of flag on the cell surface—spurs the activity of up to hundreds of downstream protein molecules to produce a signal.

Their new findings from studying genetically engineered mice show that nasal cell receptors activate, on average, far fewer of these special proteins—typically one, at most—to start a cascade of chemical reactions that reach the odor-detecting parts of the mammalian brain. And most of the time, they say, the signaling doesn't happen at all.

The researchers' findings were published Aug. 1 in *Proceedings of the National Academy of Sciences.*

The signaling pathway, called G-protein-coupled-receptor (GPCR) signaling, is ubiquitous throughout the body, and it is a major focus for drug development to treat many ailments from high blood pressure to pain to Parkinson's disease. The pathway also mediates various physiological processes, such as vision, smell, mood regulation, inflammation and the immune system.

"This signaling pathway is found in cells all over the body, serving all kinds of functions," said said King-Wai Yau, Ph.D., professor of neuroscience and ophthalmology at the Johns Hopkins University School of Medicine.

The mainstream idea in the 1980s was that a GPCR molecule on the cell's surface, when stimulated, would activate hundreds of guanine nucleotide-binding proteins, called G proteins. Activating a high level of these G proteins is called high amplification. This, in turn, would set off a chemical chain reaction.

This idea began with research on light-sensing cells called rod photoreceptors in the retina. Their visual pigment, called rhodopsin, is a GPCR that absorbs particles of light called photons. Other researchers

reported finding that when a rhodopsin molecule absorbs a photon, it activates up to 500 G proteins. The signal eventually arrives at the brain, triggering vision.

"In fact, for the next 30 some years, scientists extrapolated, or generalized, this idea of high amplification to other GPCR signaling pathways involving G proteins," said Yau.

In the current research on olfaction, however, the Johns Hopkins team found that the signal amplification is actually very low—so low that the probability of an odorant receptor activating just one G protein would be perhaps only 1 in 10,000. Yau said that, as such, the activation level "is very weak."

For the experiments, Yau's team, including first author Rong-Chang Li, Ph.D., genetically labeled mouse nasal olfactory cells in a lab dish with fluorescence. Then, they stimulated one of these cells with an odorant in solution for exactly 30 milliseconds.

In this way, they could estimate how many times the odorant molecules intercepted the odorant receptor during stimulation. Lastly, they calculated how many collisions were needed to activate one G protein molecule. For the probability calculation, the team looked at 20 cells and performed about 45 trials for each cell.

The findings suggest that when the odorant and the receptor interacted, 99.99% of the time the scent wouldn't trigger the chemical chain reaction that sends a signal to the brain.

"The result is very different from rod vision," said Yau.

In the future, the researchers will focus on whether the low probability of activating G proteins applies to other types of odors and their

associated receptors. They also plan on studying other kinds of receptors to confirm the team's findings.

The researchers speculate that light receptors activate more G proteins than odor receptors because light receptors are highly sensitive to light, to the point that they can absorb and signal a single photon of light. In the future, the researchers will check whether the low signaling probability they found for a particular odorant receptor applies to other odorant receptors.

More information: Rong-Chang Li et al, Low signaling efficiency from receptor to effector in olfactory transduction: A quantified ligand-triggered GPCR pathway, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2121225119

Provided by Johns Hopkins University School of Medicine