LETTER

Olfaction is a chemical sense, not a spectral sense

Franco et al. (1) argued that molecular vibrations contribute to odor detection by *Drosophila*. They claimed that deuterated odorants have a unique C-D stretch vibration that produces a "deuterium odor character" independent of the "structure and chemical properties of the odorant molecules." The discrimination of normal and deuterated odorants by flies is a clear and convincing finding, but such isotope effects do not prove that the animals are sensing infrared molecular vibrations using inelastic electron tunneling spectroscopy (IETS) (2).

The ability of humans to discriminate isotopes by smell is not as great as has been suggested (2). One study found no discrimination between normal and deuterated acetophenone (3). Hydrogen and deuterium compounds generally have very similar odors even when they can be distinguished. Notably missing from the Franco et al. article (1) are descriptions of the odors of the compounds in humans.

The vibration theory seems to be based in part on the idea that olfaction functions like "the other spectral senses, vision and hearing" (2). However, there is no continuous odor dimension that would be needed for a truly spectral system. The IETS mechanism (2) has not been observed in any biological system. NADPH cannot generate free electrons as proposed in the model.

The hypothesized correlation between odor similarity and spectral similarity fails in two ways. First, odors can be very different even when infrared spectra are very similar. The infrared spectrum of civetone, a macrocyclic ketone with a musk odor, is practically identical to that of its odorless acyclic analog (4). Odor differences in optical isomers with identical infrared spectra also do not support the vibration theory.

Second, odors can be very similar even when spectra are very different. In the case of isotope substitution reported in the Franco et al. article (1), the great difference between C-H and C-D infrared stretch vibrations (3,000 vs. 2,200 cm^{-1}) would be equivalent to half the entire spectral range in human vision or half an octave in hearing, extremely easy discriminations compared with isotope discriminations by odor. Isotope substitution does not lead to large chemical or odor differences despite large frequency differences. An attempt to establish a quantitative relationship between odor similarity and spectral similarity would likely refute the vibration theory of olfaction.

The depiction of the vibration theory as an alternative to "shape" theory or a "lock-and-key" mechanism is misleading. Odor chemistry involves many factors besides shape. Ethanol and ethanethiol may have roughly similar shapes, but chemically they are as different as roses and skunks. Using vibrations to detect isotopes by odor is biochemically irrelevant because animals have no need to make such distinctions. Olfaction is a chemical sense, not a spectral sense. The relation between odor similarity and chemical similarity is evident when one considers not only shape but other concepts like molecular weight, functional groups, polarity, acidity, basicity, and steric interactions. Whether in humans or flies, odorants bind and activate receptors through a combination of chemical features no different from other types of receptor-based molecular signaling in biology (5).

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