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INVITED REVIEW

Use it or lose it: molecular evolution of sensory signaling in primates

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Abstract Sensory organs provide key and, in many cases, species-specific information that allows animals to effectively forage, find mates, and avoid hazards. The primary sensors for the vertebrate senses of vision, taste, and smell are G-protein-coupled receptors (GPCRs) expressed by sensory receptor cells that initiate intracellular signal transduction cascades in response to activation by appropriate stimuli. The identification of sensory GPCRs and their related downstream transduction components from a variety of species has provided an essential tool for understanding the molecular evolution of sensory systems. Expansion of the number of genes encoding sensory GPCRs has, in some cases, expanded the repertoire of signals that animals detect, allowing them to occupy new niches, while, in other cases, evolution has favored a reduction in the repertoire of receptors and their cognate signal transduction components when these signals no longer provide a selective advantage. This review will focus on recent studies that have identified molecular changes in vision, smell, taste, and pheromone detection during primate evolution.

Keywords Evolution · Molecular · Receptors · Sensory · Vomeronasal · Vision · Smell · Taste · Pseudogenes · Receptors · G-protein-coupled

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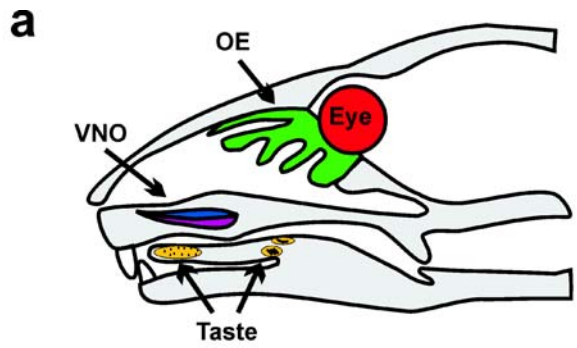
Introduction

Most sensory systems in animals have, at their core, a set a of signaling molecules that include sensory receptors that bind the ligand, downstream-signaling molecules that amplify the signal, and ion channels that convert this biochemical process to an electrical impulse sent to the brain. The receptors for vision, taste, smell, and pheromones all belong to the superfamily of G-protein-coupled receptors, with each receptor being specifically tuned to detect the appropriate sensory signal. In humans, there are four visual receptors, 28 taste receptors, and 388 odorant receptors (reviewed in [52]) (Fig. 1), which are expressed in the eye, tongue, and olfactory epithelium, respectively. Downstream-signaling molecules are structurally related to signaling molecules used throughout the body, such as G-protein, phospholipases, cyclases and second-messenger regulated ion channels, and, in many cases, the isoforms expressed in sensory cells are not found in other parts of the body, suggesting a specialized function in sensory signaling [3, 37, 38, 43, 44].

The evolutionary analysis of genes involved in sensory signaling has been an especially fruitful area of research for two reasons: (1) sensory receptors and transduction components are generally "non-essential," as seen by the viability of mice in which these genes are selectively deleted (e.g., [58, 70]), and (2) changes in these genes can allow animals to occupy new ecological niches. For example, the ion channel TRPV1 responds to capsaicin and to heat and protons, all of which cause a burning sensation [5]. The capsaicin in chilies serves as a deterrent for consumption of the plant by small rodents, which are poor dispersers of its seeds. Birds have evolved a variant of TRPV1, which retains sensitivity to heat and protons but is insensitive to capsaicin [25]. Presumably, this mutation



b

	Eye	OE	VNO		Taste	
					Bitter	Sweet Umami
	Opsin	OR	V1R	V2R	T2R	T1R
Mouse	3	1037 (354)	165 (165)	61 (148)	35 (6)	3
Human	4	388 (414)	4 (~200)	0	25 (11)	3

Fig. 1 Sensory receptor repertoire in mice and humans. **a** Schematic diagram showing the location of the eye and the major chemosensory organs in the mouse. **b** The number of functional receptors genes and pseudogenes (*in parentheses*) in mice and humans (based on data reviewed in [53])

arose because it allowed birds to occupy a new niche, to the advantage of the plants whose seeds the birds disperse [60]. The identification of nearly all major sensory receptors has allowed similar inferences to be made about the evolution of other sensory systems, as will be discussed below.

Genome mining and methods of molecular evolution

The sequencing of the human and other genomes has provided a wealth of information on the genetic basis of sensory capabilities of different animal species (e.g., [18, 69]). Odorant, taste, and pheromone receptors, which belong to large multigene families, have been identified in many species and species-specific expansions, and contractions of the repertoire of receptors have been identified (reviewed in [53]). Moreover, the remnants of once functional genes can be identified in the genome, providing a window on the evolutionary history of these genes and their associated functions [71]. These nonfunctional genes, called "pseudogenes," can be of two forms: (1) duplicated or (2) processed (also called retrotransposed). Processed pseudogenes are intronless and are the product of viral retrotransposition of mRNA into the genome. These genes may never have been functional. In contrast, non-processed pseudogenes are the result of a gene-duplication event followed by a relaxation of selective pressure on the gene that leads to disruption in the coding sequence; in some cases, duplicated genes were redundant and thus quickly eliminated from the genome, but in other cases they acquired a function only to become obsolete at a later time in evolution. By determining when these genes were "lost," we can learn about when in evolution the function they subserved no longer contributed to an animal's fitness.

Additional information about the functionality of a gene can be obtained by examining the pattern of nucleotide substitutions between genes from different species [22, 47, 66]. When the gene is functional in both species and subserves similar physiological roles, mutations that change the coding sequence will be selected against (presumably because individuals that carry these mutations are less likely to reproduce); this is purifying or negative selection. On the other hand, positive selection acts to change the amino acid sequence of a protein. For chemosensory receptors, positive selection may be exerted on regions of the receptors that bind ligands, where a change in amino acid sequence may expand the repertoire of chemosensory signals that the organism can detect. Finally, when there is no selective pressure on the gene, mutations that change the coding sequence and those that preserve it will be fixed with equal probability. This occurs when a gene serves no function and, thus, mutations in the gene do not change the fitness of the individual.

Computer programs have been devised to measure and discriminate among these three scenarios: these programs measure the number of nucleotide substitutions that preserve the amino acid sequence, called synonomous substitutions, and those that change it, called nonsynonymous substitutions. These values are normalized for the number of synonymous and nonsynonymous sites, giving values d_s (number of synonymous substitutions/ number of synonymous sites) and d_n (number of nonsynonymous substitutions/ number of nonsynonymous sites), respectively (also called K_s and K_a) [22, 47] (see Fig. 2d). The ratio d_n/d_s then gives the selective pressure on the gene: if $d_n/d_s<1$, nonsynonymous (amino acid changing) substitutions are disproportionately underrepresented and selective pressure is purifying; if $d_n/d_s>1$, nonsynonymous substitutions are disproportionately overrepresented and indicative of positive selection [31, 42, 66]. This type of analysis becomes even more powerful when combined with the ability to reconstruct the probable sequence of ancestral genes, based on maximum likelihood methods. By comparing the sequence of living (extant) species with sequence from ancestral species, one can determine the selective pressure on specific branches of the phylogenetic tree. Such an analysis was used by Messier and Stewart to identify specific lineages of primates in which the enzyme lysozyme came under positive selection [41] and a similar analysis was

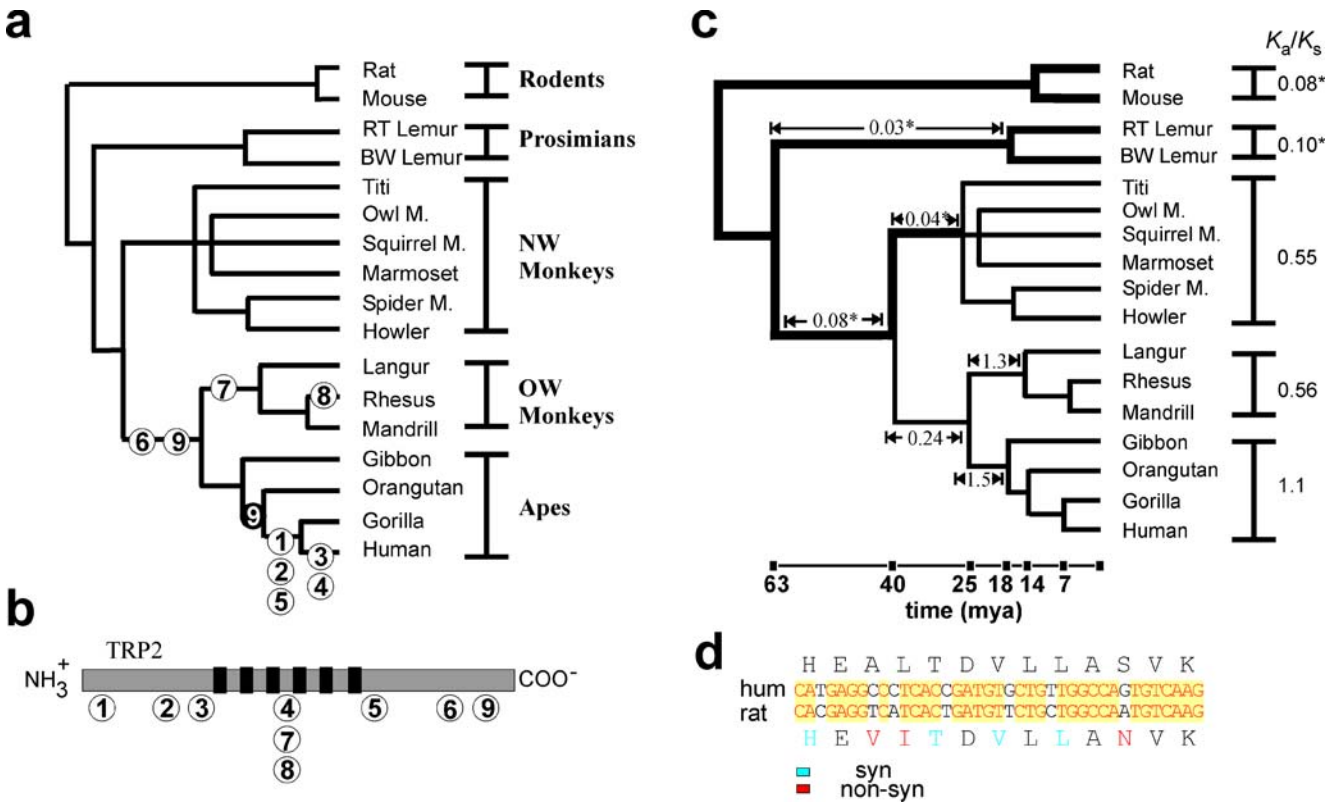


Fig. 2 Evolutionary fate of the TRPC2 gene. **a** Inferred time of occurrence of deleterious mutations in TRPC2 during primate phylogeny. **b** A schematic representation of the TRPC2 ion channel indicating the position of each mutation. **c** Rates of synonymous and nonsynonomous substitutions in the TRPC2 gene across primate phylogeny. Within-group values show the average K_a/K_s ratio for all pairwise comparisons in a group. K_a/K_s values computed using predicted ancestral sequences are shown *above the corresponding branch of the tree*. Both types of analysis show that selective pressure was relaxed on the TRPC2 gene 25–40 mya. **d** Nucleotide sequences of human and rat TRPC2, aligned and conceptually translated. Synonymous substitutions (which preserve the amino acid sequence) and nonsynonymous (which change the amino acid sequence) are shown in *blue* and *red*, respectively. (Modified from [35] with permission)

used to determine that selective pressure was relaxed on vomeronasal function in primate evolution (see below; [35]).

Trichromacy in primates

Changes in color vision during primate evolution provide a beautiful example of how changes in sensory function correlate with ecological niche [46, 59]. Human, apes and old world (OW) monkeys (catarrhine primates) are trichromatic—the cone photoreceptors in our eyes contain one of three distinct photopigments, which maximally absorb blue, red, or green light. The photopigments consist of a G-protein-coupled receptor called an opsin and a covalently bound light-absorbing chromophore, retinal, a derivative of vitamin A. The three human opsin proteins absorb different wavelengths because they "tune" the spectral sensitivity of the retinal. Rodents, new world (NW) monkeys and prosimians are mainly dichromats—their cones contain one of two color opsins, which absorb blue or green/red light maximally.

How and why did catarrhine primates evolve trichromacy? As to "how," it is clear that the green opsin gene arose as a duplication of the red opsin gene, as these genes are nearly identical and are present in tandem array on the X chromosome [46]. This duplication occurred in the common ancestor of catarrhine primates, as can be inferred by the presence of trichromacy in OW monkeys and apes but not in most NW monkeys. Some NW monkeys have a polymorphism in their red/green opsin gene that changes the spectral sensitivity of the opsin; because the gene is on the X chromosome, which is subject to inactivation, females may possess "allelic trichromacy" [23, 59]. In fact, the presence of this common polymorphism suggests that "allelic trichromacy" might have predated the emergence of full trichromacy [59]. In addition, one species of NW monkeys, the howler monkey, has evolved full trichromacy, in an independent duplication event [21, 23, 26]. Trichromacy in catarrhine primates most likely evolved to improve the success of foraging for ripe fruits and possibly for young shoots [46].

Loss of vomeronasal function in primate evolution

Molecular analysis of sensory systems has been particularly informative in instances where it is otherwise difficult to measure function. Such is the case for the study of pheromone detection in vertebrates. There has been considerable dispute about whether humans can perceive pheromones, and if so whether it is through a nasal sensory organ called the vomeronasal organ [40, 64]. The vomeronasal organ (VNO) in mice is a paired tubular structure located beneath the nasal cavity. In humans, a small pit can be detected in the nasal cavity which, some have argued, may contain functional sensory cells that respond to pheromones. To determine whether the human VNO is functional is a difficult problem which has been, perhaps, best addressed with molecular tools [35, 68].

In rodents, the vomeronasal organ expresses two families of GPCRs that are candidate pheromone receptors (V1Rs and V2Rs) [10, 20, 39, 56]. In mice, there are 165 functional V1R genes and 61 functional V2Rs genes [65, 67]. V1R-expressing cells appear to respond to small hydrophobic molecules, whereas V2R-expressing cells appear to respond to peptides [28, 29]. A role for V1R receptors in pheromone sensation has been substantiated by the observation that targeted deletion of one cluster of 16 receptors leads to changes in maternal aggressive and male sexual behavior [8]. Vomeronasal sensory neurons also express a unique ion channel, called TRPC2 [34], which is activated by second messengers downstream of the V1R and V2R receptors, with which it is co-expressed [34, 36, 73]. In the absence of TRPC2, male mice do not show typical pheromone-mediated male–male aggression, indicating that this ion channel is essential for normal VNO function [30, 58]. Moreover, when confronted with a castrated male mouse (which is not aggressive), male TRPC2 knockout mice will attempt mating, at a similar frequency with the attempt of mating with female mice, suggesting that the VNO plays a role in gender identification [30, 58].

The identification of essential components of VNO sensory transduction has made it possible to determine, solely with molecular methods, whether a particular species is likely to have a functional VNO. For humans, the preponderance of evidence shows that the VNO is vestigial; the TRPC2 gene contains four nonsense and two insertion/deletion (in/del) mutations [34, 35, 61, 68] and most of the V1Rs are also pseudogenes [55]. By identifying mutations in the TRPC2 gene of extant species and parsimoniously assigning the time in evolution that these occurred, two groups determined that the first deleterious mutation in the gene occurred in the ancestor of OW monkeys and apes 25–40 million years ago (mya) [35, 68] (Fig. 2a,b). This first mutation was a truncation of the C terminus of the protein, and the effects of this mutation, although likely to be deleterious, were not known. Additional evidence that selection was relaxed at this time in evolution comes from an analysis of the Ka/Ks ratio along branches of primate phylogeny (Fig. 2c). This ratio is significantly less than one on branches of the evolutionary tree leading up to the ancestor of OW monkeys and apes, showing purifying selective pressure, and thereafter is not different from 1, showing that selective pressure was relaxed at this time [35]. The excellent agreement between these two types of analysis strongly supports the view that selective pressure on the TRPC2 gene was relaxed 25–40 mya.

The V1R receptor genes most likely came under relaxed selective pressure at this time, as evidenced by the large number of human V1R pseudogenes (~200) and presence of only four possibly functional genes [55]. It is not known whether these four receptors are functional in humans. Computational methods show that this is the number of genes expected by chance to have escaped pseudogenization, given that selective pressure was relaxed ~25 mya [68]. Moreover, none of these four receptors are conserved in chimps [68], thus one would have to argue that whatever function they subserved in the common ancestor of humans and chimps was lost in modern chimps. On the flip side, these receptors have retained many of the highly conserved residues found in other V1Rs, an observation that is inconsistent with relaxed selective pressure on the genes [55]. One of these receptors appears to be expressed in the main olfactory epithelium [54], suggesting that it might have been co-opted for a different chemosensory function. Solving this mystery will not be easy as there are no direct mouse orthologs of these genes [19].

Together these results show that critical components of vomeronasal transduction were lost in human evolution 25–40 million years ago. Interestingly, this is the same time when trichromacy appeared, suggesting that visual signaling may have replaced pheromone signaling. Indeed, catarrhine primates show prominent female sexual swelling and other sexual dimorphisms, which provide a visual signal of reproductive and social status. Thus, it is likely that as primates began to rely on these signals over chemical signals, the VNO became redundant, and selective pressure was relaxed on molecules it uniquely expresses.

Contraction of the odorant receptor repertoire in human evolution

Changes in olfactory receptors have been well documented along different animal lineages, but the large size of the gene family has made it difficult to understand the functional consequences of these changes. Odorant receptor (OR) genes are intron-less and have structural similarity to other GPCRs [2]. Of the hundreds to thousands of receptors

available to it, each olfactory neuron expresses just one [7], allowing for the identification and discrimination of millions of distinct odorants. OR genes are present at many different loci in the genome, with structurally similar genes appearing in clusters (reviewed in [50]. The size of the repertoire is highly dynamic, having undergone expansion and contractions in many different animal lineages. The repertoire of functional odorant receptors in humans is considerably smaller than it is in rodents, and a large fraction of the genes are pseudogenes (~50% of the 802 human genes and 25% of the 1,391 mouse genes; reviewed in [53]). The difference in the size of the human and mouse repertoires reflects both expansion in the murine lineage and pseudogenization in the primate lineage [51].

The large number of human OR pseudogenes appears to be the result of two separate times in evolution at which selective pressure on these genes was relaxed. Selection pressure was relaxed first in the ancestor of OW monkeys and apes, as deduced from the observation that all OW monkeys and apes have a higher fraction of OR pseudogenes (~30%) than do NW monkeys (~18%); thus, pseudogenization of the OR repertoire coincided with the appearance of trichromacy in primates [16]. A similar deterioration in the repertoire of functional OR genes is observed in the howler monkey, a NW monkey that has independently evolved trichromacy, providing additional support for the notion that olfactory function became less important as primates developed more powerful visual systems [16]. A more recent relaxation in selective pressure on OR genes appears to have occurred specifically in the human lineage, as humans have a significantly higher percentage of OR pseudogenes as compared with other OW monkeys and apes [15]. Indeed, pseudogenization of human OR genes may be ongoing as evidenced by the presence of common polymorphisms that disrupt the coding region of the genes [14]. The reason for the increase in pseudogenization of human OR genes is not known but may be attributed to a reduction in the use of olfactory signals as a means to identify and discriminate foods.

Evolutionary changes in taste sensation

Receptors for taste specify attraction or aversion to food [45, 72], and, thus, changes in these receptors may be directly related to adaptive changes in foraging behavior and diet. Taste allows animals to determine the nutritive content of food before ingestion: of the five identified taste modalities, three—sweet, umami, and salty—signal the presence of essential nutrients and lead to ingestive behavior. The other two modalities, bitter and sour, signal the presence of toxins or the spoilage of food, respectively, and, to most animals, are aversive. The molecular basis for sour and salty tastes is not yet well understood, and candidate receptor molecules await validation with genetic methods [37, 38, 44]. In contrast, receptors for sweet, bitter, and umami have been well described; a small family of three class C GPCRs (T1Rs) mediates sweet and umami taste and a larger family of class A GPCRs (T2Rs) mediates bitter taste [6, 37, 38, 44]. Heterodimers of T1Rs form the sweet (T1R2/T1R3) and umami receptors (T1R1/T1R3) [33, 48, 49].

Taste receptors have now been identified in a large number of species, including humans and other primates. Interestingly, the three sweet and umami receptors are well conserved among all land vertebrates, with the exception of cats, for which the sweet receptor T1R2 is a pseudogene [32, 57]. The loss of the T1R2 gene and sweet taste perception in cats is consistent with dietary choice in these animals that are obligate carnivores. Chickens also appear to be missing a functional T1R2 gene, although the significance of this observation is not known [57]. While most species retain functional T1R receptors, it is likely that the ligand specificity of these receptors varies across species in such a way as to allow the detection of species-specific naturally occurring nutrients. For example, sweet receptors of humans and mice differ in sensitivity to brazzein, a protein produced by certain African plants; this protein tastes intensely sweet to humans, whereas mice are indifferent to it. The structural basis for this difference has been mapped to a cysteine-rich region in the T1R3 receptor [24]. This may represent yet another example of co-evolution of a vertebrate sensory receptor with a natural plant product.

Bitter receptor genes are present in variable numbers among different species, having undergone rapid expansion and pseudogenization [11, 53]. Humans have 25 functional bitter receptor genes as compared with 35 in mice [11, 17, 53, 57]. Three receptors have become pseudogenes specifically in the human lineage, which is a somewhat higher rate of pseudogenization than is seen in other primates [17]. It has been argued that a loss of selective pressure on bitter receptor genes in human evolution could be the result of a decreased reliance on nutrients from toxin-containing plants [57].

Selection has acted not just to eliminate functional bitter receptor genes from the human genome, but also to change their ligand specificity. This is perhaps nowhere more evident than in the case of the phenythiocarbimide (PTC) taste receptor, TAS2R38 [63]. In 1931, a common variation in the ability of people to taste PTC was reported, which was shortly thereafter shown to be genetically determined [1, 13]. Variation in PTC sensitivity was also found in chimpanzees, suggesting that the genes responsible for it became fixed before the divergence of the two species [12]. The stability and prevalence of this polymorphism made it a textbook example of "balancing selection," where two or more forms of the gene are maintained in the population as a result of heterozygote advantage.

The genetic basis for the phenotypic variation in PTC sensitivity is now known; three missense mutations generate two common alleles that can explain the phenotypic variation in the human population [4, 27]. Interestingly, chimpanzees do not share these alleles and instead the non-taster allele contains an interrupted reading frame [62]. A detailed analysis of human data shows that the two common human alleles are both too divergent and too prevalent to be the result of simple genetic drift and instead reflects balancing selection. It has been speculated that the non-taster TAS2R38 allele still detects bitter chemicals, whose identity is not yet known, and, thus, heterozygotes have the advantage of being able to detect a larger variety of potentially toxic chemicals [9]. This is reminiscent of the visual system of NW primates where a polymorphism in the red opsin gene allows females to have allelic trichromacy (see above) [21, 59]. It is tempting to speculate that gene duplication in the future may result in the presence of both variants of the TAS2R38 gene on the same chromosome and that what we are observing now is an intermediate step in evolution.

Summary and challenges for the future

The identification of a growing number of chemosensory receptors in different organisms provides a unique opportunity to understand how selective forces have shaped the evolution of sensory systems. Work in the vomeronasal system, showing that genes expressed there are nearly all pseudogenes, has provided the strongest support for the idea that this sensory modality is vestigial in humans. Other sensory systems have clearly changed during human evolution, with contractions in the repertoires of both olfactory and bitter taste receptors. The significance of these contractions are presently the subject of conjecture, and will only be understood when the cognate ligands for the pseudogenized OR and bitter receptors have been identified, and their natural occurrence in the environment understood. Moreover, changes in OR and bitter receptors are ongoing in the human population and the identification of polymorphisms in these receptors may lead to a better understanding of the variation in human food preference.

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