Current Biology, Vol. 14, R918–R920, November 9, 2004, ©2004 Elsevier Ltd. All rights reserved. DOI 10.1016/j.cub.2004.10.013

Olfaction: Attracting Both Sperm and Dispatch the Nose

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Odorant receptor genes are expressed not only in the nose but also in testes, where they have been hypothesized to play a role in sperm chemotaxis. New data demonstrate that human odorant receptor hOR 17-4 may play similar roles in both tissues, lending support to the idea that chemical attraction is important for reproduction.

We use our noses to perform a number of important tasks, from detecting the smell of fire to distinguishing palatable from spoiled foods. But whether the sense of smell in humans is used to mediate social and sexual communication is the subject of intense debate. While many other vertebrate animals possess a specialized vomeronasal organ that detects pheromones, this structure is vestigial in humans, as are most of the genes that mediate pheromone detection [1,2]. 'Love at first sight' and 'chemistry' between couples notwithstanding, to what extent does the sense of smell actually matter in reproduction? A study by Spehr *et al.* [3], published recently in *Current Biology*, suggests that the answer may be appealingly direct. In psychophysical and physiological experiments, the authors demonstrate that odorant receptor hOR 17-4 may play the same role in both sperm and the nose (Figure 1).

These two organs have in common a role in chemotaxis — directed movement toward chemical substances in the environment. For species that use external fertilization, such as sea urchins and fish, it is crucial to reproductive success that sperm are able to recognize and swim toward the egg. This is accomplished by a combination of signal transduction components loaded onto mature sperm and chemical ligands secreted by the egg [4–6]. That sperm in internally fertilizing species, such as mammals, would require active chemotaxis is less obvious. However, shortly after publication of the landmark paper that described a super-family of odorant receptors [7], another group isolated members of this gene family expressed in mammalian testes, associated with mature sperm [8,9]. This intriguing finding led to the suggestion that mammalian sperm are indeed capable of 'smelling' their way to the egg.

Until last year, this hypothesis awaited a direct test, and was based solely on gene expression in testes. Genomic analysis suggested that approximately 5–10% of the odorant receptor repertoire, on the order of 50 genes in rodents, is transcribed in testes [10]. However, testes are known to be permissive for expression of many genes that have no functional relevance in sperm biology. Evolutionary analysis of coding sequences [11] from nasal and testes odorant receptor genes suggested that those genes expressed in testes are under strong selection pressure and more conserved than their olfactory counterparts. Based on these findings, a number of functions have been proposed for testicular odorant receptors. Their expression may be important for general motility of sperm, by providing non-specific G protein-coupled activation of signaling cascades. Alternatively, sperm odorant receptors may confer directed chemotaxis toward the egg, either generically for all sperm or more specifically to attract only those sperm possessing the particular odorant receptor tuned to the scent of the egg.

The availability of the complete set of odorant receptors in the human genome permitted a test of these various competing hypotheses for sperm odorant receptor function [12,13]. In a previous study, Spehr *et al.* [14] cloned an uncharacterized human testicular odorant receptor known as hOR 17-4 and examined its ligand preferences in heterologous expression system. This technique involves expressing the odorant receptor in tissue culture cells and challenging it with a variety of pure odors and odor mixtures. They found that hOR 17-4 responds strongly to floral odors such as bourgeonal, which smells like lily-of-the-valley. In accord with previous studies of conventional odorant receptors [15–17], this sperm odorant receptor has a receptive range of a number of structurally related odors that suggest a constrained binding pocket for ligand.

Interestingly, Spehr *et al.* [14] found that activation of hOR 17-4 is completely inhibited by simultaneous presentation of a structurally unrelated odorant, undecanal, a green, leafy odor. This type of pharmacological inhibition has been previously demonstrated in an elegant study on the pharmacology of conventional odorant receptors [18]. Therefore, hOR 17-4 has functional properties resembling those of odorant receptors expressed in the nose. Further, this suggests that sperm are likely to gain specific and nuanced chemotaxis if they express this particular receptor protein. These studies on the pharmacology of the sperm odorant receptor were then extended to the sperm themselves: human sperm showed functional activation and chemotaxis toward bourgeonal that was blocked by undecanal, although it was not possible to ascribe these behaviors directly to the function of hOR 17-4 itself [14].

In the new study, Spehr *et al.* [3] make the interesting finding that this sperm receptor is in fact also expressed in the olfactory system. Careful analysis of human tissues revealed *bona fide* expression of hOR 17-4 in nasal epithelium. This prompted the authors to investigate whether hOR 17-4 shows the same functional properties in the nose and sperm. To do this, they asked several hundred human subjects to

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rate the perceived intensity of bourgeonal before and after a brief sniff of undecanal. The subjects reported a marked decrease in the intensity of bourgeonal when preceded by undecanal. This inhibitory or masking effect was specific to the bourgeonal–undecanal series, was not seen with other odors that do not activate hOR 17-4, and showed a clear undecanal dose-dependence. The same phenomenon was seen in direct electrical measurements of odor-evoked potential in human nasal epithelium.

Remarkably, the human nose showed the same types of pharmacology as human sperm, and the authors [3] suggest that hOR 17-4 mediates both responses. Although direct proof that hOR 17-4 alone mediates these responses is still missing, these findings have several important implications. As hOR 17-4 activity is detected in both tissues, this receptor may have evolved a common function in reproduction that is carried out in the nose and sperm. Secondly, it suggests that the functional properties of odorant receptors are similar in these two tissues and that in both instances they mediate specific responses to odors. This effectively rules out the non-specific activation hypothesis offered earlier.

Going beyond this correlation of hOR 17-4 with odor perception and sperm chemotaxis to a direct functional proof will provide many future challenges. The simple prediction would be that humans with loss of function mutations in hOR 17-4 should show neither the specific sperm chemotaxis nor psychophysical pharmacology to bourgeonal/undecanal. The extremely large variation in human odorant receptor repertoires between individuals provides some hope that such subjects can be found [19]. Definitive experiments to probe the role of sperm odorant receptors would be more tractable in the mouse, which is suitable for direct genetic manipulation of such dual function odorant receptors. Behavioral experiments coupled with sperm chemotaxis and fertility experiments could illuminate the role of these genes in reproduction.

If sperm do undergo chemotaxis toward the egg using odorant receptors, it will be of great importance to characterize the chemoattractants that they are responding to. It is unlikely that bourgeonal itself is released by the egg, but endogenous mimics of this odorant that are within the receptive range of hOR 17-4 may be. Large-scale purification of mouse egg extracts, coupled with new techniques of deorphanizing odorant receptors will likely be a powerful approach to identify such substances. These experiments have obvious practical applications, in that sluggish sperm could be activated to swim by synthetic egg odor [20]. Alternatively, inhibitors such as undecanal could act as potent contraceptives that paralyze or disorient swimming sperm.

What remains to be understood is the purpose of a dual function of the same receptor in both sperm and nose. If, as Spehr *et al.* [3] suggest, the ligand properties and pharmacology of hOR 17-4 are indistinguishable, perhaps the receptor mediates a type of synergy in reproductive choice. One might speculate that a potential female mating partner would produce a specific cocktail of chemoattractants for her eggs and a similar body odor scent. Such a chemical display would first attract a male mate through the olfactory system and subsequently ensure a productive mating by attracting his sperm. Less romantically, this dual function may simply reflect the diversity of gene expression of an extremely large family of odorant receptors. Time will tell if love at first sight is mediated by such concerted chemical communication.

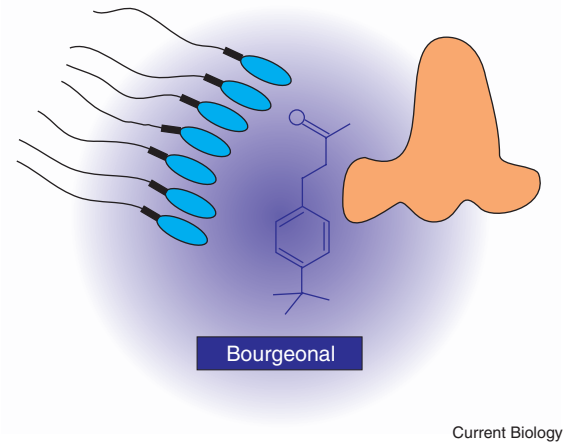

Figure 1. Testes and the nose both express members of the odorant receptor super-family of G protein-coupled receptors.

The testes odorant receptor hOR 17-4, previously shown to interact with the floral odor bourgeonal, is now shown to be expressed in the nose as well. This suggests that hOR 17-4 has evolved a dual role in chemoreception: perhaps guiding sperm to the egg and providing a conscious perception of odors through the nose. A gradient of bourgeonal is shown to attract sperm (left) and to be smelled by the nose (right).

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