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CELL BIOPHYSICS

The Mechanisms of Chemoreception and Thermoreception in the Grueneberg Ganglion

E. V. Bigdai[a], *, V. O. Samoilov[a], and A. A. Sinegubov[a]

[a] *Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, 199034 Russia*

**e-mail: bigday50@mail.ru*

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Abstract—The Grueneberg ganglion is one of the peripheral parts of the olfactory sensory system that specializes in detecting life-threatening stimuli. This article focuses on the chemoreceptors of ganglion neurons and their associated signaling pathways, which together provide a multimodal receptor function. The molecular organization of the receptor apparatus of neurons of this organ undergoes significant changes during ontogenesis, providing a shift in specialization in the direction from thermoreception in the neonatal period to chemoreception at later stages of development.

Keywords: Grueneberg ganglion, therrmoreception, chemoreception, guanylate cyclase

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INTRODUCTION

The cluster of nerve cells at the entrance of the mouse nasal cavity, called the Grueneberg ganglion (GG), was first discovered in 1973 [1]. The GG has been identified in many mammals, including humans [2]. In rodents, it has approximately several hundred neurons separated from the connective tissue by GFAP- and S100β-positive glia-like cells [3]. Unlike other parts of the peripheral part of the olfactory system, GG cells are not part of the epithelium and do not form a compact structure; they are scattered in their own plate of the mucous membrane at the entrance of the nasal cavity, forming clusters of several dozen cells that are not directly exposed to the external environment [4].

The atypical structure of this organ for the olfactory system led to the hypothesis that this ganglion is part of the terminal nerve; however, the markers of its neurons, that is, the gonadotropin-releasing hormone and acetylcholinesterase, were not detected [5, 6]. The population of neurons at the entrance of the nose is detected for the first time on the 14th day of embryogenesis and forms part of the epithelium. By the 16th day, they migrate into the thickness of connective tissue, acquiring a morphology characteristic of adults [7]. In 2006 the authors of the work [8] obtained the first evidence that the GG is a part of the olfactory system: using transgenic mice that express the green fluorescent protein under the promoter of the olfactory marker protein (OMP), a characteristic marker of differentiated neurons of the main olfactory epithelium and the epithelium of the vomeronasal organ, they found the expression of the reporter in the GG neurons. The main part of the axons of these cells formed synapses in the glomeruli of the anterior part of the additional olfactory bulb, which was independently confirmed by various methods [9, 10]. Thus, at the beginning of the 21st century, it was proved that the GG belongs to an additional olfactory sensory system, as shown by axon projections.

At the same time, the glomeruli they form have a "necklace-like" structure similar to the structures to which neurites expressing the receptor guanylate cyclase D of neurons of the main olfactory epithelium are directed [12].

Despite the unusual localization, GG neurons are somewhat homologous to the sensory cells of the main olfactory epithelium. As an example, in response to the removal of the olfactory bulb, they also degenerate and regenerate within an average of 11 days in the neonatal period [13]; however, the pool of progenitor cells has not yet been identified. The similarity is also expressed in the presence of flagella, specialized organelles, in which chemoreceptors and components of their signal transduction are localized [2]. It was found in the early studies of the GG of the Asian house shrew (*Suncus murinus*) that, unlike neurons in other parts of the olfactory system, they do not directly contact the external environment and are covered with satellite cells throughout, like the body of the neuron [5].

The GG structure was described in detail for four rodent species: C57BL/6J mice (*Mus musculus*), Wis-

Abbreviations: GG, Grueneberg ganglion; OMP, olfactory marker protein; TAAR, trace amine-associated receptors.

tar rats (*Rattus norvegicus*), Syrian hamsters (*Mesocricetus auratus*), and Mongolian gerbils (*Meriones unguiculatus*) [14]. Although common features, such as the presence of invaginated flagella and glia-like auxiliary cells are present in the ganglia of all the considered species, the details of their structure differ significantly. Namely, the ratio of the number of satellite cells and neurons, the number and length of flagella, as well as the shape and size of the bodies of neurons vary widely. It is particularly unusual to find atypical flagella with a cytoskeleton configuration of more than 9 + 0 in Syrian hamsters. Unlike neurons of the main olfactory epithelium, distinct clustering of chemoreceptor signal transduction components within the cilia is observed only in mice and is significantly less pronounced in other species. In sum, the data we obtained indicate a high degree of divergence of this organ even in closely related species, which is not observed for other parts of the olfactory sensory system [15].

THE CHEMORECEPTORS OF NEURONS OF THE GRUENEBERG GANGLION

It should be noted that unlike other peripheral parts of the olfactory system, the functional role of the GG changes as the animal matures and the repertoire of receptors undergoes significant changes during ontogenesis. The GG reaches its peak of development in the late embryonic period, and then it steadily atrophies [16]. Along with the decrease in the number of cells, there is a change in the dominant types of receptors. It was found that olfactory receptors characteristic of the main olfactory system are absent in the GG. The expression of ten olfactory receptors was detected by reverse transcription PCR, while only one of them, OR256-17, was identified by in situ hybridization [17]. Its expression, as well as immunoreactivity to anti-adenylate cyclase III and anti-$G_{olf/s}$, the main components of canonical signal transduction, was detected only in a small fraction of cells (<1% of the entire population) and was limited to the E16–P0 stages.

The authors of [15] using reverse transcription PCR with degenerative primers to the mRNA of olfactory receptors, vomeronasal receptors of subtypes I and II, found an almost complete absence of the mRNA of these genes, except for those corresponding to type II vomeronasal receptors of the C family. The previously unidentified V2r83 was the main one. V2r83-positive cells make up the majority of all GG neurons at all stages of ontogenesis, reaching a peak at the neonatal period (83.2% of all OMP-positive neurons). The V2r83 neurons slightly decrease in number later, while they make up the majority throughout life.

Trace amine-associated receptors (TAAR) are another class of chemoreceptors represented in the GG [18]. In mice, this class consists of 15 intact genes, all representatives of which, with the exception of *Taar1*, are found in the main olfactory epithelium, forming a separate functional subsystem of amine detection [19]. Using reverse transcription PCR, the expression of six genes was detected: *Taar2*, *Taar4*, *Taar5*, *Taar6*, *Taar7A* and *Taar7D*. The total number of TAAR-positive neurons decreases significantly, starting with E17.5; they make up a population of only a few dozen cells in adult animals. The ratio of the different types was determined only in newborn mice, in which *Taar6* and *Taar7* were dominant.

The V2r83 receptor, which is a trace amine-associated receptor, and the transiently expressed OR256-17 make up the entire repertoire of GG chemoreceptors at the embryonic stage of development and during the neonatal period [18]. At the same time, according to immunohistochemistry and in situ hybridization, one neuron expresses one receptor during these stages of ontogenesis. However, in adult animals (6–8 weeks), the total number of V2r83- and TAAR-positive cells is five times lower than the number of all OMP-positive cells.

The above-mentioned receptors have previously been found in other parts of the olfactory system. However, the authors of [20] identified neurons that are representatives of the family of type II taste receptors which are responsible for the perception of bitter as chemoreceptors of the GG. Three of the 35 known functional genes of this family are expressed in the GG: *Tas2r115*, *Tas2r131*, and *Tas2r143* [19]. The frequency of occurrence of these proteins, as well as the possibility of their co-expression with classical "olfactory" receptors, is unknown. However, TAS2R-positive neurons were also detected immunohistochemically in newborn mice, in which, according to previously published data [18], all OMP-positive neurons expressed either V2r83 or one of the trace amine-associated receptors; this indirectly indicated their colocalization with TAS2R within a single neuron.

In addition to G-protein coupled receptors (GPCRs), the neurons that express the guanylate cyclase receptor have been identified in rodents. In a subpopulation of olfactory neurons, the cells that express the guanylate cyclase D (GC-D) receptor were found [22], which use a cGMP-mediated transduction mechanism, responding to such stimuli as uroguaniline and guaniline, which are Na-uretic peptide hormones [23]. The family of receptor guanylate cyclases in mice consists of seven genes [24], of which only the receptor guanylate cyclase G (GC-G) is represented in GG. It is co-expressed by all V2r83-positive cells and is absent in TAAR-positive cells [25].

THE COMPONENTS OF SIGNALING PATHWAYS IN THE GG

Transduction in TAAR- and OR256-17-Expressing Neurons

The chemotransduction starts with the interaction of the stimulus with a specific receptor. The main

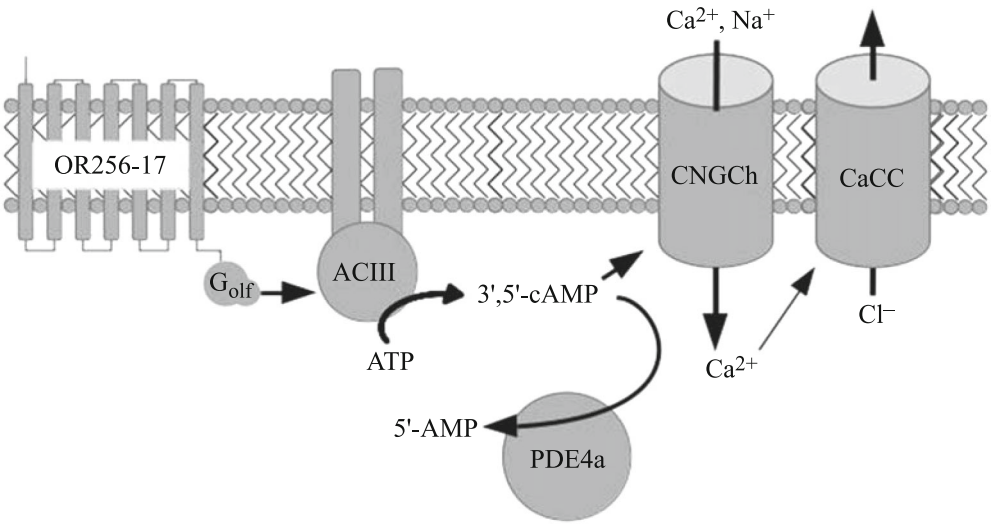

Fig. 1. The mechanism of canonical signal transduction in neurons of the main olfactory epithelium includes G-protein G_{olf}, adenylate cyclase III, cyclonucleotide-dependent and calcium-activated chlorine channels. Components found in OR256-17-expressing GG neurons are highlighted.

olfactory epithelium is characterized by the heterogeneity of olfactory reception mechanisms [26]. The mechanisms that are carried out through G_{olf}, which stimulates adenylate cyclase III in response to the action of the odorant, are better studied than others. Calcium-activated chlorine channels and cyclonucleotide-dependent channels that are selective for cAMP are also obligate components of olfactory transduction [27] (Fig. 1).

A fraction of the cells that express adenylate cyclase III and $G_{olf/s}$ were found in the GG [15]. It is only a small fraction, similar in number to OR256-17 according to in situ hybridization data and is present only in mice at the E16 stage. The dominant cAMP phosphodiesterase 4a of the main olfactory epithelium, as well as OR256-17, was not detected after this stage [28]. At the early stage of mouse development GG neurons probably provide olfactory reception; the mechanism of this transduction is carried out through the OR256-17 olfactory receptors coupled with adenylate cyclase III and $G_{olf/s}$. At a later period, this function disappears. This is shown by the data that G_{olf}, PDE4a and CNGA2, CNGB1 and CNGA4 cyclonucleotide-dependent channels that are selective for cAMP were not detected in newborns.

The neurons that express OR256-17 are replaced by cells with a different type of receptor. Among them, the receptors of trace amines, which are associated with G_{olf} in the main olfactory epithelium, are of particular interest [29]. Unlike OR256-17, TAAR-positive neurons make up a significant population of newborn GG cells. Colocalization of TAAR and G proteins of the $G_{i/o}$ type characteristic of the signaling system in vomeronasal organ cells was detected immunohistochemically [28]; however, neither the functional conjugation of these proteins nor other components of their signaling pathways were detected in TAAR-positive neurons. Therefore, the role played by TAAR in GG neurons is still controversial.

Gustducin (G_t) is a protein associated with these receptors in taste sensory cells, which are responsible for bitter reception [30]. The expression of mRNA encoding the alpha subunit of this protein, *Gnat3*, was detected in GG neurons isolated by laser microdissection, as well as in taste cells [20]. The immunoreactivity to anti-GNAT3 and anti-TAS2R143 was colocalized in the same cells. At the same time, reverse transcription PCR with primers to phospholipase β2 (*Plcb2*) and melastin channel M5 (*Trpm5*), the GNAT3 targets, did not detect the amplification product. Functionally, the effect of the proposed ligands of these receptors on GG neurons leads to an increase in the concentration of cytosolic calcium. Similar results were obtained in experiments with heterologous expression of TAS2R143. Taken together, this indicates a mechanism of transduction in GG neurons that is different from taste receptor cells.

The Components of Signal Transduction of V2r83-Expressing Neurons

The largest cell population in the GG at all stages of ontogenesis is represented by neurons that express V2r83. In the vomeronasal organ, signal transduction is carried out via $G_{i/o}$, whose main target is phospholipase Cβ [31]. The secondary mediators formed in this process open inositol triphosphate-sensitive calcium channels of the endoplasmic reticulum and melastin channels, primarily TRPM2.

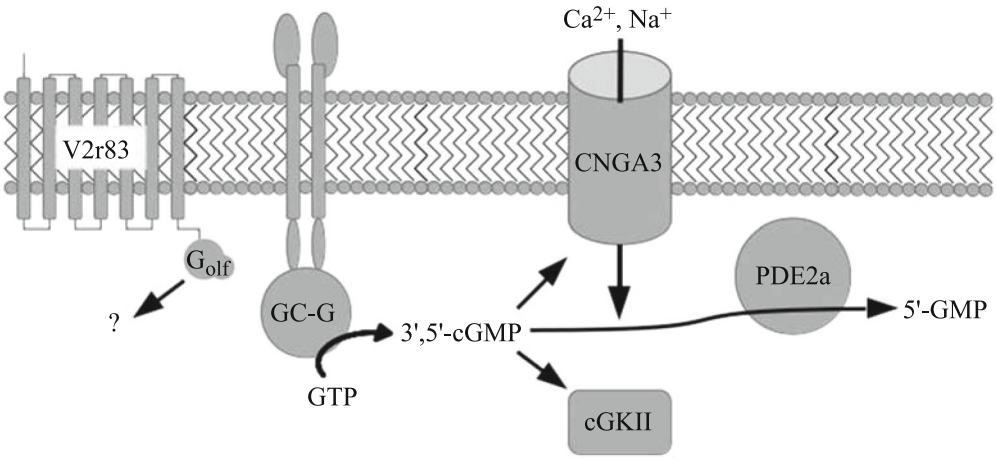

Fig. 2. The mechanism of GC-G transduction in a subpopulation of V2r83-positive neurons includes cyclonucleotide-dependent channels and cGMP-dependent protein kinase II; PDE2a is a key enzyme of cGMP degradation.

However, despite the fact that V2r83-positive GG neurons express the initial components of the signaling pathway inherent in vomeronasal cells ($G_{i/o}$), melastin channels in GG were not detected. The mechanism of transduction in GG cells expressing V2r83 probably involves the guanylate cyclase signaling system and not the phosphoinositide one, since the GG-specific receptor guanylate cyclase G (GC-G) was detected in these neurons [29]; in addition, such components of the guanylate cyclase cascade as phosphodiesterase 2a (PDE2a) [32], cGMP-dependent protein kinase II (GMKII), as well as typical GG cyclonucleotide-dependent channels containing the CNGA3 subunit that are sensitive to cGMP, were identified in this fraction of cells of newborn mice and adult animals [28].

MULTIMODALITY OF RECEPTION IN THE GG

The chemoreceptor function of the GG was detected for the first time by the authors of [3] when an unidentified mixture of substances adsorbed from the atmosphere during the killing of mice in a CO_2 chamber was used as an odor stimulus.

Analysis of the activation of "necklace-like" glomeruli in the GG in response to chemostimulation revealed their reaction to 2,5-dimethylpyrazine and 2-heptanone [33]. Based on this observation, the authors of [34] studied the reaction of GG neurons to a series of substances that are structurally similar to 2,5-dimethylpyrazine. They were able to find only one ligand, 2,3-dimethylpyrazine, among the entire list of odorants, whose interaction was confirmed by electrophysiological methods [35].

The cells that reacted to the drug belonged to the v2r83-positive subpopulation. The V2R cells are the second major class of sensory cells in the vomeronasal organ. They contain several families of peptide and protein pheromones that are important for chemical communication and the regulation of social behavior. Potential ligands for V2Rs include three families of polypeptides: major urinary proteins (MUPs), major histocompatability complex (MHC) peptides, and exocrine gland-secreting peptide (ESP). The vomeronasal sensory cells expressing V2R exhibit combinatorial co-expression of various V2Rs, meaning that these cells appear to constitute an exception to the "one cell—one receptor" rule for chemosensory cells [36].

CNGA3 and GC-G knock-out mice, that is, mice with no functional signaling system of guanylate cyclase G, did not respond to 2,3-dimethylpyrazine by depolarization of neurons; this indicated that this substance involved this signaling system in the transduction mechanism (Fig. 2). However, cells sensitive to 2,3-dimethylpyrazine were detected only at the early stages of the postnatal period, when 2,3-dimethylpyrazine is likely to perform an important role for the survival of young animals.

This is shown by the data obtained in [37], in which the search for ligands based on pyridine and pyrazine-containing motifs was carried out. The results led to a conclusion about the structural homology of GG receptor ligands with substances secreted by predators in their urine. Behavioral experiments showed that these identified ligands induced an avoidance response accompanied by an increase in blood pressure and were a stressor for adult mice.

As well, 2-sec-butyl-4,5-dihydrothiazole was identified as a ligand that acts on the GG. Like other ligands, it initiated an avoidance response in mice and increased the level of cytosolic calcium in the GG cells [37]. Both behavioral responses and receptor potential formation in response to stimulation were absent in GC-G knock-out mice, which also indicates the role of cGMP of the intracellular signaling system in the

mechanism of sec-butyl-4,5-dihydrothiazole transduction. This idea was convincingly proved by the authors of [38], who, using heterologous expression, confirmed for the first time that 2-sec-butyl-4,5-dihydrothiazole bound to the extracellular domain of GC-G, stimulating the catalytic activity of the enzyme, and obtained a value of K_D = 78.3 nM.

As can be seen from the above, the GG reaches its peak of development at the early stages of ontogenesis. This feature stimulated the search for a possible role of this sensory organ in the interactions between a mother and child.

In fact, their separation led to the activation of neurons, which was manifested in an increase in the expression of c-Fos, a proto-oncogene, which was previously used to monitor the activation of neurons in the main olfactory epithelium by odorants [43]. This phenomenon was unusual in that the unilateral occlusion of the nasal passage did not cause the disappearance of the reaction, which was observed only in V2r83-positive cells. It was suggested that chemoreception was not involved in this phenomenon [40]; as an explanation, the hypothesis of thermal sensitivity of these neurons was proposed and further confirmed [11, 40–42].

The heat-sensitive receptors in the peripheral nervous system of mammals belong to the TRP family. Among them, TRPM8 and TRPA1 play the main role in the reaction to a decrease in temperature. The authors of [42] did not receive a significant increase in the concentration of calcium in the cells in response to the action of their agonists menthol, icilin and allylisothiocyanate, which might indicate the absence of TRPM8 and TRPA1 in the GG. This assumption was confirmed by the absence of *Trpm8* expression in ganglion cells [32], as well as by the fact that weakening of thermal sensitivity in GG neurons was not detected in the *Trpa1* knock-out mice.

The fact that cGMP is the main intracellular mediator in these neurons has led to a discussion about the similarity of the GG with the thermoreceptor and chemoreceptor apparatus of the nematode *Caenorhabditis elegans*. In addition to the similarity in adequate stimuli and homology of transduction mechanisms, these neurons showed similarity in the sequences of genes that encode the components of the cGMP-dependent pathway: GC-G has a 29% identity and 65% similarity with DAF-11; CNGA3 and TAX-4 have 44% and 91%; PDE2A and pde-2 have 38% and 58%; and cGKII and egl-4 have 47% and 96%, respectively [43]. This similarity between mammalian GG neurons and nematode AWA neurons indicates the conservation of the molecular mechanisms of chemoreception and thermoreception preserved in the evolution.

In fact, thermotaxis in *C. elegans* occurs mainly due to the functioning of the DAF-11receptor guanylate cyclase, which is located in the membrane of the flagella of AWA neurons. The signal stage is represented by TAX-4, pde-2 and egl-4. The reaction of V2r83-positive GG neurons to a decrease in temperature occurs via a similar signal transduction mechanism. Studies on GG neurons have shown that L-cis-dylthiazem, an antagonist of CNG channels, completely blocked the response to cooling, while 8-bromine cGMP mimics the effect of temperature [42]. CNGA3 in the flagellar membrane is assumed to be the target of the secondary mediator [44]. This was indicated by the data obtained on CNGA3 knock-out mice. Their GG neurons responded to temperature changes by increasing the concentration of calcium in the cytosol; at the same time, heat-sensitive cells responded to an increase in the intracellular concentration of cGMP when they were administered with 3-isobutyl-1-methylxanthine (a nonselective phosphodiesterase inhibitor) and were not sensitive to the adenylate cyclase III activator forskolin [42]. Thus, guanylate cyclase GC-G participates in the mechanism of thermotransduction as a temperature sensor, its activation increases the intracellular concentration of cGMP, which opens cyclonucleotide-dependent channels, generating a receptor potential in flagella. Bumbalo et al. [11] obtained similar data by measuring the activation of glomeruli in response to temperature exposure of GG by the level of c-Fos expression: they found that the sensitivity to cooling decreased in the CNGA3 knock-out mice; similar results were obtained using the same technique on GG preparations [45].

Later, an action potential is generated in the axons of these neurons, which propagates to the glomeruli. Electrophysiological methods revealed the spontaneous generation of the action potentials, which is characteristic of GG neurons; this allowed the entire population to be divided into three groups: (1) a group generating repeated single potentials, (2) a group with phase activity, and (3) a group with sporadic activity [46]. It is possible that this activity is caused by the functioning of CNG channels in the membrane of the flagella of GG cells in the absence of an external stimulus, as occurs in the olfactory flagella of sensory neurons of various types of animals [47]. The action potential in response to a decrease in temperature arises due to the total incoming sodium current in these cells, consists of two fractions, one of which is relatively resistant to the action of tetrodotoxin.

The receptors found in the GG, their signaling cascades and adequate stimuli are summarized in the table. Thus, the guanylate cyclase G receptor is a key enzyme in chemoreception and thermoreception in most neurons of the Grueneberg ganglion. When activated by a temperature shift in the range from 11.9 to 21.9°C or binding to a ligand, GC-G catalyzes the formation of cGMP, a secondary intermediate that opens A4 cyclonucleotide-dependent channels. The gustducin-coupled subtype II taste receptors are another receptor subsystem in the GG. The signaling cascade that is activated in response to ligand binding remains

Table 1. The identified receptors of the GG neurons, as well as the their adequate stimuli and mechanisms of transduction

Receptors	Adequate stimulus	The mechanism of transduction
V2r83	?	?
GC-G	1. Low temperature in the range from 11.9 to 21.9°C 2. A number of natural kairomones of predators and their synthetic analogues	GC-G–cGMP–CNGA3
TAS2R115, TAS2R131 and TAS2R143	A number of substances previously identified as bitters and similar to metabolites in the urine of predators*	GPCR–Gt–?**
OR256-17	A wide range of odorants, including trace amines*	GPCR –G_{olf}–adenylate cyclase III–CNG**
TAARs	Trace amines *	?

* Ligands, interaction with which was shown in other parts of the olfactory system and/or in systems of heterologous expression; ** the proposed mechanism based on morphological data.

unknown. Together, these two systems provide detection of life-threatening stimuli. In the early postnatal period, the thermoreceptor function of the GG dominates, providing regulation of interactions with the mother. In adult animals, this organ functions primarily as a chemoreceptor, providing, on the one hand, the perception of substances emitted by other animals during danger, and on the other hand, perception of the kairomones of predators.

The role of transient expression of OR256-17 in the GG at the embryonic stage of development remains unclear. OR256-17-positive cells in the main olfactory epithelium exhibit an extremely wide sensitivity profile, including trace amines [48].

As well, the functions and mechanisms of transduction for V2r83 and TAAR, other GG receptors, are currently unknown. Previously, they were identified in other parts of the peripheral part of the olfactory sensory system; however, based on the sum of the presented data, the associated signaling pathways are different from those typical for the vomeronasal organ and the main olfactory epithelium, respectively.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

COMPLIANCE WITH ETHICAL STANDARDS

This paper does not describe studies using humans and animals as objects.

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