PERSPECTIVES

The scents of androstenone in humans

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Specific anosmia, the inability to detect a particular odour, has been well documented for decades in human and animal populations. Indeed, the existence of specific anosmias was a favoured argument used to support a receptor-mediated mechanism of odourant detection prior to the molecular identification of a large family of olfactory G-protein-coupled receptors (GPCRs) in the early 1990s (Amoore, 1974; Buck & Axel, 1991). One well known anosmia in humans is the inability to sense 5-α-androst-16-en-3-one (androstenone). Androstenone is variously described as having an unpleasant (urine, sweat) or pleasant odour (sweet, floral), yet a fraction of the population cannot detect its presence. Moreover, androstenone is a pheromone in boars and is found in urine and axillary sweat in humans, making it a prospective candidate for odour-mediated communication in humans. While a role for androstenone as a human pheromone is open to debate, a widely accepted finding is the ability of humans who are initially insensitive to androstenone to acquire sensitivity to it upon continued exposure (Wysocki *et al.* 1989). Since the 1989 anecdotal discovery of C.J. Wysocki, several other studies have shown that humans and other species can acquire sensitivity to androstenone as well as to other odourants (Wang *et al.* 1993; Pause *et al.* 1999; Dalton *et al.* 2002). However, the mechanism(s) of this increased sensitivity are poorly understood. In this issue of *The Journal of Physiology* Wang *et al*. (2004) provide evidence for a mechanism of increased sensitivity in the olfactory epithelium of humans.

The testing of induced sensitivity to androstenone generally involves the selection of an experimental group that shows complete insensitivity or an abnormally high detection threshold. These subjects are repeatedly presented with androstenone over a period of 2–8 weeks, and their detection threshold monitored. As a result of this treatment some individuals show a decrease in their threshold of detection. Recently, it has been shown that the prevalence of true anosmia to androstenone in humans is much lower than originally documented (Bremner *et al.* 2003). Only ∼2% (*versus* ∼30%) of the population is truly anosmic and Bremner *et al.* showed that individuals classified *a priori* as anosmic could under a more rigorous test be classified as hyposmics. This finding highlights the requirement that a careful distinction between anosmia and hyposmia is necessary for fully understanding the mechanisms by which induced sensitization occurs.

Two possible mechanisms have been postulated for the increase in androstenone sensitivity, a peripheral mechanism, involving the sensory epithelium and a central mechanism, with a less defined source. In the former, interaction of androstenone with a population of maturing olfactory sensory neurones (OSNs) leads either to an increase of androstenone-specific receptors or to an increase in the number of androstenone-sensitive OSNs (Yee & Wysocki, 2001). Alternatively, a recent study argued that the increased sensitivity involves central components of the olfactory system (Mainland *et al.* 2002). In this study only one of the subject's nostrils was exposed to androstenone. Nonetheless, subjects showed increased sensitivity to androstenone in both nostrils, as evidenced by an increase in detection accuracy. However, the authors caution that a peripheral mechanism could also contribute to the increased sensitivity.

The studies of Wang *et al*. (2004) presented here are in agreement with a peripheral site for this increased sensitivity to androstenone. They show, for the first time in humans, that both the electroolfactogram (EOG) responses and the olfactory event-related potential (ERP) are increased. An important issue that these studies raise is that of the relationship between the threshold for detection of a particular odourant and the possibility of acquiring sensitivity to it. While the threshold for androstenone decreased as the subjects were repeatedly exposed to this compound, the threshold for another test compound, amyl acetate, was unchanged. However, the threshold of detection for amyl acetate was initially lower than the threshold for androstenone, suggesting the possibility that only compounds with high thresholds can exhibit increases in sensitivity.

What is the molecular mechanism by which continuous exposure to a particular odourant results in increased sensitivity? The proposed peripheral mechanism points to an increase in the number of androstenone-sensitive receptors. The availability of microarray chips containing olfactory receptor probes could be useful to examine this possibility. For other anosmias, most notably to isovaleric acid, the genomic locus is known, at least in mice (Griff & Reed, 1995; Zhang & Firestein, 2002), and the androstenone anosmia could be similarly identified. However, it is possible that sensitization of other components of the transduction pathway, beside the receptors themselves, could account for increased sensitivity. Although the present results seem to clearly indicate a peripheral mechanism, the varied perceptions of androstenone in humans, from unpleasant to pleasant, suggest that more than one mechanism is responsible for modulating sensitivity in the olfactory system. A more difficult question to answer is how the repeated exposure to androstenone induces a cellular change in the sensory cell (or basal cells). A possible clue may already exist in the vast literature describing the mechanisms by which neurotransmitters and synthetic compounds decrease or increase the activity of the many other GPCRs in neural and other systems.

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