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UPDATE

Vomeronasal organ and human pheromones

D. Trotier*

CNRS, INRA, FRE 3295, Neurobiologie Sensorielle, domaine de Vilvert, bâtiment 325, 78350 Jouy-en-Josas, France

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Summary For many organisms, pheromonal communication is of particular importance in managing various aspects of reproduction. In tetrapods, the vomeronasal (Jacobson's) organ specializes in detecting pheromones in biological substrates of congeners. This information triggers behavioral changes associated, in the case of certain pheromones, with neuroendocrine correlates. In human embryos, the organ develops and the nerve fibers constitute a substrate for the migration of GnRH-secreting cells from the olfactory placode toward the hypothalamus. After this essential step for subsequent secretion of sex hormones by the anterior hypophysis, the organ regresses and the neural connections disappear. The vomeronasal cavities can still be observed by endoscopy in some adults, but they lack sensory neurons and nerve fibers. The genes which code for vomeronasal receptor proteins and the specific ionic channels involved in the transduction process are mutated and nonfunctional in humans. In addition, no accessory olfactory bulbs, which receive information from the vomeronasal receptor cells, are found. The vomeronasal sensory function is thus nonoperational in humans. Nevertheless, several steroids are considered to be putative human pheromones; some activate the anterior hypothalamus, but the effects observed are not comparable to those in other mammals. The signaling process (by neuronal detection and transmission to the brain or by systemic effect) remains to be clearly elucidated.

Introduction

A variety of products containing ''pheromones'' are on offer here and there, especially on the Internet: erotic ''pheromone-based'' perfumes keep appearing on the market, promising enhanced attractiveness and personal performance. What do the scientists say? Apart from the methodological issues involved in such studies [1], the claim that human pheromones exist implies being able to demonstrate activation of a sense organ capable of transmitting such information to the brain and to identify relevant behavioral and/or physiological effects. Is the vomeronasal organ, involved in detecting pheromones in other mammals, functional in humans? Can certain steroids be considered as genuine human pheromones, able to induce appropriate effects?

The concept of pheromones

Establishing a hierarchy, encountering members of the opposite sex and estimating their reproductive potential while maintaining genetic diversity, or again signaling a threat are

* Corresponding author. Tel.: +33 01 34 65 29 55.
E-mail address: didier.trotier@jouy.inra.fr

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essential tasks for any animal species. To these ends, individuals deploy a range of sensory signals, in which chemical signals play an important role. When a chemical message triggers specific effects in the receiver, the substance is said to be a pheromone. Two main types are generally distinguished. Releaser pheromones act on the receiver's behavior: e.g., an alarm releaser pheromone is perceived and quickly interpreted so as to elicit flight or alert behavior. Primer pheromones have a deeper and more enduring action on the receiver's physiology: e.g., a dominant male's pheromones alter the endocrine function of subordinate males so as to reduce their sexual aptitude; likewise, a sexually mature male mouse is able to trigger puberty in young females. This concept of ''pheromone'' thus covers different effects, some eliciting a rapid characteristic response while others produce deep and sustained changes in the target's hormonal biology and corresponding behavior.

The molecular nature of animal pheromones is not known in most cases. Studies of rodents, however, showed that small airborne molecules are involved [2] along with nonvolatile substances such as steroids [3], peptides [4,5] and proteins [6]. Air-transport enables volatile pheromones to reach the olfactory system; nonvolatile substances, however, accompanied by volatile substances in solution, can be detected only by the vomeronasal organ.

The role played by proteins and peptides in pheromonal communication is surprising. One example is aphrodisin [7], a protein found in the vaginal secretions of the hamster and which triggers reproductive behavior in young males by activating the vomeronasal organ. Likewise, major urinary proteins (MUPs) are proteins emitted in abundance in mouse urine (several milligrams per day!). The MUPs set produced by a given individual acts as an authentic signature [8]. Detection of such molecules involves the vomeronasal organ. Aphrodisin and MUPs are lipocalins: i.e., water-soluble proteins but equipped with an internal sac in which small hydrophobic molecules can lodge [9]. Apart from their role as pheromone carriers, these proteins, or peptide derivatives, also seem to play a signaling role themselves.

In invertebrates, the specificity of the pheromonal message often derives from some particular molecule: e.g., bombykol, which enables males to attract females over long distances. In vertebrates, message specificity, particularly as regards primer pheromones, seems rather to derive from a combination of several molecular entities associating small molecules and macromolecules [10]. This molecular diversity greatly hinders precise description of the substances at work in any given pheromonal effect. Our knowledge of pheromonal effects mainly concerns rodents, which live mainly in darkness, making chemical communication essential. As far as other mammals are concerned, it must be admitted that the molecular nature of pheromones and their physiological effects remain largely obscure.

The animal vomeronasal organ

The location of the animal vomeronasal organ [11], in a forward position on the base of the septum near to the nasopalatine duct (Fig. 1A), allows a pumping action pro-

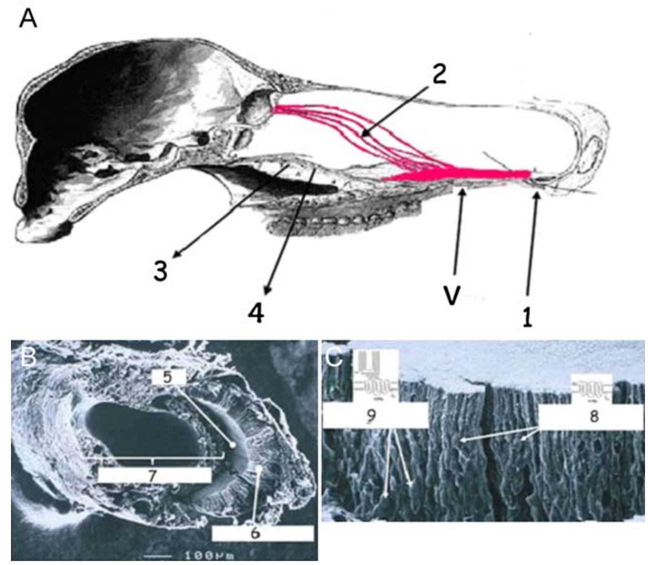

Figure 1 A: Location of a vomeronasal organ (V) in the nasal cavity of a deer, after the original drawing by Ludvig Jacobson. The opening of the organ is near the nasopalatine duct (1). The vomeronasal neuron axons (2) transmit information to the accessory olfactory bulbs behind the main olfactory bulbs. The organ is vascularized (3) and innervated by sympathetic/parasympathetic fibers (4). B: Cross-section of a rat vomeronasal organ, showing the internal canal (5) covered on one side by sensory epithelium (6) containing the neurons and on the other by erectile tissue and a blood vessel (7). Variation in tissue turgescence actively pumps stimuli into the internal canal. C: Cross-section of sensory epithelium, showing the two types of sensory neuron carrying distinct receptor proteins. The short-dendrite neurons (8) expressing V1R proteins transmit information to the posterior part of the accessory olfactory bulbs, whereas the long-dendrite neurons (9) expressing V2R proteins transmit information to the anterior part of the accessory olfactory bulbs.

viding direct contact with biological substrates emitted by congeners. Information is transmitted via the accessory olfactory bulbs, which lie behind the main olfactory bulbs, toward the amygdala and the anterior hypothalamus, which is directly involved in gonadoliberin (GnRH) secretion and thus in sex hormone activity via the anterior hypophysis [12]. During the evolution of species, the vomeronasal organ appears with the advent of amphibians and adaptation to life on land. Fish do not have it: pheromones are detected by specialized neurons in the olfactory epithelium, and the information is processed in cerebral pathways distinct from those of the general olfactory neurons.

The vomeronasal organ was discovered by Ludvig Jacobson in the 1810s [13]. Jacobson showed that it was to be found in mammals, but also pointed out that in humans it appeared to be vestigial. The organ comprises two tubular structures in a low and forward position on either side of the nasal septum, near the vomer bone (Fig. 1A). Its internal duct is closed at the back and communicates forward via a small aperture which, depending on the species, opens either onto the nasopalatine ducts which connect the oral cavity to the nose, or onto the nasal cavities. The