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Odor and nutrition

Part 1: Fundamentals of smelling

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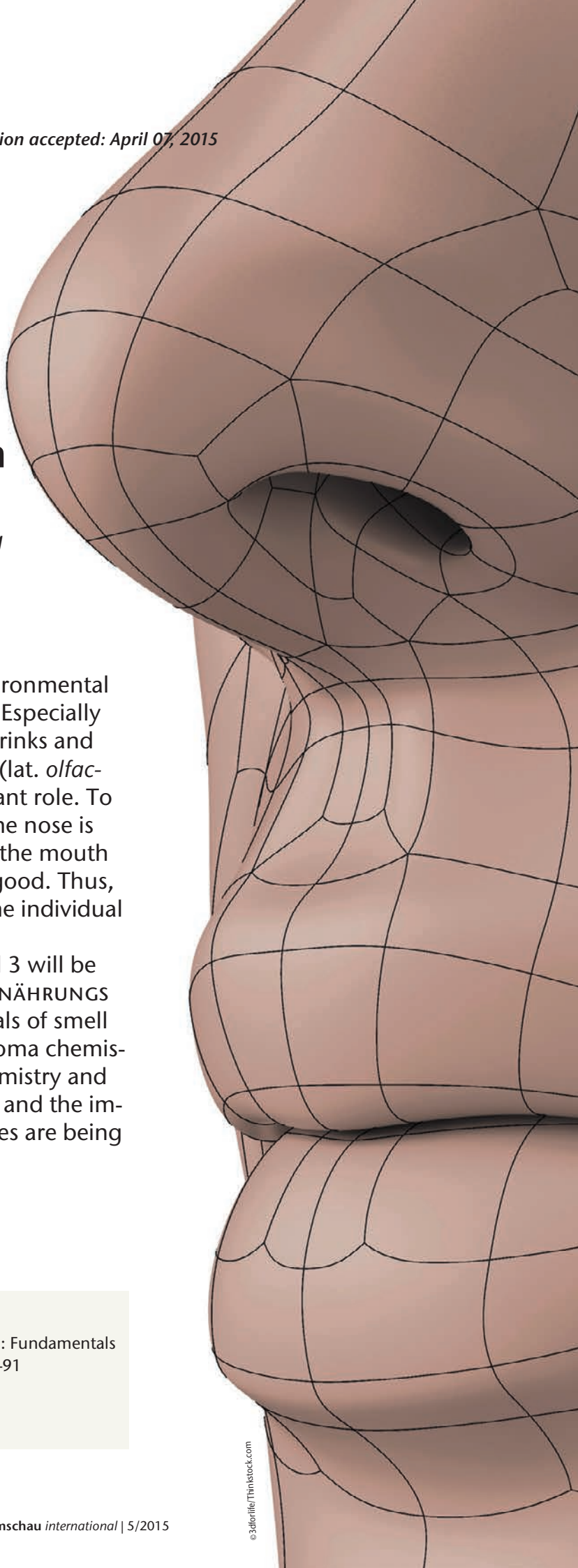

A major part of our everyday environmental perception is mediated via smell. Especially for the evaluation of foodstuffs, drinks and tobacco the olfactory perception (lat. *olfactere* = to smell) plays a predominant role. To meet with this special function, the nose is anatomically located right above the mouth and thus inspects any incoming good. Thus, the sense of smell also controls the individual food preferences.
In a three-part article (parts 2 and 3 will be published in later issues of the Ernährungs Umschau), firstly the fundamentals of smell are discussed in the context of aroma chemistry, before the interactions of chemistry and biology for food sensory sciences and the impacts on personal food preferences are being targeted.

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Distinction of the senses in sensory perception

The term „taste" often is representatively used for any kind of chemical sensory perception. Especially when dealing with food, where essentially all sensory systems act concertedly, a differentiation between the individual senses is difficult. Besides taste itself [1, 2] which is limited to the perception of sweet, sour, salty, bitter, and umami, further impressions add to the total perception of taste. Sensory percept such as burning, hot, astringent, tingling, or cooling is mediated by the trigeminal system (*Nervus trigeminus*). The most sensorial versatility, however, is mediated by the sense of smell. This sense detects volatile[1] organic compounds (VOC), with highly sensitive receptor molecules and allows the perception of characteristic food odors. Also compounds that are not volatile under standard conditions may be subject to the sense of smell, when transmitted to the nose as aerosols or as part of steams for example.

The sense of smell is basically limited to the recognition of VOC, but is a major contributor to the sensory perception required to selecting and evaluating food.

Functions – more than just smelling

Besides its obvious functions, the sense of smell mediates – more or less unconscious – major decisions and has an important influence on our emotional state. Infants for example find and recognize their mother's breast securely using their sense of smell [3, 4], moreover it can be expected that the function of the famous cosy towel is also subject to their olfactory characteristics and thus provide the children with a feeling of security. Of course the sense of smell contributes to the choice of mating partners. This list can easily be extended: We use the sense of smell to gather additional information for navigation; we enjoy the smell of freshly ground coffee and know the smell of geosmin after a mild summer rain.

The important role odorants play in all situations of daily life has generated a market for natural and also synthetic odorants and thus reaches a worldwide annual turnover of about 18 billion € for 2014. Accordingly, used-car-dealers perfume their cars with the typical fingerprints of new cars; and in a drug store there is virtually no product whose aroma profile was not specifically adjusted to the desires of the customer.

In foodstuffs, more than 10,000 VOC can be detected with the potential to be odorants. But only some of them actually contribute to the aroma of food or the fingerprint of specific foods. We are far away from a full understanding of the complex performance of the sense of smell and the relevance of individual odorants and their contribution to the multitude of food aromas.

The anatomy of smell

Finally, one of the major functions of the sense of smell is the selection and evaluation of our daily diet and to prevent us from taking in of rotten food. For this reason, the nose is located directly above the mouth and thus, any food has to undergo an olfactory inspection. The olfactory epithelium is located in the upper rear part of the nasal cavity with a surface area of about 2 x 5 cm and is covered with a thin layer of mucus. This tissue is composed of supporting cells, basal cells, microvilli cells (brush cells), Bowman's

[1] Volatile organic compounds (VOCs) are chemical substances with a vapour pressure sufficient to be gaseous (at least partially) at ambient or physiological conditions.

[2] The bicyclic alcohol ($C_{12}H_{22}O$) geosmin is produced e.g. from soil microorganisms. The human nose can detect concentrations as low as 0.1 ppb (parts per billion)!

Summary

A major part of our everyday environmental perception is mediated via smell. Especially for the evaluation of foodstuffs, drinks and tobacco the olfactory perception (lat. *olfactere* = to smell) plays a predominant role. To meet with this special function, the nose is anatomically located right above the mouth and thus inspects any incoming good. Hence, the sense of smell also controls the individual food preferences.

With more than 400 olfactory receptors being subject to high genetic dynamics, it is expected that no two persons exist with the identical olfactory perception. This complexity is yet being increased by the number of potential odorants and moreover, their occurrence in mixtures such as food. To understand the impact of single food odorants, a deep understanding of the molecular fundamentals of smell, the interaction of odorants with olfactory receptors, the respective physiology and molecular biology of olfaction is required.

Keywords: sense of smell, olfactory receptor, GPCR, signal transduction, food preferences, sensory sciences

Glossary:

action potential	nervous impulse, sharp change of membrane potential (resting potential) with constant intensity. The stimulus intensity is coded by the frequency of periodic action potentials.
allosteric effect	interaction of OR with molecules (e.g. other proteins or small molecules such as odorants) modifying the pharmacology of the odorant-OR-pair
axon	extension of neurons, which disposes electric impulses away from the cell body
cAMP	circular adenosine mono phosphate, intracellular chemical messenger (second messenger) which is formed from ATP after activation of an adenylyl cyclase enzyme
CNG-channel	cyclic nucleotide gated channel, a class of ion channels, that, upon activation, e.g. due cAMP, change their conductivity and contribute to the depolarization of a cell
ektopic expression	expression of a gene in tissues other than the one it is typically expressed in
endocytosis	internalization of membrane components (e.g. receptors) by means of invagination of specific membrane areas
GPCR, G-protein coupling receptor	biologic receptors (proteins) that are activated by external stimuli and transmit their signal through biological membranes to G-proteins
intrinsic activity	a specific activity of a molecule which is viable without influence of external factors
intron	non coding DNA segments inside genes which are being spliced out during maturation of RNA
inverse agonism	capability of a ligand to elicit an inverse reaction of a receptive unit, e.g. to decrease the intracellular cAMP concentration after OR stimulation
mitral cell	primary networking neuron of the olfactory bulb which processes the signals of the incoming axons and forwards them to higher brain areas
monoallelic expression	expression of only one of the gene copies of a cell in di- or more ploidic organisms
multigene family	group of similar genes with an expectably common origin, which gene products fulfil the same or similar functions
second messenger	lower molecular chemical substances which are formed or relieved as part of the activation of specific signaling cascades and elicit subsequent reactions
Soma	part of a cell in the area of the nucleus, without any cellular extensions
vomeronasal organ/Jacobson organ (VNO)	an anatomic chemosensory organ of many vertebrates in which vomeronasal type receptors (VNR) are being expressed. The VNO is relevant for the perception of social cues, such as pheromones. In humans, however, there is no functional VNO.

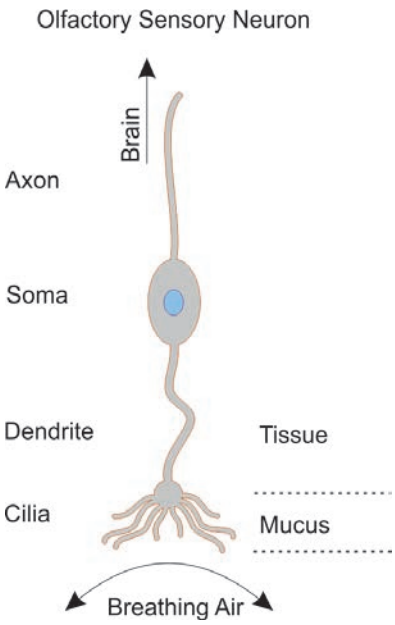

Figure 1: **Anatomy of an olfactory sensory neuron (OSN).** The cilia reach into the olfactory mucus and expose the odorant receptors (OR) towards breathing air. At the opposite side of the soma at the axon hillock, a depolarization is encoded into action potentials which are transferred via the axon through the ethmoid bone into OR-specific glomeruli in the olfactory cortex of the brain.

glands which secrete the mucus, and the definitive smelling cells, the olfactory sensory neurons (OSN). On average, humans possess of 10 to 30 million OSN which are replaced by means of several weeks from basal cells.

The dendritic extensions of the bipolar neurons reach, in form of cilia, into the mucus of the olfactory epithelium and reflect the interface between the organism and the surrounding of humans (◆ Figure 1). The unequivocal players of the vertebrate's sense of smell are located just on the dendritic surface inside the mucus: the odorant receptor molecules (OR). They are G-protein coupling receptors and directly interact with the odorant molecules; this interaction is the sole stimulus. This stimulus is then forwarded as action potentials along the axon through the ethmoid bone into the olfactory cortex, where all axons target into specific glomeruli (mitral cells) of the olfactory bulb (*Bulbus olfactorius*). From here all information is pre-processed and redirected into higher brain areas. In the medical nomenclature, the olfactory nerve (*Nervus olfactorius*) is considered the first brain nerve. From the anatomic view, however, the olfactory nerves are no real brain nerves, since the OSN are part of the olfactory epithelium and only project their axons into the olfactory cortex.

The physiology of smell

Although all anatomic and most of the molecular components of smell have been long known, the OR itself and the organization of the sense of smell have first been described by Buck and Axel in 1991 [5]. They received the Nobel Prize for Physiology or Medicine for their work in the year of 2004. The latest publications count a total of 413 human OR-genes, encoding for functional OR [6]. They belong to the largest multi gene families of the human genome.

OR-proteins are composed of about 320 amino acids on average and belong to the group of A-type or rhodopsin-like GPCR; they are outlined by an extracellular N-terminus, seven transmembrane spanning

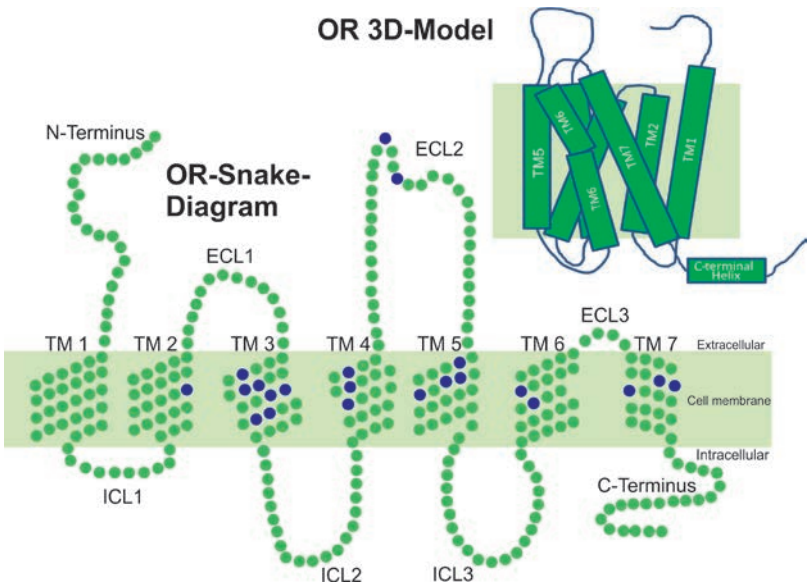

Figure 2: **Schematic display of an odorant receptor (OR) as snake diagram** Single points reflect individual amino acids. The 22 amino acids proposed by Man et al. are colored in blue. An approximated 3-dimensional model of the helix configuration is given in the upper right hand side corner. The model was generated by comparing the sequence of OR with the human rhodopsin protein whose structure is solved. The correctness of the displayed model is limited to the orientation of the trans-membrane helices and is not valid for the intracellular or extracellular loops.
OR = Odorant Receptor

helices (TM1–7) and an intracellular C-terminus (◆ Figure 2). This topography results in three intracellular (ICL1–3) and three extracellular loops (ECL1–3) of which in particular the intracellular ones mediate important functions, e.g. serving as an interaction handle for intracellular effectors such as the G-protein. It is commonly believed that the transmembrane domains form a hydrophobic intramembrane pore in which the specific interaction with the odorant is arranged. As of this interaction, the 3-dimensional arrangement of the receptor conformation is altered and the stimulus is transmitted to the intracellular side of the membrane.

It has been known for long, that one odorant can activate several OR and that, in turn, one OR can be activated with several odorants [7]. This allows an early combinatorial coding which is referred to as the "olfactory receptor code"; this is the molecular prerequisite for the sense of smell's capability to distinguish the innumerable amount of odors, way more than the plain number of individual odorants or OR.

Along with these results it was observed that any OSN only expresses one OR type in a mono allelic manner which is today known as the "one gene – one neuron rule". This rule fits the observation that, as described above, all neurons expressing the same receptor type converge into the same mitral cell. For this impressive performance of OSN we yet lack explanation. However, it is known that cAMP generated by OR activity is significantly involved in the targeting of OSN axons (◆ Box) [8, 9]. This direct wiring secures a 1:1 superimposition of the sensory profile of a given food in the brain.

The initial combinatorial code of the sense of smell which allows us to distinguish thousands of stimuli is generated just on the level of OR in the olfactory epithelium.

First part of the stimulus triggered signaling cascade (◆ Figure 3) is the dissociation of the intracellular heterotrimeric G-protein, of which only the α-subunit remains at the OR. This G-protein consists of an α-subunit and unitedly operating β/γ-subunits, which are all fixed in the plasma membrane by acylation or isoprenylation. In OSN, the G-protein consists most likely of the olfactory α_{Olf}-subunit and the β_1- and γ_{13}- subunits. Both units may have different effectors and thus mediate different physiological responses. In the canonical olfactory signaling cascade, however, the adenylyl cyclase type three (AC3) is activated by the α_{Olf}-subunit, which in turn hydrolyses ATP to the first second messenger cAMP and pyrophosphate. The formed cAMP subsequently activates a cyclic nucleotide activated ion channel (CNG channel) which mediates the depolarization of the cell, because after opening of a trans-membrane pore, cations are allowed to enter the cell. This CNG channel is a hetero-tetramer consisting of four closely related subunits with six transmembrane spanning helices each. The molecular stoichiometry of the olfactory CNG channel is 2x CNGA2, 1x CNGA4 and 1x CNGB1b. Following the CNG channel mediated cation influx of the second second messenger calcium, chloride channels open up additionally which also contribute to the depolarization of the OSN. However, the importance of the chloride-ion efflux for olfaction is being controversially discussed. Once the cell depolarizes to a certain threshold, the axon hillock sends frequency coded action potentials along the axon through the ethmoid bone into the respective glomerulus (mitral cell) in the olfactory cortex of the brain.

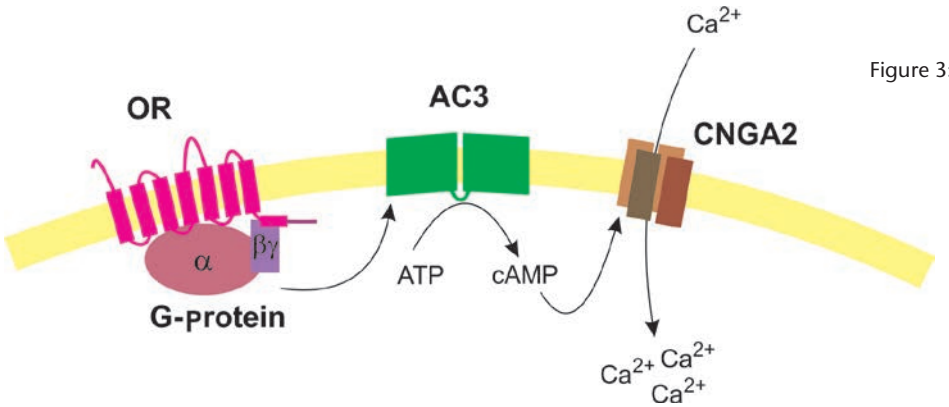

Figure 3: **The canonical signaling cascade mediating smell,** including the odorant receptor (OR), G-protein, adenylyl cyclase type 3 (AC3), and the cyclic nucleotide gated ion channel hetero-tetramer (CNGA2)

Box 1: **Signaling cascade in olfactory sensory neurons (OSN)**

The olfactory signaling cascade employs linear signal propagation; the signal finally reaching the brain is thus proportional to the primal stimulus intensity. The stimulus intensity on the other hand is correlated to the concentration of the stimulus eliciting odorant and its physical chemical characteristics, which together determine the specific potency and efficacy (compare ◆ Figure 4). This is also secured by maintaining short dwell-times of the odorant-OR interaction and secures a real-time reproduction of our olfactory environment. Despite the short dwell times, the sense of smell is very sensitive: less than 20 of such short interactions are sufficient to pass the threshold that triggers an action potential [10]. The intensity of the olfactory perception is encoded by the frequency of the resulting action potentials.

To realize such fast reactions and concentration changes, the spatial action radii of all involved proteins (and subunits), second messengers, and ions need to be maintained at diminutive size. To achieve the aforementioned, the existence of so called signalosomes is expected. Signalosomes are spatial concentrations of all molecules involved in signal processing and propagation just underneath the cellular membrane.

Pharmacology of OR

Pharmacologically one can describe the interaction of odorants and OR with the two parameters **potency** and **efficacy**.

The curves in ◆ Figure 4B show a shift of potency. Potency is a measure of the concentration that is required to elicit the full response of an odorant-OR pair. The potency is usually expressed as the concentration of an odorant needed to elicit 50 % (EC_{50}) of the full activation.

The efficacy of an odorant describes its intrinsic activity, which indicates to which extent an odorant is capable to activate a receptor at ligand saturation. The efficacy as explained in the curves in ◆ Figure 4A is independent from the odorant concentration. An odorant may have a low EC_{50} but only activates the OSN at a high concentration moderately and vice versa. The pharmacological effects resulting from this even add to the sole combinatorial code of receptor and odorant, which yet increases the versatility of olfaction.

Adaptation, olfactory inhibition and habituation

An enduring activation of the OSN is hampered by mechanisms that terminate any physiological response after a short time. This is mainly facilitated by the intrinsic GTPase activity of the G-protein α_{Olf}-subunits that hydrolyze the bound GTP to the inactive GDP. Without this GTPase activity, any olfactory impression would consist over minutes once perceived, even after vanish of the initial stimulus. Further, ATP-dependent ion pumps are restoring the polarization of the cells and render the neuron susceptible for new stimuli. In order to keep the sense of smell functional even in the presence of odorants, there are diverse mechanisms of adaptation, acting on different timescales and thus allow the perception of changes in the surrounding odorant composition. At a first instance in the sub second level, the increase of intracellular calcium activates calmodulin, which reduces the CNG channel permeability by binding to the CNGB1b unit to terminate the cation influx. Thereafter kinases, activated from metabolites of the signaling cascade, phosphorylate players of this cascade and, on a scale of seconds, inhibit the response prolongation. This affects the OR itself which may be deactivated when their ligand is present permanently, but also the ACIII may be switched off, and phosphodiesterases may be activated to decompose cAMP. At even longer activation of the neurons, OR can be internalized by means of clathrin-mediated endocytosis. Finally, the OR expression can be affected directly in the nucleus by the activation of phosphorylation cascades.

Especially the fast adaptation mechanisms may hamper food sensory approaches in practice. Therfore, breaks or "olfactory alternation" are required during sensory sessions.

Habituation on the other hand is a sole central nervous process which allows the brain to ignore permanently returning stimuli. An advantage of habituation, compared to molecular processes, is the flexibility to retain responsivity to changes in the surrounding stimuli composition. Thus, habituation allows us to not permanently perceive our own body smell or perfume.

Interactions/pharmacology

Beneath receptor activation, odorants may have influence on the physiology of the signaling cascade. It was shown that very lipophilic odorants may block CNG-channels and reduce the effectivity of smell in an unspecific manner [11]. The broad range of receptor specificity and the often similar structures of odorants occurring in food result in additional possibilities for pharmacological effects. One example is antagonism, since partial agonists compete in the receptor agonist equilibrium with full agonists for binding capacities. It must be expected that potentiation, inverse agonism, and other pharmaco-dynamic modulations, including allosteric effects described for classical (non-olfactory) GPCR, also apply for OR. This implies that also volatile compounds without any intrinsic aroma may be a factor in the perception of odorant mixtures and thus indirectly contribute to the aroma of food.

Genetics of odorant receptors

The human genome harbors about 851 intron free loci for OR, spread across all chromosomes except chromosome Y and chromosome 20. By comparing the nucleotide sequence of all OR-genes, they can be separated into the smaller class-I- and the larger class-II-OR. Class-I-OR are also referred to as fish-like OR because vertebrates share this phylogenetically elder OR group with fish. Interestingly, there exist some hints that these OR may have conserved their function over the times and, compared with class-II-OR, rather prefer water soluble odorants as ligands, such as short chain organic acids and esters [12].

All class-I-OR are located on chromosome 11, from where they spread over the entire genome by gene duplication events and formed the class-II-OR. The duplication of one gene opened the possibility for a mutation of the duplicate gene in the early evolution of vertebrates, which in turn increased the olfactory diversity and implied an evolutionary advance for the carrier of the mutation. This favored the generation and expansion of class-II-OR and may still be proceeding. Along with these processes, mutations may also have occurred that are rather detrimental to the function of the transcription produced, e.g. when important positions were mutated, or stop-codons were introduced.

Due to a lack of evolutionary pressure on many of these newly generated genes (when they meant no advantage, but particularly no disadvantage to the carrier) the dysfunctional alleles were not or only partially purified from the genome. This lead to the fact that every species has at least a certain fraction of so called OR pseudogenes in their genome. In OR and other multigene families these processes are called birth-and-death-evolution[3]. Especially in primate genomes including human genomes, a high fraction of pseudogenes can be found. This observation led to the Vision-Priority-Hypothesis, according to which the development of the trichromatic vision in primates replaced major functions of smell (finding of food and detection of danger) and so the importance of smell for survival of primates attenuated accordingly [13]. The latest data based on the 1000 Genomes Project count 413 functional OR genes in the human genome [6].

Up until today, the olfactory genome remains highly dynamic: On average, for each of the 413 functional OR about eight non-synonymous single nucleotide polymorphisms (ns-SNPs) have been described, those SNP, that lead to an altered primary structure of the corresponding OR. For comparison: In non-olfactory GPCR this number is about 3.5. ns-SNPs may lead to pseudogenes, isofunctional OR or expression products with modified functionality.

Due to the high genetic variability of odorant receptors, there are probably no two individuals in the world, having exactly the same perception of smell. In the course of evolution, this high dynamic has likely helped to quickly adopt to new habitats with novel food sources.

From the mono allelic manner of OR expression and the possibly different phenotypes of individual alleles results an increase of the total number of different OR in an individual, so that the number of different OR can actually be much higher than 413. In humans, the distribution of functional OR is not homogeneous along ethnic groups. Whereas Asians on average harbor about 500 different functional alleles for OR, Caucasians have around 530 and Africans even more than 550 different functional OR alleles. The number of different alleles for individuals ranges from 350 to 650 [6]. In another study, using probes for 356 OR loci in the olfactory epithelium of 26 test persons, the expression of 273 genes was shown of which 90 have been expressed in all 26 epithelia [14].

Evolutionarily it must be expected that any extra information an individual can perceive with his OR repertoire can also mean an advance. It is thus no surprise that the OR-repertoire seems to be programmed to cover a greatest possible versatility of odorants; this may partially explain the high dynamics and the high SNP-rate of the olfactory genome.

Some amino acid positions, however, serve for the fundamental functions of OR, e.g. the interaction with G-proteins, intracellular transport or the specific intracellular localization underneath the membrane. A mutation of one of these positions is likely detrimental for the functionality of the respective OR. High mutation rates can be expected mainly on those positions that allow a positive effect on the biological fitness of the carrier. These are mainly those positions that contribute to an enlargement of the ligand spectra of OR, i.e. those amino acid positions that constitute their ligand binding pocket. With similar considerations and by comparing the sequences of hundreds of murine and human OR, Man et al. predicted 22 amino acid positions which likely contribute in the coordination of odorants inside

[3] Geneticists differentiate three types of gene family development: divergent (all genetic offspring develops independent), concerted (parallel developments of offspring in groups of genes in phylogenetic branches), and birth-and-death-evolution (in offspring, individual copies of genetic families can be lost). A short introduction into this topic is given here: http://sandwalk.blogspot.de/2007/01/evolution-of-gene-families.html

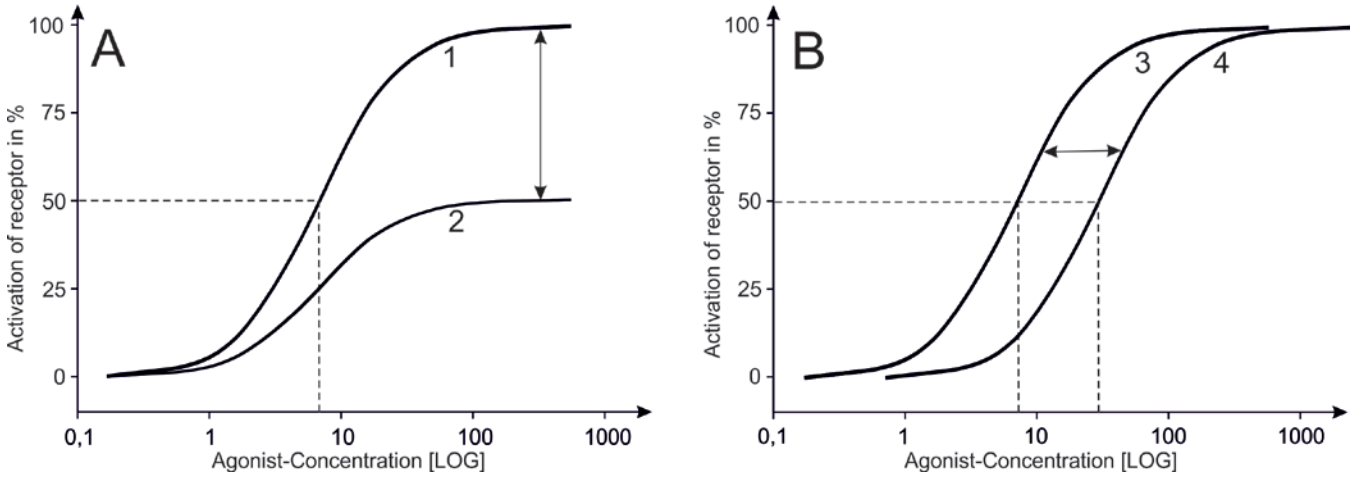

Figure 4: **Typical concentration-response relations of G-protein coupling receptors, such as olfactory receptors (OR)**
A: Shift of the potency of an OR-odorant pair.
B: Shift of the efficacy of an OR-odorant pair.
The spotted lines indicate the level of the odorant concentration at 50 % of the maximum response (EC_{50}).
The EC_{50} does not change in A, but is affected in B. The EC_{50} is a characteristic measure for each odorant.
It is influenced by pharmacologic effects which can be expected in odorant mixtures, such as the aroma of food.

the binding pocket [15]. Only two of those positions are located outside the transmembrane helices in ECL2 (compare ◆ Figure 2). Since this loop is extraordinarily long, it is expected that it may also stretch into the membrane area. Moreover it is commonly believed that a disulphide bridge between two cysteine residues in ECL2 and TM3 stabilizes this architecture. Indeed, some of the predicted positions could experimentally be validated in functional studies to be important for the ligand specificity of respective OR.

Olfactory dysfunctions: anosmia, hyposmia, and hyperosmia

In some conditions it may come to a total or partial deficiency or absence of smell. This condition is called **anosmia** and may have diverse physiological, anatomical and genetic reasons. Different pathologic conditions, such as virus infections and blunt traumata of body regions involved in smell may cause total anosmia. The complete loss of olfaction means a harsh psychological and social impact for the concerned persons: flavor can only be perceived via the five basic tastes and patients are always unaware of their own body odors.

Much more often occurs specific anosmia, triggered by SNPs [6, 16]. Basis for this is the already mentioned highly dynamic character of the olfactory genome. Single genes may be rendered dysfunctional pseudogenes by means of SNPs and thus fail as chemo sensor for their particular ligand. Even if there may exist several OR for the same odorant, the fail of one of the odorant specific OR will cause changes in the respective olfactory code. However, if very specialized OR are affected with a sharp ligand profile, this means a complete loss of the odorant induced aroma quality.

Beneath the losses of olfactory quality perception, also the quantity of perception may be altered, which is referred to as **hyposmia** in the case of attenuated sensitivity and **hyperosmia** in the case of elevated sensitivity towards specific odors. Also these phenomena can be caused by SNPs, albeit due to the individualized perception it is critical to consider anything a normal condition, thus hyposmia and hyperosmia can rather be used in a relative manner. The majority of minor deviations and differences in olfaction are not noticed and remain unknown. Next to genetic reasons there is a set of temporary causes for olfactory aberrations, such as changes in physiological state or temporal pathologic conditions.

Hyposmia plays a particular role in the catering of elderly people, because the sensitivity of smell decreases with increasing age. This raises special challenges for the communal feeding of elderly people in order to serve tasty food and to retain a pleasure for eating. As outlined in Ernährungs Umschau 1/2015 in a detailed review article by Chmelar et al., in oncology olfactory aberrances often occur which

are side effects of aggressive cancer therapies [17].

Certainly, all olfactory dysfunctions and anosmia may cause fundamental changes regarding nutrition. This affects primarily the selection of food. It was reported that some patients suffering from total anosmia prefer food with increased levels of basic flavor carriers [18]. An important notion from this point of view is to actively compose the daily diet in a healthy manner, since the endogenous stimuli of food (i.e. aroma) does not serve enough appeal to select healthy food only for sensory reasons.

Further olfactory receptor groups

Next to odorant receptors which make up the essential part of what we consciously perceive as smell, there is a series of other receptor groups whose expression in the olfactory epithelium was shown and are thus considered olfactory receptors. On the one hand these are the so called trace amine associated receptors (TAAR), of which the human genome harbors six functional genes and three or two pseudogenes. These receptors can be activated by volatile amines, such as phenylethylamine as was described to be an agonist for TAAR1, and the fishy smelling trimethylamine for TAAR5 [19, 20]. Which function TAAR have as chemo sensors for olfaction, whether they simply increase the functional OR repertoire with some special ligand specificities, remains to be studied so far.

On the other hand, there are five human vomeronasal-type-1-receptors (VN1Rs) whose function in other species is associated with the detection of social cues, such as pheromones in the vomeronasal organ. However, in human this organ is degenerated and the issue of the existence of human pheromones is controversially discussed and not finally solved. At least the functional expression of these receptors (VN1R) in the olfactory epithelium of human could be shown and designated to linear aldehydes and alcohols as ligands [21, 22]. These may not be the major endogenous ligands, but issuing the described ligands and their location of expression, they may likely take up functions of regular olfactory perception in the olfactory epithelium. Next to the VN1Rs, another VNR-group exists in many vertebrates: the vomeronasal-type-2-receptors (VN2R), but in human there only exist pseudogenes.

Ectopic expression of olfactory receptors

The experimental findings of many working groups imply that the functions of odorant receptors (OR, TAAR, VN1R) go far beyond the perception of smell. Due to the wide chemical range, with which olfactory receptors can be activated, they serve as a valuable genetic source of the organism. Surprisingly, but finally it made sense: olfactory receptors are expressed in a variety of body tissues.

Olfactory receptors were found to be expressed in gut mucosa where they were correlated to contribute in controlling gut motility, renin secretion, and regulation of blood pressure [23, 24]. Moreover, they are described in the context of wound healing of skin irritations and injuries [25]. One popular example of ectopic OR expression has been sperm: here, OR1D2 was believed to mediate the sperm chemotaxis along a chemical (odorant) gradient towards the ovule [26]. In *in-vitro* experiments performed, bourgeonal, a synthetic lily of the valley like odorant, could be identified to specifically activate OR1D2, the endogenous ligand that mediated this chemosensory performance. However, the endogenous ligand for this phenomenon was not known until recently. In a more recent publication of Strunker et al. the responsibility of OR1D2 for this phenomenon could be disproved [27]. According to their data, the chemotaxis of sperm is indeed sensitive to bourgeonal, but is mediated via a newly identified metabotropic ion channel named Catsper which mediates the chemotaxis of sperm.

On sub-populations of granulocytes, T- and B-cells, the expression of TAAR1 and TAAR2 was described, and it could be shown that they contribute to the chemotaxis of blood cells [19]. In granulocytes, T- and B-cells, also the expression of mRNA of class-I-OR could be shown together with those of taste receptors, which is quite plausible for those OR with a preference towards rather hydrophilic odorants, in an aqueous environment such as the blood stream [28]. Class-II-OR could not be found to be expressed in the blood stream in their experiments. It was discussed that these chemosensory receptors also contribute to the control of chemotaxis in blood cells. Moreover, there are hints that the primarily involved signaling cascade of OR in blood cells tackles an alternative route via $G_{\alpha i}$ despite the usage of $G\alpha_{Olf}$ in OSN.

Until today, the expression of OR was shown for a wide variety of tissues including lung, heart, liver, and cancer cells without knowing any concrete functions nor endogenous ligands in most of the cases. Since all food constituents, after uptake from the gut, end up in the blood stream, olfactory receptors provide a potent physiological tool to monitor the current individual nutritive state. This awareness and the resulting hypotheses open a fully new field of research at the cutting edge between biomedicine, food chemistry, and nutrition.

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Conflict of Interest
The author declares no conflict of interest according to the guidelines of the International Committee of Medical Journal Editors.

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