acta medica

REVIEW

Is Human Vomeronasal Organ A Myth or A Neglected Structure?

Ayşegül Fırat[1]
ORCID: 0000-0001-5105-0057

Özlem Önerci Çelebi[2]
ORCID: 0000-0001-8170-7443

Hatice Mürvet Hayran[3]
ORCID: 0000-0001-6058-6304

[1]Department of Anatomy, Faculty of Medicine, Hacettepe University, Ankara, Türkiye.

[2]Departmant of Ear, Nose, Throat Diseases, Istanbul Training and Research Hospital, Istanbul, Türkiye.

[3]Department of Anatomy, Faculty of Medicine, Izmir University of Economics, Izmir, Türkiye.

Corresponding Author: Ayşegül Fırat
Department of Anatomy, Faculty of Medicine, Hacettepe University, Ankara, Türkiye.
E-mail: aysfirat@hacettepe.edu.tr

Received: 11 January 2022, Accepted: 11 May 2022, Published online: 13 June 2022

ABSTRACT

The human vomeronasal organ (VNO) is a structure situated under the anteroinferior side of the nasal septum. It is mainly described in the rodents and found as a part of the accessory olfactory system. It has been shown to consist of specialized olfactory sensory cells, which function in perception of pheromones. With a large number of literature on the human VNO, there is little concensus of its persistence and functionality in human. During a routine dissection of nasal cavity, we recognized a one-sided vomeronasal pit in one of the six fresh-frozen cadavers (17 %) and described the position and structure of this rare structure morphologically.

The present study summarizes the literature about the VNO and describes its structural and functional findings.

Keywords: Human vomeronasal organ, nasal biopsy, vomeronasal pit, nasal septum

INTRODUCTION

The vomeronasal organ (VNO) is a structure situated under the anteroinferior side of the nasal septum. It is part of the accessory olfactory system and has been shown to consist of specialized olfactory sensory cells, which function in perception of pheromones and also they produce gonadotropin-releasing hormone [1]. VNO has been extensively studied in vertebrates, but there is still a lot to be understood on its function and persistence.

If a chemical message triggers specific effects in the receiver, this chemical substance is said to be a pheromone. The pheromones either act rapidly on receiver's behaviour or cause a sustained change on receiver's hormonal physiology. For example, a sexually mature male mouse's pheromone is able to trigger puberty in young females. Our knowledge about pheromones mainly covers rodents that live mainly in darkness and essentially communicates thru chemicals [2]. The chemical structure of the pheromone is mainly not known. In some rodent studies, volatile pheromones are small airborne molecules that contain steroids, peptides and proteins [3-5]. Aphrodisin is an example of proteins that is found in the vaginal secretions of female hamster and it triggers reproductive behavior in young males by activating the vomeronasal organ. Likewise, major urinary proteins emitted in mouse urine are detected by the other's vomeronasal organ and they act as an authentic signature of that individual [2].

The VNO contains two tubular structures on either side of the nasal septum. They open either onto the nasopalatine ducts which connect the oral cavity to the nose, or onto the nasal cavities. The pheromones reach the opening either via the nostrils or by the nasopalatine duct, depending

on the species. It has an internal duct that is closed at the back and communicates outside thru a small aperture depending on the species, Medial side of the lumen is lined by the sensory epithelium containing receptors and lateral side containes vascularized erectile tissue innervated by autonomic nervous system. Stimulation of this tissue induces contraction that results in pumping of the chemicals into the lumen. An accessory olfactory bulb that lies behind the main olfactory bulb transmits information towards the amygdala and the anterior hypothalamus in vertebrates. These regions are involved in gonadotropin secretion and sex hormone activity [2].

VNO is first indicated in human by Ruysch (1703, 1724), a Dutch anatomist, as an organ near the nasal septum of an infant. He did not mention an accurate description or provide a name, but he identified a nasal canal close to palate to represent the VNO [6-8].Then Kölliger (1877) became the first investigator of the VNO histologically in both fetus and adult human [9]. VNO is also known as Jacobson's organ, because Jacobson (1811) intensively studied the VNO across a variety of mammals, but he denied the existence of VNO in humans [10].Potiquet (1891) first discussed the VNO in human and he named the structure as Jacobson's organ [1,6,7,11].

The human VNO develops very early in utero [2,8-13]. The nerve fibers of the VNO extend together with a cluster of migrating gonadotropin releasing hormone (GnRH)-secreting cells from the olfactory placode toward the brain. It contains bipolar neurons and also generates GnRH secreting cells as in other species. Embryologically, these GnRH-secreting cells, developed from the olfactory placode and migrating to the arcuate nucleus of hypothalamus, are responsible from the development of reproductive system at puberty [13]. Subsequently compared to other mammals the VNO of the adult human shows some signs of regression [10-13]. Most of the studies agree on its non-functional status. The cavity of the openings can be visible on some endoscopical examinations but not in all patients. In gross descriptions, there is a depression on the side of nasal mucosa, along the anteroinferior 1/3 of the nasal septum, approximately 3-16 mm inside the nares.14 The opening into the nasal cavity is a depression called VNO pit. In a recent demonstration by Trotier et. al., endoscopically VNO pit can vary in appearance and may be invisible on inspection. In this study, they estimated around 92% of evidence of at least one VNO pit in subjects with no septal surgery [14]. But the position remarkably changes among researches. There are many reports of VNO located in the nasal septum in adult humans describing VNO as a blind ended diverticulum or a tube like sac with a diameter of approximately 0.2-0.6 cm and a depth of approximately 2 mm in the septal mucosa [14-16]. Smith et al. (1998) gave a distance of 7 to 10 mm from the depressions attributed to the VNO pit at the base of the nasal cavity [17]. Trotier et al. (2000) described vomeronasal "cavities" as 6.2 to 10.7 mm above the "crest of the palatine bone" [14]. Other studies have located the VNO openings 1-3 mm above the nasal cavity floor [18,19]. Such varied descriptions may be due to methodological differences, regional variations existing within the human VNO itself, individual variation of VNOs among humans, or due to the description of multiple, non-homologous structures that resemble the human VNO [20]. In addition, some authors have suggested that gross indicators are highly unreliable for locating the VNO [15,21]. In the literature, the frequency of the VNO in human ranges from 25 to 90% [22]. This wide variation may be related to the investigation method and the difficulty of detecting the opening of the VNO [18]. Zbar et al., described three types of openings of the VNO according to its size, while Besli et al. (2004) reported three types based on the shape of the opening: oval, fissural or elliptical [18,23]. Even with a large number of literature on the human VNO, there is little concensus of its persistence and functionality. While its precise function is unknown, it is believed to be associated with pheromone recognition and food flavour perception [15,16].

According to the histological studies, the VNO is covered with simple or pseudo-stratified columnar epithelium with microvilli lining the tubular sac, supported by a lamina that is rich in capillaries [24].Some authors have indicated the presence of cells similar to bipolar sensory neurons, but

did not identify any axons between the epithelial cells [16,25]. On the other hand, Monti-Bloch et al. demonstrated depolarization in the epithelium of the VNO, during local stimulation using substances secreted by the human skin [25]. Trotier et al. showed that most cells in the vomeronasal epithelium expressed keratin, a protein that is not expressed by the olfactory neurons [14]. Vomeronasal epithelial cells of human were not stained by an antibody against the olfactory marker protein, a protein expressed in vomeronasal receptor neurons of other mammals. Moreover, an antibody against protein S100, expressed in Schwann cells, failed to reveal the existence of vomeronasal nerve bundles that would indicate a neural connection with the brain. Positive staining was obtained with the same antibodies on specimens of human olfactory epithelium. The lack of neurons and vomeronasal nerve bundles, together with the results of other studies, suggests that the vomeronasal epithelium, unlike in other mammals, is not a sensory organ in adult human [14]. Notably, it has recently been shown that there are morphological connections of the VNO cells with the underlying capillaries. These, along with the expression of calcium-binding protein in part of these cells, suggest a potential endocrine activity [26]. If so, we would have the first evidence of an alternative function than the usually assumed pheromone sensing one for the VNO.

Some odorant chemicals like steroids have been studied as human pheromone prototypes in adults and some have activated the anterior hypothalamus. The effects observed are more psychological (mood shift, increased attention) than physiological and are context-dependent. Such effects are very far from the pheromonal effects observed in animals (stereotypic behavioral effects, neuroendocrine changes). They can at most be considered to be possible modulators of certain psychological variables [27].

MATERIALS AND METHODS

This study was approved by the Ethical Committee of the Faculty of Medicine. The cadaver dissections are conducted at the Department of Anatomy, Faculty of Medicine. For this study, the anteroinferior part of the septum were sampled bilaterally from six fresh frozen head and neck specimens using standard punch biopsy. For each specimen a careful exploration for possible vomeronasal pit area was conducted. Suspected sites were sampled by three biopsies taken appoximately 5 mm apart. The biopsy was about 5 mm x 2 mm in diameter and provided sufficient depth for examining the epithelium and lamina propria. The specimens were immediately fixed in 2.5% gluteraldehyde (R 1010, Agar Scientific Ltd.) and post-fixed in 1% osmium tetroxide (Catalogue number: 56H1140, Sigma-Aldrich, Germany). After post-fixation tissues were dehydrated in increasing ethanol (159010, Merck KGaA, Germany) concentrations. After washing with propylene oxide (Catalogue number: 8.07027.1000, Merck KGa, Germany) for 30 minutes, samples were embedded in epoxy resin (Araldite CY212 kit, AGR 1030, Scientific Ltd.). Semi-thin sections, approximately 2 µm in thickness were stained with 1% methylene blue solution (methylene blue 1 g, BDH Ltd. Standard stain, borax 1 g, distilled water 100 ml) and examined under the camera lucida of a Nikon Optiphot (Nikon Corporation, Japan) light microscope. Histologic evaluation of the epithelium, glands, vessels, connective tissue and neural elements from nasal mucosa was performed for each sample.

RESULTS

In one of the six cadavers (17 %) we recognized a one-sided vomeronasal pit on the right side. The epithelium of sample taken from the vomeronasal pit had the appearance of a pseudostratified epithelium lining a lumen (Figure 1). It is critical to describe the positional and structural variations in the human VNO where histological verification has been made. To that end, the present study describes the location of the adult human VNO as it relates to grossly identifiable surface marking the vomeronasal pit on the cadaveric nasal septum, 8.2 mm above the nasal floor. This study was not designed for a functional molecular evaluation nor was further immunohistochemistry staining

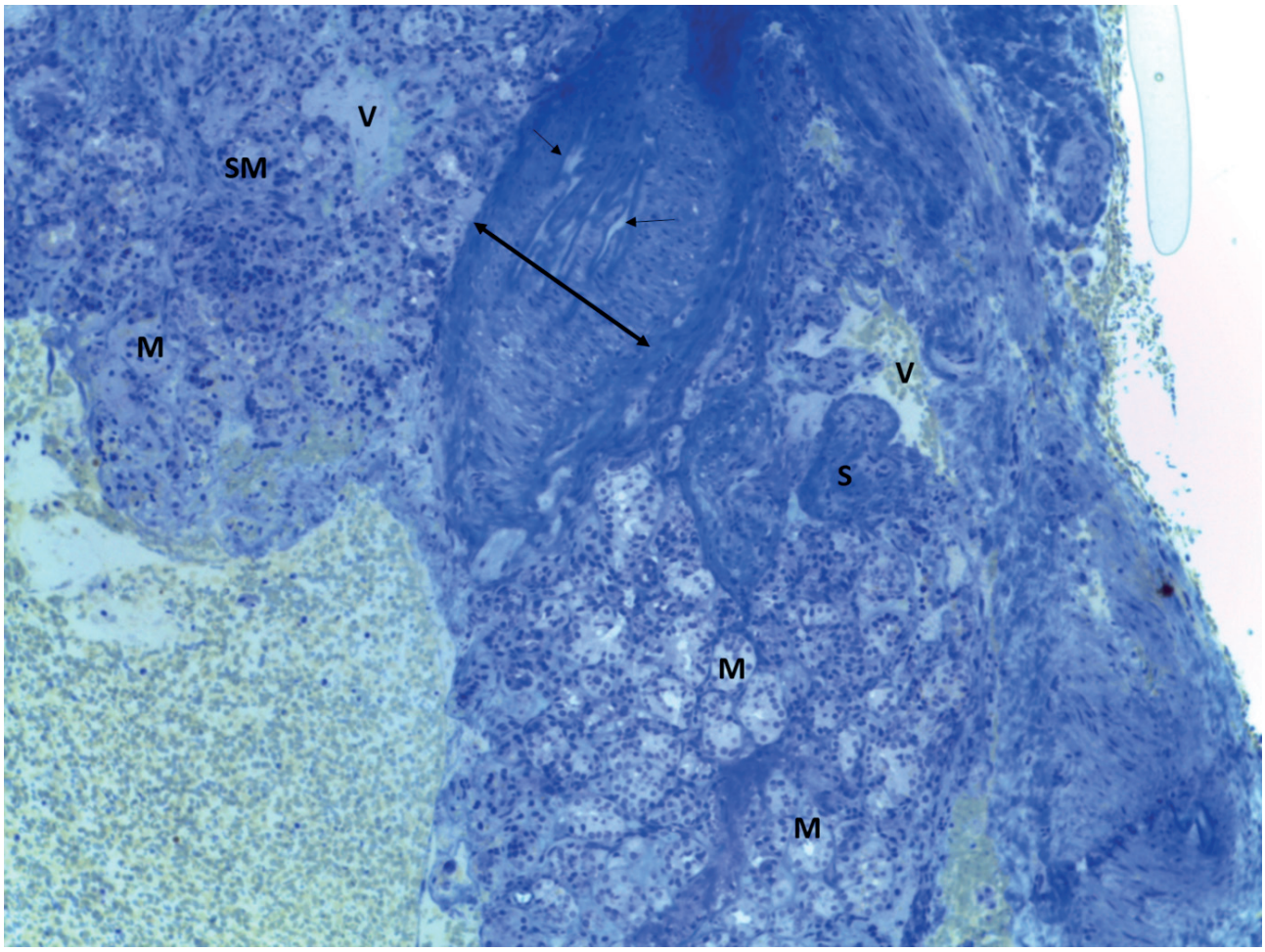

Figure 1. Human vomeronasal organ (double-sided arrow) lined by pseudostratified epithelium.around a lumen (arrow). (M: mucous gland; S: serous gland; SM: seromucous gland; V: vessel). Methylene- blue staining, x200.

planned. The aim was to microscopically examine and recognize the microanatomy of nasal epithelium and related normal nasal cavity tissue components using accessible cadaver samples.

In general, epithelial lining of the anterior-inferior septum was keratinized stratified squamous cilliated epithelium. We observed a thin lamina propria and few connective tissue fibers in all samples. Serous, seromucous and mucous glands were shown in the anteroinferior septum. We have also recognized abundant blood vessels with smaller diameter than other parts of the nasal cavity that we reported in a previous study [28]. In the anteroinferior site of the septum, we haven't differentiated any axons or neuronal extensions.

CONCLUSION

During a routine nasal mucosa dissection we had a chance to describe the histology of human VNO from one of our head and neck specimens. We processed our sample by routine preparation techniques for nasal cavity investigations using transmission electron microscopy. The samples were fixed, processed, embedded, sectioned, and stained for transmission microscopy. However, this preparation technique is not ideal on cadaver tissues and should only be used for live patients. Therefore we could not had a chance to show the ultrastructure of that sample. We thought that the final decision would be made by performing immunohistochemical studies, due to the fact that whether these cells carry the properties of gustatory receptors and contain any axons at their basal portions. These features cannot be determined by standard light microscopy methods.

In this study we reviewed and summarized all perspectives of a neglected and rare structure: the human vomeronasal organ. Questions still remain unanswered about its function, role and persistence in humans. The VNO still continues to incite interest and argument. Recovering the literature, we should finally say that generally in

adult human, the only sensory channel that might possibly allow detection of pheromones and all odorable chemicals in the nasal cavities would be the olfactory system itself.

Acknowledgement

The authors sincerely thank those who donated their bodies to science so that anatomical research could be performed.

Author contribution

Study conception and design: AF and HMH; data collection: AF and ÖÖÇ; analysis and interpretation of results: AF and HMH; draft manuscript preparation: AF, ÖÖÇ and HMH. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

This review study does not require ethical approval.

Funding

The authors declare that the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

[1] Stoyanov GS, Matev BK, Stoyanov P, et al. The Human Vomeronasal (Jacobson's) Organ: A Short Review of Current Conceptions, With an English Translation of Potiquet's Original Text. Cureus 2018;10(5): e2643.

[2] Trotier D. Vomeronasal organ and human pheromones. Eur Ann Otorhinolaryngol Head Neck Dis 2011;128:184-190.

[3] Nodari F, Hsu FF, Fu X, et al. Sulfated steroids as natural ligands of mouse pheromone sensing neurons. J Neurosci 2008;28:6407-6418.

[4] Leinders-Zufall T, Ishii T, et al. Structural requirements for the activation of vomeronasal sensory neurons by MHC peptides. Nat Neurosci 2009;12:1551-1558.

[5] Touhara K. Sexual communication via peptide and protein pheromones. Curr Opin Pharmacol 2008;8:759-764.

[6] Bhatnagar KP and Smith TD. The human vomeronasal organ. V. An interpretation of its discovery by Ruysch, Jacobson, or Kölliker, with an English translation of Kölliker (1877). Anat Rec B New Anat 2003;270:4-15.

[7] Bhatnagar KP and Reid KH. The human vomeronasal organ - I: Historical perspectives. A study of Ruysch's (1703) and Jacobson's (1811) reports on the vomeronasal organ with comparative comments and English translations. Biomed Res 1996(7);pp.219-229.

[8] D'Aniello B, Semin GR, Scandurra A, et al. The vomeronasal organ: a neglected organ. Frontiers in Neuroanatomy 2017;11:70.

[9] Kölliker A. Über die Jacobson'schen Organe des Menschen. Leipzig: Wilhelm Engelmann. 11 p + 2 plates with explanation of figures. 1877.

[10] Jacobson L. Description anatomique d'un organe observe dans le mammiferes. Ann Mus Hist Natl 1811;18:412–424.

[11] Potiquet M. Le canal de Jacobson. Rev Laryngol 1891;2:737–753.

[12] Smith TD, Siegel MI, Mooney MP, et al. Prenatal growth of the human vomeronasal organ. Anat Rec 1997;248:447–455.

[13] Wray S. From nose to brain: development of gonadotrophinreleasing hormone-1 neurones. J Neuroendocrinol 2010; 22:743–753.

[14] Trotier D, Eloit C, Wassef M, et al. The vomeronasal cavity in adult humans. Chem Senses 2000;25:69–380.

[15] Bhatnagar KP and Smith TD. The human vomeronasal organ. III. Postnatal development from infancy to the ninth decade. J Anat 2001;199:289–302.

[16] Meredith M. Human vomeronasal organ function: a critical review of best and worst cases. Chem Senses 2001;26:433-445.

[17] Smith TD, Siegel MI, Burrows AM, et al. Searching for the vomeronasal organ of adult humans: preliminary findings on location, structure, and size. Microsc Res Techn 1998;41:483-491.

[18] Zbar RI, Zbar LI, Dudley C, et al. A classification schema for the vomeronasal organ in humans. Plast Reconstr Surg 2000;105(4):1284-1288.

[19] Moran DT, Jafek BW, Rowley III JC. The vomeronasal (Jacobson's) organ in man: ultrastructure and frequency of occurrence.J Steroid Biochem Molec Biol 1991;39:1545-1552.

[20] Smith TD, Buttery TA, Bathnagar KP, et al. Anatomical position of the Vomeronasal Organ in postnatal humans. Ann Anat 2001;183:475-479.

[21] Jacob S, McClintock MK. Psychological state and mood effects of steroidal chemosignals in women and men. Horm Behav 2000;37:57-78.

[22] Abolmaali ND, Kühnau D, Knecht M, et al. Imaging of the Human Vomeronasal Duct. Chem Senses 2000;26(1):35-39.

[23] Besli R, Saylam C, Veral A, et al. The existence of the vomeronasal organ in human beings. J Craniofac Surg 2004;15(5):730-735.

[24] Knecht K, Kfihnau D, Hiittenbrink K-B, et al. Frequency and localization of the putative vomeronasal organ in humans in relation to age and gender. Laryngoscope 2001;111:448-452.

[25] Monti-Bloch L, Jennings-White C, Berliner DL. The Human Vomeronasal System. A Review Ann. N.Y. Acad Sci 1998;855:373-389.

[26] Wessels Q, Hoogland PV, Vorster W. Anatomical evidence for an endocrine activity of the vomeronasal organ in humans. Clin Anat 2014;27:856–860.

[27] Savic I, Berglund H. Androstenol–a steroid derived odor activates the hypothalamus in women. PLoS One 2010;5:e8651.

[28] Firat A, Onerci-Celebi O, Tuncel A, et al. Microscopic study of human nasal cavity microanatomy using semi-thin resin embedding and methylene blue staining. J Histotechnol 2019;42(1):13-18.