C&T

Odor Reception: Structure and Mechanism

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Key words

Olfaction, odor receptor protein, G-protein coupled receptor, glumeruli, signal transduction, DNA, amygdala

Abstract

Olfaction is a multi-step process involving the odorant molecule, the odor receptor protein, the pockets for odorant ligand docking, and the odor patterns formed by the glumeruli and decoded by the brain.

Odors play a key role in the personal care industry. They are the raison d'être of the multi-billion dollar fragrance industry. Cosmetic products have base odors to be fragranced, or at least masked. The major marketing difference between shampoos and bath products is usually fragrance. Fragrance is typically the most expensive ingredient in a cosmetic formula. Yet despite the unquestioned importance of fragrance, our knowledge of the sense of smell is often surprisingly sketchy.

There is a good reason why odor recognition is poorly understood. It is a new and evolving field. Much of the information is still confined to technical journals and chemoreception seminars of an advanced nature. Comprehending the current state of the field requires knowledge of genetics and the genome, cloning, biology, biochemistry, anatomy and physiology, protein chemistry, molecular modeling, signal transduction and the inner workings of the brain. It is no wonder that olfaction has largely remained in the domain of specialists. The current review aims to reveal the scope of contemporary research in relatively simple terms, and the extensive references will assist the interested reader in locating the key papers and investigators.

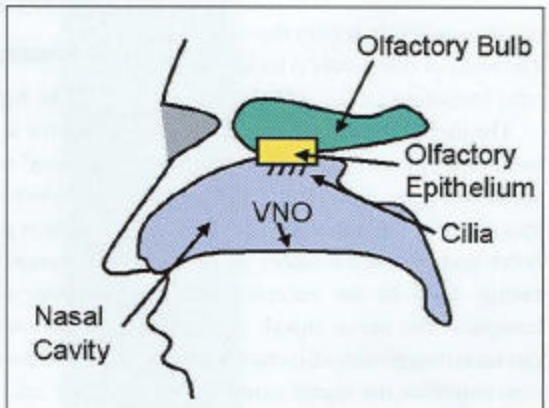

Figure 1. The olfactory system

Background

The human olfactory system: Chemoreception is a general term for all the mechanisms by which living things sense chemicals in the environment. In humans, for external airborne stimuli, it consists of the olfactory system (the sense of smell), the trigeminal nerve (a hazardous chemical sensor) and the vomeronasal organ (VNO, the putative pheromone receptor). Figure 1 shows the gross anatomy of the olfactory system and the location of the VNO. Other examples of human chemoreception are taste and hormone recognition.

Odorant molecules are detected by hair-like cilia located on the roof of the nasal cavity, in a region known as the olfactory epithelium. Until recently the exact mechanism of odor reception – indeed, what property of matter creates a perception of odor – was not understood with anything like the precision of the analyses of sight or hearing.

By 1950, two theories emerged to provide a connection between molecular properties and olfactory stimulation. Robert Wright led the proponents of the vibrational theory, now advanced by Luca Turin. John Amoore championed the stereochemical theory.

Stereochemical theory: The stereochemical (or "lock-in-key") approach is easy to visualize. The odor receptors are postulated to have a configuration that can host a specific shape. When a molecule arrives with the appropriate shape and size, it occupies the receptor site and triggers the olfactory response.

Vibrational theory: The vibrational theory attributes odor recognition to

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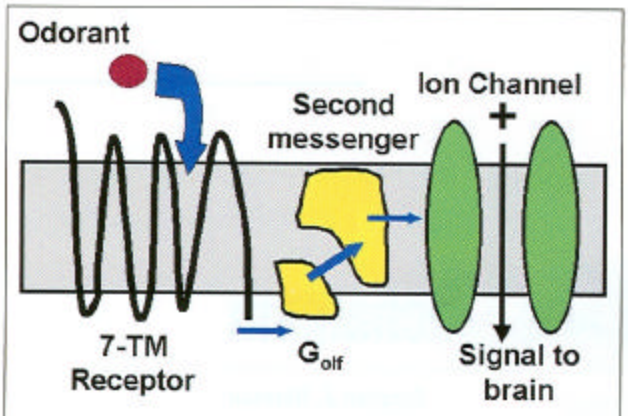

Figure 2. Simple model of the olfactory process, according to Buck and Axel[1]

the energy levels within the molecule. The basis of this model is inelastic electron tunneling.

The model assumes the receptors to be minute spectroscopes. In traditional spectroscopes, light is the probe; in this process, electrons are used. A gap is bridged between a higher and lower energy level in the receptor site to complete the nerve signal. Once the circuit is completed, a biochemical process amplifies the signal, opens an ion channel, and sends an impulse to the olfactory bulb.

The vibrational theory works well with some odors, but fails with others. The same can be said for the stereochemical theory.

G-Protein activation: In 1991 Buck and Axel published one of the seminal papers[1] in olfactory research, based on work conducted at Columbia University. They identified the odor receptor gene as a seven-transmembrane (7-TM) domain protein, a snake-like protein that crosses a lipid membrane seven times. The loops are of various sizes. The external end is always NH_2, and the internal end always terminates in COOH. When the odorant molecule fits into a receptor site, it twists the protein, sending a signal to the end of the molecule. Such a structure is referred to as a coiled-coil protein.

Buck and Axel's work, combined with a major contemporaneous effort conducted at Johns Hopkins University, raised our understanding of the smell mechanism to near parity with our understanding of the other senses. An essential key was establishing the process of signal transduction, by which the chemical energy of binding is converted into a neural impulse of electrical nature.

A simple model of the olfactory process as determined following Buck and Axel's initial work is reflected in Figure 2, showing the general state of knowledge by the end of 1991. In the most succinct terms, the odorant molecule interacts with the 7-TM odor receptor protein, activating a G-protein, which triggers the cyclization of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), opening an ion channel, and sending a signal via the olfactory bulb to a neural network leading to the olfactory cortex.

The following sections will examine some of the progress made in the last decade toward understanding the details of olfactory recognition. A synthesis of the current state of olfactory understanding will be presented in the final figure.

G-Protein Coupled Receptors

The human body uses 7-TM spanning serpentine receptors for a variety of signaling functions. Indeed, it was by analogy to these other systems that the olfactory odor receptor was discovered. The receptor triggers the communication process by stimulating an adjacent G-protein. The G-protein takes its name from its role in binding to the guanine nucleotide GTP (guanosine triphosphate). The G-protein sends the signal further into the cell when it is in its active state. After a short period of time, the G protein shuts itself off, thus acting like a binary switch. This process typically takes a few seconds or less.

The G-protein is not one precisely defined molecule, but rather a family of structures classified by their biological role. The G-proteins are often named for their activities, so the one associated with olfaction can be designated G_{olf} or G_o.

The G-proteins associated with G-protein coupled receptors consist of three components: α, β and γ. The units are typically different sizes: the α subunit is 39-46 kD, the β 35-39 kD, and the γ approximately 8 kD. Genetic studies thus far indicate the existence of 20 α, 6 β and 12 γ possible subunits. In the inactive state, the α subunit binds to GDP (guanosine diphosphate) and the 3 subunits are attached. When the α subunit binds to GTP, its affinity to the β and γ subunits is decreased and the molecule dissociates. This separation enables the reactions that amplify and continue to propagate the signal, an essential step in the signal transduction process. The activation/deactivation cycle is shown schematically in Figure 3.

In its active state, the G-protein causes ATP to convert to cAMP, which is the second messenger in the signal cascade. The cAMP alters the permeability of the nerve ion channel to different ionic species, changing the electrical potential, and communicating the sensory response into the brain. This process is not unique to olfaction, and the interested reader can find the details in any biology text, although the role of G-proteins will not appear in older volumes.

DNA Basics

Deoxyribonucleic acid (DNA) is structured as a double helix chain with a phosphate-sugar backbone and four possible bases, adenine (A), guanine (G), cystine (C) and thymine (T) (Figure 4). The bases can only be paired A-T or C-T. When DNA replicates, the chain unravels and a new chain is made from complementary bases; that is the process used to perpetuate life itself. The main functional role of DNA is to serve as a template for protein synthesis.

The *homo sapiens* genome contains all the genetic information to create a human. It contains 3 billion bases in human DNA, divided between 23 chromosomes. The DNA sequence encodes the instructions to make proteins. A surprisingly large group of these instructions, consisting of about 2% of the entire genome, provides the information for constructing the odor receptor proteins.

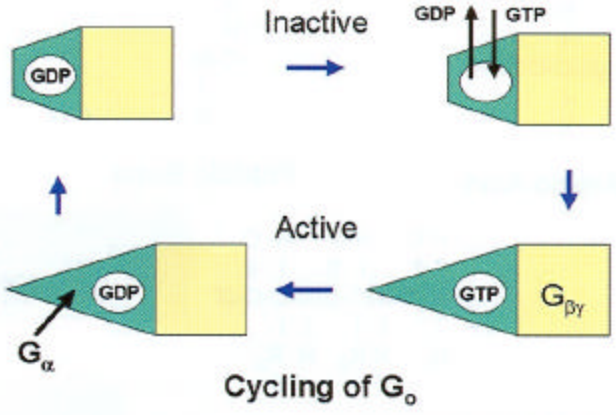

Figure 3. Cycling of G_o

Proteins are chains built of amino acid units (Figure 5). One end of the chain is always an amine group (the N terminal), and the other end is always a carboxylic acid (the C terminal).

When DNA is uncoiled to replicate, the four bases must encode 20 amino acids. A sequence of three bases, called a codon, corresponds to an amino acid. DNA first encodes ribonucleic acid (RNA), which is the template for protein synthesis. In RNA, the base uracil (U) replaces thymine. Since 64 combinations of the four bases are possible, there is redundancy in the code, usually in the third component of the codon. The sequence AUG begins a sequence, and the end is signaled by UAG, UAA or UGA.

Within genes, there are also sections of DNA called introns, which do not carry protein-making instructions. When a cell makes protein, it edits out the introns to produce a continuous stretch of bases coding for precisely the correct sequence of amino acids needed to build the protein. A convention has established single letter symbols for all the essential amino acids in proteins, and these are shown in Table 1.

A simple illustration will show how a snake-like transmembrane protein arises from the DNA code. Start with the sequence:

AUGCGCCGCACCGAU-
ACCCGCACCGAUGAUGAUCGC-
ACCACCCGCCGCUGA

AUG initiates, CGC is a codon for arginine, ACC encodes threonine, GAU encodes aspartic acid and UGA terminates the chain, creating a protein consisting of RRTDTRTDDDRTTRR, beginning with the N terminal, ending with the C terminal. Figure 6 shows this chain winding through a lipid membrane.

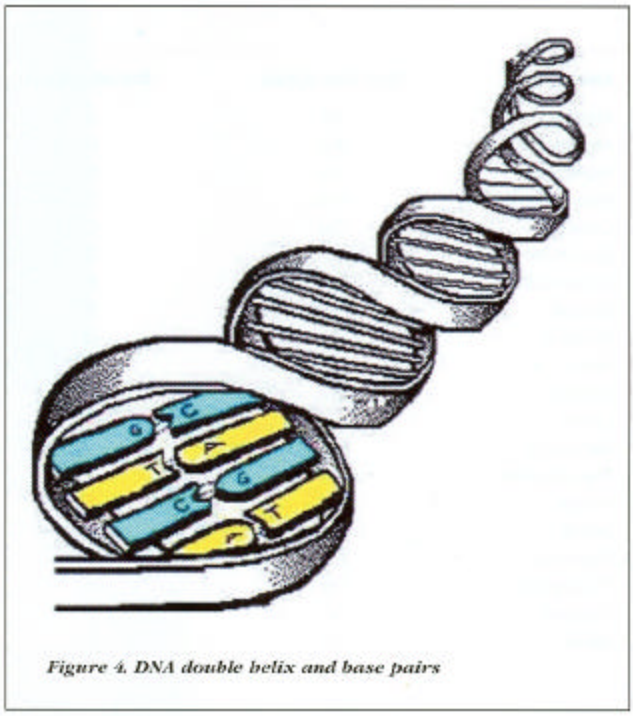

Figure 4. DNA double helix and base pairs

The Odor Receptor Code

Searching for the odor receptor gene, Linda Buck made the inspired decision to look for members of the seven-transmembrane receptors. This was a key assumption, because it narrowed the search considerably – and it was correct. Gene mining is the term used to find parts of the genome with identifiable characteristics.

In Buck and Axel's paper, several odor receptor genes were identified. Two of them, in abbreviated form, are shown in Figure 7. Several points must be understood about the gene analysis that was conducted. Some locations have the same protein in all or most of the genes in the family, forming a "con-

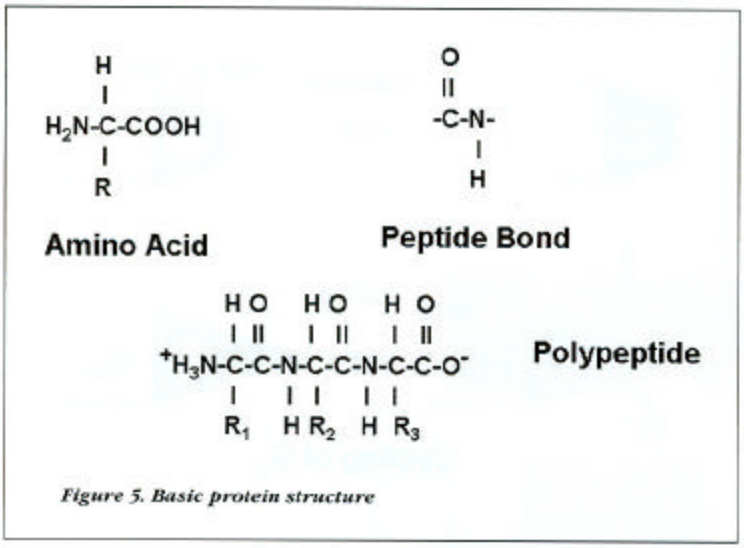

Figure 5. Basic protein structure

Table 1. Single-letter amino acid symbols

Amino acid	Three-letter symbol	One-letter symbol
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Ieu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V

sensus." Several consensus locations are circled in the figure. Only two human receptor genes are shown, but human nonreceptor genes and nonhuman odor receptor genes were compared, much like the synoptic gospels, to find patterns that characterize the gene families.

The availability of the entire genome, plus powerful computer programs, has allowed the identification of close to 1000 odor receptor genes. Many of these are pseudogenes, but easily 400-500 express functioning receptors. The large collection of raw data available from the genome databases has enabled the explosion of studies in molecular modeling and genetic modification that has characterized the recent stages of olfactory research.

Protein Modeling

Rhodopsin, a G-coupled protein receptor used in photoreception, is often employed to model the odor receptor. It works by a mechanism similar to chemoreception, it has been studied extensively, and its three-dimensional structure has been precisely determined – no small feat when dealing with such complex molecules.

Establishing the three-dimensional structure of the odor receptor requires a combination of science, computer modeling and guesswork that enables a topology prediction of membrane protein. The prediction technique relies on residue compositional differences in the protein segments exposed at each side of the membrane. For example, the amino acid residue types Asn, Asp, Gly, Phe, Pro, Trp, Tyr and Val are preferably found on the extracellular side, and Ala, Arg, Cys and Lys mostly occur on the intracellular side. One frequently used parameter is the "positive inside rule," which is based on charge differences in the amino acid residues. There are many web sites where amino acid sequences can be inputted to yield a predicted three-dimensional structure, and the specific algorithms explained.

Leffingwell has offered modeling of a number of putative odor-binding cavities; his structure for the human OR1.04.02 is shown in Figure 8. Leffingwell used sequencing data from Senomyx, which differed somewhat from that proposed by HORDE (The Human Olfactory Receptor Data Exploratorium), one of several available online. The cavities were calculated using CastP, an online protein bonding and active site calculator program. An amino acid sequence is plugged in, and an algorithm based on a number of modeling assumptions is used to design the proposed tertiary structure. Adjustments can then be made manually to rectify certain obvious anomalies. The final structure remains a good educated guess, useful for further research, but only positive results such as those provided by x-ray crystallography can be considered definitive.

The structure of the odor receptor protein is cylindrical inside the lipid bilayer area, but essentially unstructured outside it. Another descriptive feature of the molecule is that it is a "coiled-coil" protein, where different chains can overlap each other. These features are shown in Figure 9. The bonding pockets have been found between TM-3 and TM-6, and a cross section of hypothecated bonding regions (derived from Lancet[2]) are shown in Figure 10, which shows a view perpendicular to the depictions in Figures 8 and 9. Figures 8, 9, and 10 thus all show different aspects of the modeling of the odor receptor protein.

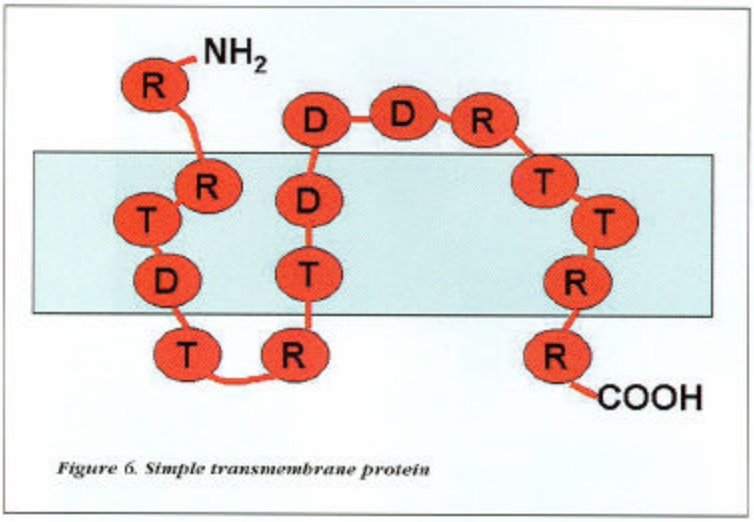

Figure 6. Simple transmembrane protein

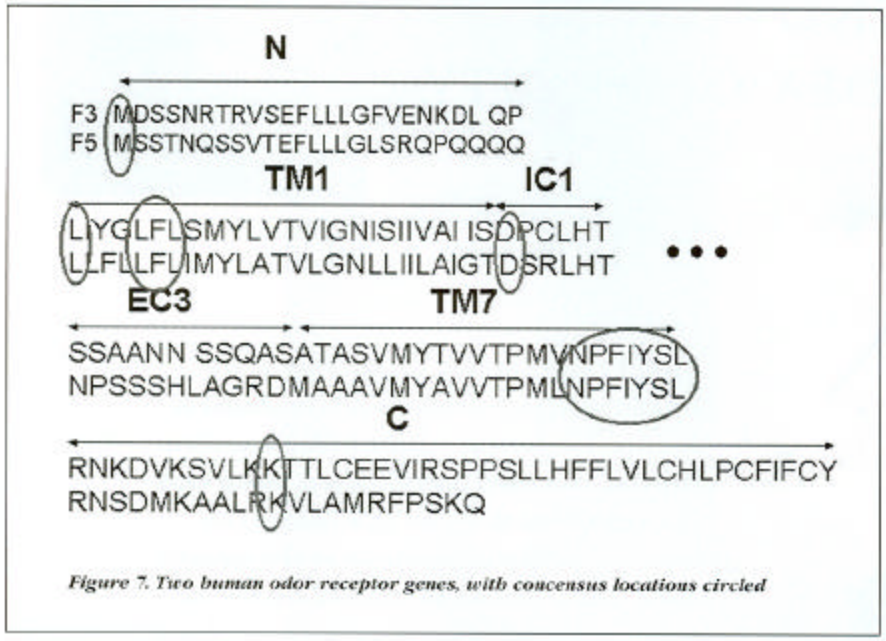

Figure 7. Two human odor receptor genes, with concensus locations circled

receptor gene. A green fluorescent protein was used as a marker, and electrophysiological testing indicated increased olfactory response in the receptor, particularly to octanal. The study showed that the receptor responds to saturated aliphatic aldehydes from C-7 to C-11.

In total, 90 compounds were tested, most of which indicated no response, in keeping with the assumption of selectivity of the individual receptor to odorants. Not all parts of the molecule are equally important in triggering the receptor. For this receptor the aldehyde group was necessary, and the chain length was clearly restricted to the range of 7 to 11 carbons. Unsaturation of the chain was not critical, although the combination of unsaturation plus an added methyl group can deactivate the compound, probably because of its effect on the geometry of the molecule versus the receptor pocket.

Firestein's conclusion that the 17 odor receptor is specific to aldehydes provides key evidence of the relation of individual receptors to chemically defined functional groups. This work is crucial to eventually establishing the structure-function relationships that could revolutionize perfumery.

Signal Transduction

Signal transduction at the cellular level refers to the movement of signals from outside the cell to inside. G-proteins are frequently involved in signal transduction, and receptors of the class that interact with G-proteins all have a structure that is characterized by seven-transmembrane (7-TM) spanning domains. These receptors are termed *serpentine* receptors; odorant receptors are examples of this class, as are certain hormone receptors.

The general principles and mechanisms of signal transduction investigated by researchers such as Firestein include receptor-ligand interactions, modulation by second messengers, and ion channel gating. Photoreception in the human eye uses 7-TM receptors that change conformation when struck by photons, a mechanism that was discovered in 1955. It should be noted by the example of sight, and the current exploratory nature of olfactory research, that detailed knowledge of how our senses work is a very recent development. Mankind discovered the hydrogen bomb before unraveling the mystery of sight.

At Columbia, Firestein has used the tools of modern genetic research to experiment with the response to odor-

Genetic Modification as a Tool

To use the genome information for olfactory research, the sequences expressing the odor receptor proteins must be identified, replicated and inserted in a simple organism. A virus is sometimes used to propagate the gene, although it is technically not a living thing. The virus can then be placed in a target organism, where it will encourage the expression of the desired trait.

In a significant example of the application of genetic modification to study olfactory response, Firestein used an adenovirus to express the rat 17 odor

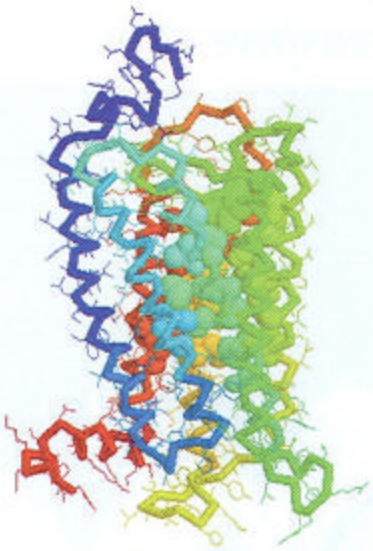

Figure 8. Putative binding cavity in human OR1.04.02 derived using CastP (used with permission of Leffingwell & Associates)

Figure 9. Coiled-coil structure of an odor receptor protein

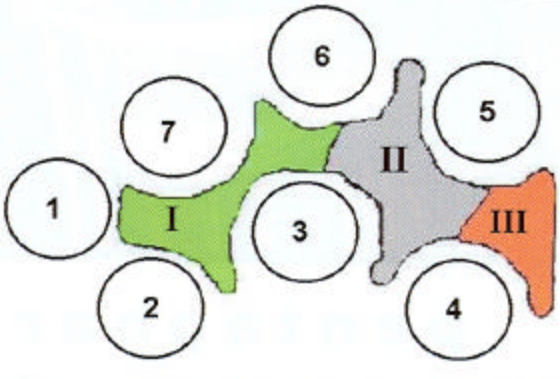

Figure 10. Odor binding pockets from the odor receptor protein in Figures 8 and 9

ants by a specific receptor. Firestein focused on the odor marker protein (OMP), postulated as a key component of the odor response cascade. The receptor gene was expressed in an adenovirus, a simple propagation media similar to the source of the common cold.

Mice were produced with the gene for the 17 OMP removed. This research animal is called an OMP-null mouse. Mice with specific gene deletion are commonly described as "knock-out" mice. Mice are commonly used in genetic research, in part because of the similarity between mouse and human DNA.

The gene was combined with a green fluorescent marker and the virus used to infect the odor-sensing neuron of mouse olfactory epithelia. The replication of the OMP in the mouse could be tracked with the green color, and the response to ligands of that receptor was noted.

Electrophysiological recordings were taken 1-4 days after infection and established the restoration of odor reception. Standard methods such as patch clamp electrophysiology are available to measure electrical activity at the cellular level, providing an additional measure of proof for Firestein.

This research provided the first concrete relationship between a family of ligands and a specific odor receptor.

Odor Reception Patterning

Linda Buck's recent work shows the combinatorial nature of odor recognition. There are approximately 1000 odor receptors (ORs), but perhaps 10,000 odors can be distinguished. Thus, there can not be a one-to-one correspondence between ORs and distinct odors.

The key account of Buck and her colleagues is reported in Malnic.[5] According to Buck, "A single receptor can recognize multiple odorants; a single odorant is typically recognized by multiple receptors; and different odorants are recognized by different combinations of receptors."

One odorant can fire several ORs, each of which transmits its impulse to an axon, which leads to a glumeruli. Glumeruli are clusters of about 10,000 axons in the olfactory bulb. The response pattern received in the glumeruli is relayed to the brain for the final decoding (Figure 11). The permanent pattern recognition in the glumeruli is crucial for odor memory, because olfactory sensory neurons have short lifetimes.

Buck's group used calcium imaging and single-cell RT-PCR (reverse transcription polymerase chain reaction) to study the effect on ORs of molecules with similar chemical structures but different odors. RT-PCR was used to identify the OR genes expressed by individual neurons. When activated, olfactory neurons show an increase in intracellular calcium that can be detected with calcium imaging.

Mouse olfactory neurons were tested with C-4 to C-9 aliphatic odorants: alcohols, carboxylic acids, bromocarboxylic acids and dicarboxylic acids. Fourteen olfactory neurons were expressed. The pattern response to three odorants is shown in Table 2.

An example of two odorants with similar structures but different odors is shown in Table 3. Buck's work proved that mammalian ORs could distinguish odorants that differ in chain length by one carbon, or that have the same chain length but different functional groups.

Different odorants activate different combinations of glumeruli. An increase in odorant concentration also increases the number of glumeruli that respond to the stimuli. Odor intensity, why some odorants are so much more potent than others, may find its solution in the combinatorial patterns and the role of the glumeruli in the recognition process.

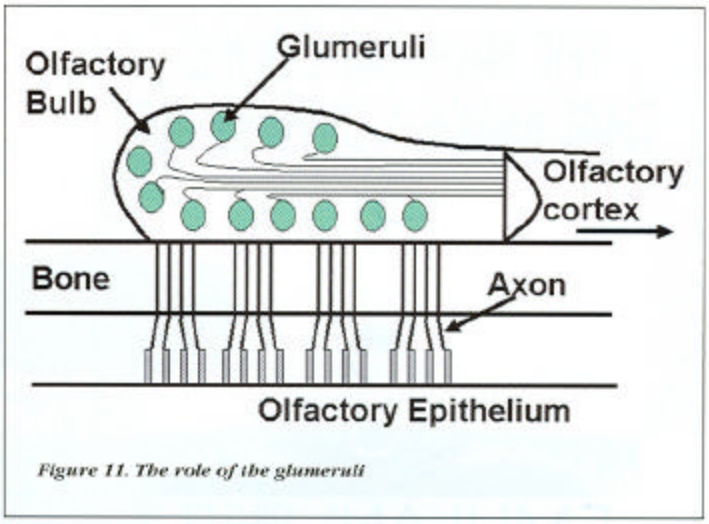

Figure 11. The role of the glumeruli

Decoding in the Brain

A fundamental difficulty in explaining why a rose smells like a rose is that it is a multi-step process ending in the middle of the brain, in an ancient, emotive area known as the limbic system. The antiquity of the olfactory system and the limbic system, and their direct connection, make it possible to speculate that the process of recognizing smells was intimately involved in the development of human emotions.

Two organisms in the limbic system have been identified as critical regions receiving olfactory information. These organisms are the amygdala and the hippocampus. The amygdala is an emotional center that also responds to fear and other basic feelings, while the hippocampus is a memory center.

There can be no better description of the amygdala than that offered by Robert Sylvester, who wrote: "The amygdala complex is composed of two almond-shaped, fingernail-sized structures that are richly and reciprocally connected to most brain areas, especially advanced sensory-processing areas. Its principal task is to filter and interpret sophisticated incoming sensory information in the context of our survival and emotional needs, and then to help initiate appropriate responses."[4]

The understanding of the brain's reaction to odors can be aided by medical tests such as a PET (Positron Emission Tomography) scan, which can identify areas of the brain that respond to certain tasks. PET images of the brain indicate that different odors activate different brain regions. Other in-

Table 2. Olfactory neuron recognition profiles[3]

	S1	S3	S6	S18	S19	S25	S41	S46	S50	S51	S79	S83	S85	S86
Hexanol		X				X								
Heptanol		X			X	X								
Octanol				X	X		X			X				

Table 3. Structure/Odor differences[3]

	S1	S3	S5	S16	S19	S25	
Hexanoic acid					X		rancid, sweaty, sour, fatty
Hexanol		X				X	sweet, herbal, woody

vestigative tools include electroencepha-lography (EEG) and electrocardiogram (ECG), as well as such easily measured physiological properties as systolic blood pressure, heart rate and electrodermal activity.

David Zald is a leading researcher in the role of the amygdala in odor response. He has used PET scans to identify the areas of the brain reacting to aversive stimulation. Zald found that the amygdala and the left obitofrontal cortex respond to unpleasant odors, specifically mixtures of sulfide gasses.

The amygdala does not seem to process less potent odors. Buck found two ORs in the rat that did not trigger the amygdala. The conclusion is that the amygdala and some other limbic areas are activated by odorants possessing strong hedonic qualities.

Because olfaction involves so many steps, the research on different aspects of the process have focused on isolated and highly specialized scientific investigations. The amygdala-related research and the decoding process in general are far removed from the study of the odor receptor proteins. Research on the amygdala involves brain specialists from both physiology and psychology. On the other hand, research on the odor receptor proteins requires genetic and protein modeling studies at the receptor site. The receptor site determines which molecules have smell by triggering a signal. The inner brain gives the signal meaning, makes odors emotionally evocative, and forms the basis of aromascience and aromatherapy.

The detailed study of brain functions is far beyond the scope of the present article, but the interested reader is referred to Schoenbaum[3] as an appropriate entry to the current research in this area.

Current Model of Olfaction

Figure 12 shows the mechanism of olfaction as it is currently understood. The odorant molecule must first come in contact with the odor receptor protein, perhaps through the mediation of an odor binding protein. The odor receptor is a 7-TM G-coupled protein possessing defined helical structure in the sections inside the lipid membrane. The helical domains contain defined pockets where the odorant ligand can dock. The exact pocket configurations participating in odorant binding and knowledge of the specific ligands that trigger a given receptor are only known in a few cases, but work is ongoing in this area.

The results obtained so far support the general theory of the olfactory mechanism derived from Buck and Axel's model, and further data should increase our detailed knowl-

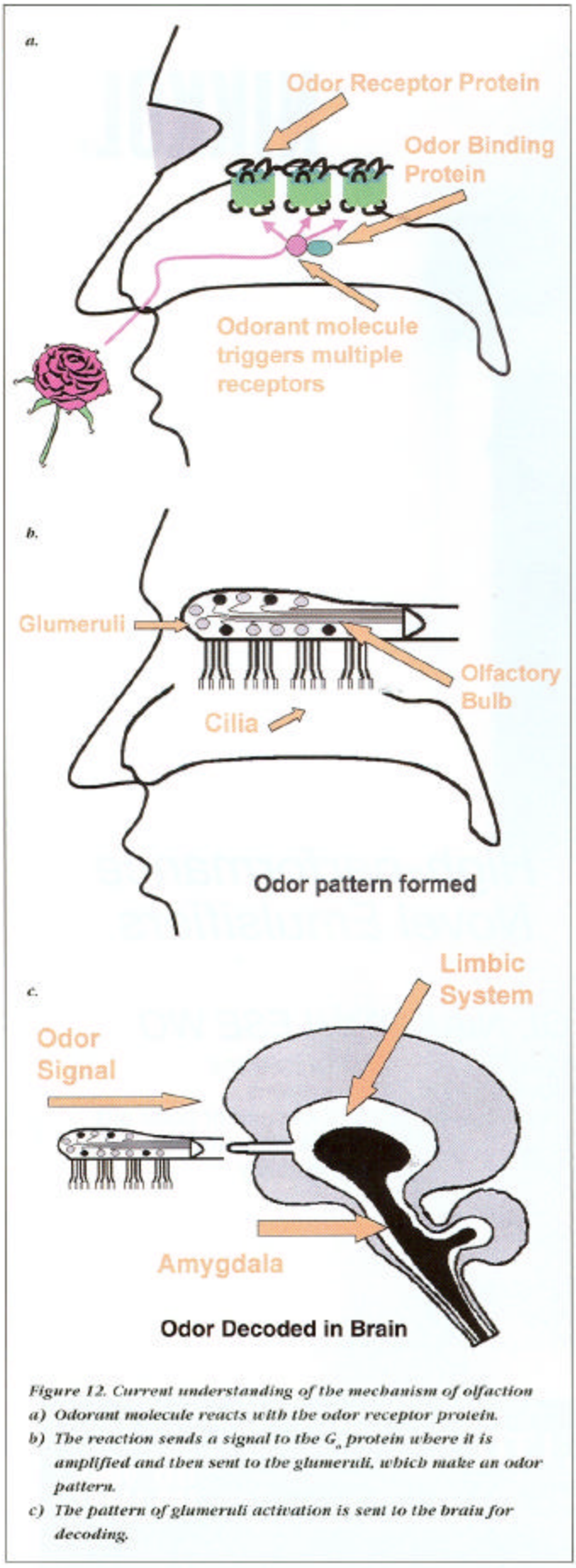

Figure 12. Current understanding of the mechanism of olfaction

a) Odorant molecule reacts with the odor receptor protein.

b) The reaction sends a signal to the G_o protein where it is amplified and then sent to the glumeruli, which make an odor pattern.

c) The pattern of glumeruli activation is sent to the brain for decoding.

edge without altering the broad outlines of the process. The interaction of the ligand with the odor receptor protein sends a signal to the associated G_o protein. That signal is amplified by a second messenger, in some way abetted by an odor marker protein. The signal is then sent to the glumeruli, a bundle of nerves in the olfactory bulb where the messages from numerous receptors converge. A single molecule can trigger more than one receptor, so a limited number of receptors used in combinations can discriminate between many thousands of different odors. Because of the efficient biochemical amplification involved, only a small number of odorant molecules are needed to initiate a signal cascade.

A pattern of glumeruli activation is sent to the brain, where it is decoded in the region of the limbic system, especially including the amygdala for certain important odors. The exact recognition process is not currently understood, but progress is being made on locating the areas of the brain that respond to particular odors.

Conclusion

Buck and Axel provided the key to our current understanding of olfaction in 1991. Identifying the odor receptor gene family brought the power of genetics to bear on the field, providing many fruitful avenues of exploration. Research has been aidedgreatly by the recent publication of the human genome and advances in the computer modeling of complex chemical structures.

The fundamental problem of olfaction is that it is a multistep process. The combinatorial nature of smell recognition and the still barely understood role of the brain in decoding the olfactory signal have left great barriers for scientists to surmount before the mystery of smell is totally solved.

The anatomical and biochemical approach outlined in the present article ignores many other aspects of olfaction: the psychology, sociology and anthropology of smell, the effect of age and disease on odor recognition, and the sister fields of aromascience and aromatherapy. The study of human odor recognition will keep researchers busy for many more years, and may someday provide the key to unlock a treasure trove of opportunities for new consumer uses of fragrance.

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A Note on Bibliography

The complete bibliography all the items specifically used in preparing this article includes the numbered references, the essential studies and reviews listed under "For Additional Reading," and finally a selection of currently available web addresses. The research in olfaction is ongoing, and books are generally far less useful than current peer-reviewed journals and reliable academic and commercial web sites.

For an indispensable account of the discovery of the structure of DNA, see James Watson's book, available in a critical edition with added commentary and the original scientific papers. J Watson, *The Double Helix*, GS Stent, ed, New York: Norton (1980)

A good popular account of the genome and the importance of recent developments in genetics is available in Matt Ridley's book. M Ridley, *Genome: The Autobiography of a Species in 23 Chapters*, New York: Harper (1999) (Perennial paperback 2000)

Some of the introductory material mentioned in this article appeared, in slightly different form, in my book from earlier this year. SJ Herman, *Fragrance Applications: A Survival Guide*, Carol Stream, Illinois: Allured Publishing (2002)

Web sites are not necessarily permanent, although many of the sites mentioned here are associated with organizations that should be online for the foreseeable future. The logical way to learn more about the subject and to keep abreast of new developments is to use a good search engine, such as Google, and search terms like "olfaction", "olfactory receptor", "G-protein receptors" or "vomeronasal organ". Many researchers have their papers available online, or will send PDF files of their work if a request is made. PubMed is a useful tool, but while the abstracts are free, there is a fee for the complete papers.

www.leffingwell.com is the best commercial site. ■ www.gene.ucl.ac.uk/nomenclature/ is the site for HUGO Gene Nomenclature Committee. ■ http://bioinformatics.weizmann.ac.il/HORDE/ offers The Human Olfactory Receptor Data Exploratorium. ■ http://senselab.med.yale.edu/senselab/ is the site for the SenseLab at Yale. ■ http://www.csa.com/crw/home.html is the site for the Chemoreception Web. ■ http://www.achems.org/ is the site for the Association for Chemoreception Sciences. ■ http://www.hhmi.org/senses/ is the site for the Howard Hughes Medical Center. ■ http://mgddk1.niddk.nih.gov:8000/GPCR.html is the G Protein-Coupled Receptor main page. ■ http://neuro.fsu.edu/research/vomer.htm#I is Florida State University's site on the vomeronasal organ. ■ http://www.macalstr.edu/~psych/whathap/UBNRP/Smell/smell.html is the neuroscience site at Macalester College. ■ http://www.monell.org/ presents findings from the Monell Chemical Senses Center.

Another way to keep abreast of progress in the field is to follow the work of the key researchers. Once again, a good search engine can quickly lead to the work of these people: Richard Axel; Linda Buck; Doren Lancet; Stuart Firestein; Peter Mombaerts; Randall Reed; Gordon Shepard; Michael Singer.

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