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Are Pheromones Detected Through the Main Olfactory Epithelium?

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Abstract A major sensory organ for the detection of pheromones by animals is the vomeronasal organ (VNO). Although pheromones control the behaviors of various species, the effect of pheromones on human behavior has been controversial because the VNO is not functional in adults. However, recent genetic, biochemical, and electrophysiological data suggest that some pheromone-based behaviors, including male sexual behavior in mice, are mediated through the main olfactory epithelium (MOE) and are coupled to the type 3 adenylyl cyclase (AC3) and a cyclic nucleotide-gated (CNG) ion channel. These recent discoveries suggest the provocative hypothesis that human pheromones may signal through the MOE.

Keywords Olfactory · Pheromone · MOE · VNO · Adenylyl cyclase type 3 · Aggression · Sexual behavior

Introduction

Pheromones are "airborne chemical signals that are released by an individual into the environment that affect the physiology and behavior of other members of the same species" [1]. Both volatile and non-volatile compounds can act as pheromones [2]. These chemical signals provide information about gender and reproductive status, while also mediating social and sexual behaviors, as well as neuroendocrine changes.

Although most tetrapod vertebrates have a complex olfactory system, including the MOE, vomeronasal organ (VNO), septal organ, trigeminal system, as well as the nervus terminalis (also called Gruneberg ganglion), all of which could potentially play roles in olfactory and pheromone detection, it is generally thought that the MOE and VNO are the two main olfactory organs (Fig. 1). The MOE resides within the posterior recess of the nasal cavity. The VNO is located in a blind-ended pouch within the septum of the nose [3] and is enclosed in a cartilaginous capsule that opens through a duct into the base of the nasal cavity. Axons from olfactory sensory neurons (OSN) of the MOE project to the main olfactory bulb (MOB), whereas axons from neurons in the VNO project to the accessory olfactory bulb (AOB). It was originally thought that volatile odorants are detected exclusively by the MOE, while pheromones are detected through the VNO [4]. Accordingly, behaviors affected by pheromone signaling such as intermale aggression, male sexual preference, puberty acceleration, maternal aggression, and pregnancy block were typically attributed to VNO control [5–9]. The MOE, on the other hand, was believed to be specialized for the detection of odorants that signal food and danger [10]. Humans, like other vertebrates, do have a VNO; however, the VNO is not functional in adults [11]. Evidence discussed in this review suggests that some pheromones may be detected through the MOE in mice, leading to the interesting possibility that humans may be able to detect pheromones through the MOE.

Stimulation of odorant receptors in the MOE generates cyclic AMP (cAMP) transients through activation of AC3 [12], which stimulates the cyclic nucleotide-gated (CNG) ion channel. In addition to the primary cAMP pathway, other pathways for odorant detected have been proposed. Some odorants increase cyclic guanosine monophosphate (GMP) in OSNs, suggesting that these odorants may be detected through activation of CNG by cGMP [13].

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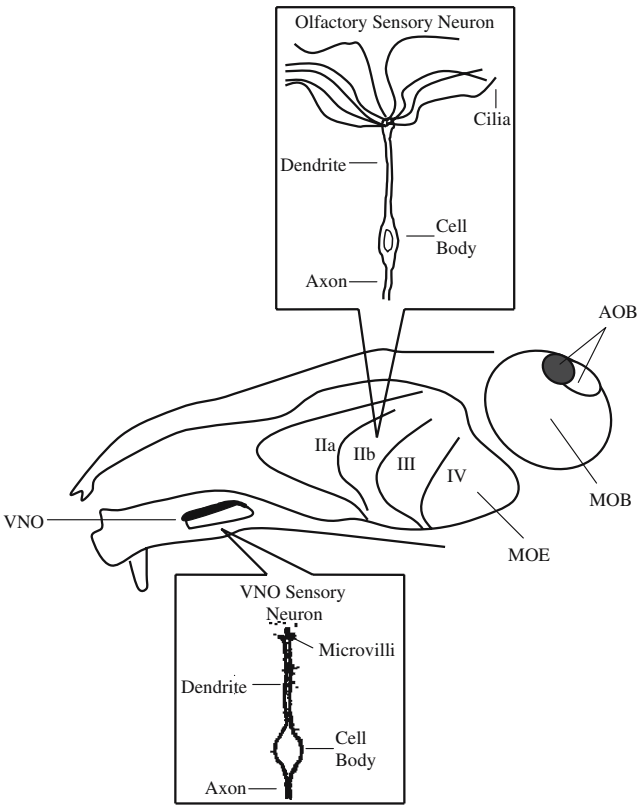

Fig. 1 An illustration of the anatomical locations of the MOE and VNO in mice. The MOE and VNO do not overlap in anatomy, and the receptor neurons employed by the MOE and VNO are also distinct. The MOE is divided into four regions; the VNO and AOB are divided into two regions

However, knockout mice lacking G-olf and AC3 display no odor-induced electrophysiological responses in the MOE, demonstrating the vital importance of the cAMP-mediated signal transduction cascade for olfactory detection in the MOE [14, 12].

Two large families of genes, V1r [15] and V2r [16–18], are expressed in the VNO, where they encode putative pheromone receptors. Neurons in the apical VNO epithelium express V1r, co-localized with the G-protein α-subunit Gαi2, while V2r is expressed in the basal epithelium with another G-protein, $G_o\alpha$. Axons from the V2r/Gαi2-expressing region project to the anterior part of the AOB, whereas those originating in the V2r/$G_o\alpha$ zone target to the posterior AOB. Also expressed in the VNO is a cation channel, TRPC2, a member of the transient receptor potential (TRP) family of ion channels [19]. Because phospholipase C (PLC) is present in these VNO neurons [20], it has been hypothesized that chemosensory activation of VNO pheromone receptors triggers G-protein-mediated stimulation of PLC. The subsequent breakdown of phosphoinositides produces inositol-1,4,5-trisphosphate (Ins (1,4,5)P3) and diacylglycerol (DAG) that gate the TRPC2 channel, allowing ion flux, depolarization, and propagation of signaling to secondary sensory organs (reviewed in [21]).

The V1r, V2r, and TRPC2 are not expressed in OSNs of the MOE, and similarly, none of the main components of the MOE signaling cascade, Golf, AC3, or CNGA2, are expressed in the VNO [22]. Furthermore, olfactory receptors expressed in the MOE show no significant sequence homology with the vomeronasal receptor genes (Vrs) expressed in the VNO (reviewed in [23]).

Despite evidence supporting the hypothesis that the MOE and the VNO are specialized for the detection of odorants and pheromones, respectively, accumulating evidence indicates that their functions are not as specialized as previously thought [24–27]. For example, odorants stimulate Ca^{2+} transients in dissociated VNO neurons in vitro [28], and $AC3^{-/-}$ mice that lack MOE-mediated olfaction are able to detect certain volatile odorants via the VNO [24]. Collectively, these observations suggest that some odorants are detected through an AC3-independent pathway in the VNO and that there are distinct mechanisms for the detection of odorants in the MOE and VNO.

Ablation of the VNO or MOE Blocks Pheromone-Mediated Social Responses

Although the VNO is implicated in the detection of pheromones as well as pheromone-based behaviors, including intermale aggression and male sexual activity [5–8], several lines of evidence indirectly suggest that the MOE may also play a role in the detection of pheromones. For example, ablation of the VNO has no effect on the suckling behavior of rabbits [29] or the mating behavior of male hamsters [30] and domestic pigs [31]. Male mice with surgically removed VNO are still able to distinguish urine odors from males, estrous females, and from mice of both sexes that are in different endocrine states [32]. Furthermore, removal of the VNO from female mice does not impair their ability to discriminate between males and females [33]. Notably, destruction of the MOE with $ZnSO_4$ reduces sexual behavior in female mice [33], suggesting that the MOE may also play a role in the detection of pheromones.

Are there Pheromone Receptors in the MOE?

Several recent studies indicate that receptors capable of pheromone detection may be expressed in the MOE. Low-level expression of the V1Rd [3] and V1R1 [34] receptor transcripts in the MOE have been reported. Furthermore, members of the trace amine-associated receptor family are expressed in OSNs (OSN) of the MOE. These receptors recognize volatile amines including some that are found in abundance in urine and are known to be important social cues [34].

Pheromones Stimulate EOG Responses in the MOE

The electro-olfactogram (EOG) response recorded extracellularly from a population of OSNs is a negative field potential that is believed to represent the summed odorant-induced membrane potential changes in the olfactory cilia [35]. In general, this recording provides a sensitive and facile assay for neuronal function [36]. Although it is conceivable that a stimulus capable of eliciting a behavioral response may be local enough to not be detected by the EOG, one may expect that if pheromones are detected through the MOE, they would elicit EOG responses. Indeed, several volatile pheromones, including 2-heptanone and farnesene, evoke EOG responses in the MOE of wild-type mice (Fig. 2). However, pheromone-stimulated EOG responses in the MOE are ablated in $AC3^{-/-}$ mice (Fig. 2), suggesting that some pheromone receptors may be coupled to AC3 and cAMP signaling [27]. Furthermore, lesioning of the MOE of wild-type mice with $ZnSO_4$ destroys the EOG responses to these pheromones [27]. In addition to volatile pheromones, there is electrophysiological evidence that nonvolatile chemicals are also detected in the MOE. The major histocompatibility complex (MHC) not only carries out functions related to antigen recognition and immune responses, but it also influences mating preference and other social behaviors in fish, mice, and humans. A recent study demonstrates that nonvolatile MHC class I peptides are able to activate OSNs in the MOE and also affect social preference of male mice in vivo [2].

Gene Disruption Studies Implicate the MOE in Pheromone Detection

Several knockout mice with targeted deletions of key signaling components in the MOE and VNO pathways have been generated. These models have brought to light the redundancy of the VNO and the necessity of the MOE for several pheromone-dependent behavioral functions. For example, sensory activation of VNO neurons requires TRPC2, an ion channel of the TRP family that is expressed in these neurons but not in the MOE [8]. $TRPC2^{-/-}$ male mice mate normally with females, indicating that signaling through the VNO is not required for initiating sexual behavior [7, 8].

Since several signaling components including CNGA2 and AC3 are required for MOE function and are not expressed in the VNO, the behavior of knockout mice lacking these proteins can be used to analyze the importance of the MOE in pheromone detection. Mutant mice lacking CNGA2 do not show normal sexual and aggressive behaviors [25]. This suggests that these behaviors are mediated at least in part through pheromone signaling in the MOE. However, CNGA2 is expressed throughout the brain [37] and other tissues [38]. Therefore, defects in pheromone responses seen with $CNGA2^{-/-}$ mice do not alone prove that pheromones are detected in the MOE. Furthermore, because the CNG is activated by cAMP, cGMP, and various kinases, behavioral data obtained with the $CNGA2^{-/-}$ mice do not indicate that pheromone receptors are directly coupled to adenylyl cyclase or any other specific effector system. Nevertheless, the lack of male sexual responses in $CNGA2^{-/-}$ mice supports the general hypothesis that some pheromones may be detected through the MOE.

$AC3^{-/-}$ mice cannot detect mouse milk, urine, or mouse pheromones measured by the odorant habituation test [27]. Furthermore, inter-male aggressiveness and male sexual behaviors are completely lost in $AC3^{-/-}$ mice (Fig. 3a,b). Moreover, adenylyl cyclase activity in membranes prepared from the MOE of wild-type mice, but not $AC3^{-/-}$ mice, is stimulated by the mouse pheromone 2-heptanone (Fig. 4a,b). Collectively, these data suggest that some pheromone receptors are coupled to AC3 in the MOE. However, as is the case for CNGA2, AC3 is not exclusively expressed in the MOE [39], and therefore, these deficits in detection and social behaviors cannot be taken as definitive evidence that pheromones are detected through the MOE. Also, because

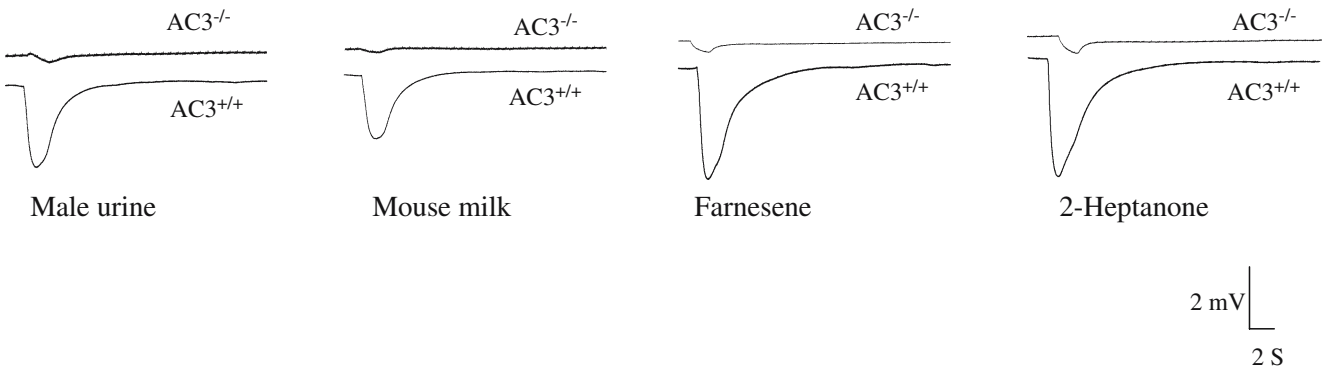

Fig. 2 The MOE of $AC3^{-/-}$ mice are deficient in pheromone-stimulated EOG response (modified from Fig. 1 in reference [27]). Male mouse urine was diluted 20-fold, and mouse milk was diluted 50-fold in water; farnesene (50 μM) and 2-heptanone (50 μM) was diluted in mineral oil

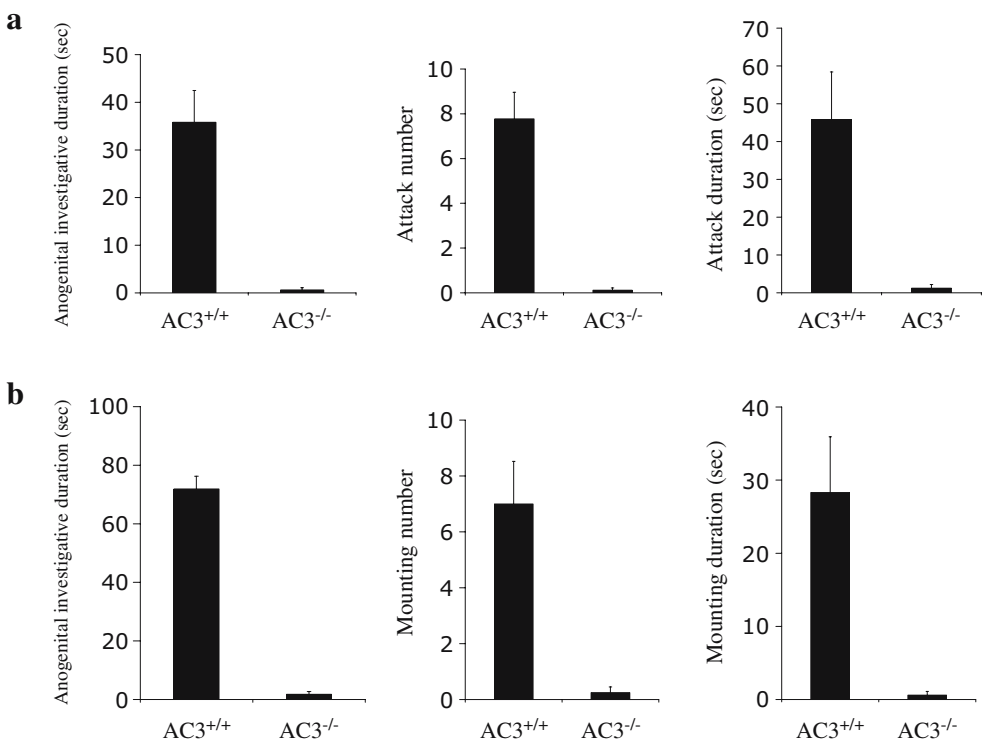

Fig. 3 AC3$^{-/-}$ male mice are deficient in aggressive and sexual behaviors. **a** Resident/intruder assay reveals that AC3$^{-/-}$ male mice fail to display any aggression toward an intruder (AC3$^{+/+}$, n=17; AC3$^{-/-}$, n=16, p<0.0001). *Error bars* represent ±SEM. **b** AC3$^{-/-}$ male mice do not exhibit sexual behavior toward females (AC3$^{+/+}$, n=14; AC3$^{-/-}$, n=15, p<0.001). *Error bars* represent ±SEM (modified from Fig. 2 in reference [27])

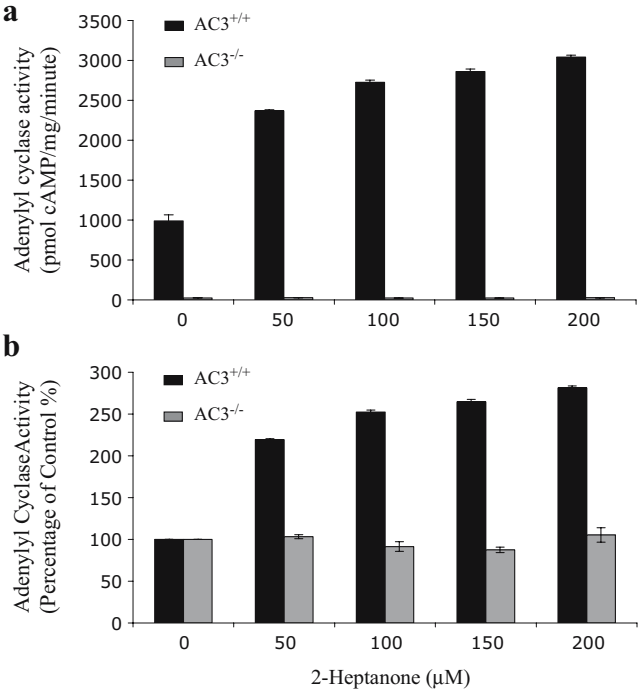

Fig. 4 Pheromone receptors in the MOE couple to AC3: Stimulation of membranes isolated from olfactory epithelium with the pheromone 2-heptanone induces adenylyl cyclase activity in wild-type, but not AC3$^{-/-}$, mice. *Error bars* represent ±SEM. **a** Results expressed as specific AC activity. **b** Results expressed normalized to vehicle control. *Error bars* represent ±SEM (adapted from Fig. 4 in reference [27])

axonal projections to MOB are perturbed in AC3$^{-/-}$ mice [24], one cannot exclude the possibility that the inability of AC3$^{-/-}$ mice to respond to pheromones may be indirectly caused by the disorganization of glomeruli in the MOB. However, AC3$^{-/-}$ mice exhibit no EOG responses to a wide variety of odorants and pheromones, indicating that the primary sensory response is disrupted locally in the MOE.

All caveats considered, phenotypic similarities between these two different genetic models strongly support the hypothesis that detection of pheromones by receptors expressed in the MOE and coupled to the AC3/CNG pathway is important for some pheromone-dependent social behaviors.

The MOB May Also be Involved in Pheromone Detection

The MOB is the first relay station for signal projection from the MOE and does not receive any direct input from the VNO. Thus, if the MOE is involved in pheromone detection, the MOB might also respond to some pheromone stimulation. Using high-resolution functional magnetic resonance imaging, it has been demonstrated that neurons in the mouse MOB respond to 2-heptanone, as well as mouse urine [26]. Furthermore, mitral cells in the MOB are activated by (methylthio)methanethiol, which is a potent and highly volatile pheromone present only in urine collected from male mice [40]. Similarly, the MOB is also activated by pheromones in ferrets [41, 42] and in hamsters [43].

Do Humans Detect Pheromones?

There is convincing evidence that human physiology and behavior may be influenced by pheromones. Perhaps, the strongest evidence suggesting the existence of human pheromones is menstrual synchrony, a phenomenon in which women tend to synchronize menstrual cycles when they are roommates or close friends [44]. The existence of pheromone-induced menstrual synchrony is supported by studies in which the menstrual cycles of women were modulated simply by applying to their upper lip compounds harvested from the armpits of other women in different ovulatory stages [45].

At least two putative human pheromone compounds, 4,16-androstadien-3-one (AND) and oestra-1,3,5(10),16-tetraen-3-ol (EST), have been identified. AND is a derivative of testosterone that is detectible in human sweat. In men, it is found in concentrations about ten times that of women [46]. EST is an estrogen-like steroid, which is present in the urine of pregnant women [47]. Both compounds function as human pheromones that induce sex-specific effects on the autonomic nervous system, mood, and context-dependent sexual arousal [48]. Furthermore, odors associated with inherited HLA alleles (the human form of MHC) can influence odor preference and may also act as social cues [49]. However, because of the extreme complexity of human social behaviors, pheromone-induced human behaviors may be mechanistically distinct from rodents.

If indeed human pheromones exist, are they detected through the VNO, the MOE, or both? Although the early human fetus does have a VNO and there is electrophysiological data that the VNO in adult humans may be functional [47, 50, 51], the preponderance of the published data indicates that adult humans do not have a functional VNO. For example, by morphology, the human VNO epithelium more strongly resembles respiratory epithelium than the VNO neuroepithelium found in other species with functional VNOs [52]. Also, olfactory marker protein (OMP), which is a reliable marker for mature MOE and VNO neurons, is not expressed in human VNO [53]. Furthermore, lectin histochemistry with the probes Con-A, ECL, PNA, RCA, S-WGA, and UAE-1 reveals patterns of reactivity unlike those of functional VNO of other mammals [54]. Additionally, TRPC2, as well as most of the genes identified as coding for receptor proteins in the mouse VNO, are pseudogenes in humans [55], and no functional pheromone receptors are known to be expressed in the human VNO. Finally, there is no AOB in the human brain [56], whereas in all other species with functional VNO, it is a structure that functions as a relay for the processing of pheromone signals. Collectively, these data indicate that adults do not detect pheromones through the VNO.

If the VNO is not functional in adult humans, how can we detect pheromones? MOE-mediated detection of pheromones in mice [27] raises the interesting possibility that humans might be able to detect pheromones through the MOE. This idea is supported by the fact that a putative pheromone receptor gene (V1RL1) is present in the human genome [57], and the receptor is expressed in the MOE. Furthermore, two closely related putative pheromone-binding lipocalin genes have been identified in humans, and one of them is also highly expressed in the main olfactory mucosa [58]. Additionally, it has been reported that the putative human pheromone compounds, AND and EST, induce sexually dimorphic neural responses in the human hypothalamus [59]. In light of recent studies in mice that indicate that main olfactory inputs can modulate pheromone responses in luteinizing hormone-releasing hormone (LHRH) neurons in the hypothalamus [60, 61], it is plausible that AND and EST pheromone responses also originate in the human MOE. Whether pheromone detection in humans does indeed occur by odorant or pheromone receptors in the MOE still remains to be determined experimentally.

Conclusions

Humans can detect pheromones, but the identity of the chemosensory organ responsible for this task has remained elusive. Early anatomical and electrophysiological reports suggested that human pheromones might be detected through the VNO, as in other species. However, the majority of the data does not support a role for the VNO in human pheromone responses. The evidence that pheromones may be detected in the MOE in mice and other species suggests the interesting hypothesis that we may be able to detect some pheromones through the MOE. The behavioral and electrophysiological deficits demonstrated by the $AC3^{-/-}$ and $CNGA2^{-/-}$ mice implicate cAMP as a second messenger for some pheromone responses in mice, and possibly humans. These speculations concerning the possible role of the MOE in the detection of human pheromones must be tempered by the fact that the majority of data supporting a role for the MOE in pheromone detection was obtained with species, including mice, for which olfaction is the primary sensory process. Proof of this hypothesis will require additional studies of human pheromone detection, which are now guided by these discoveries made in mice.

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