Genetics of Chemosensory Transduction: Taste and Smell
Dr. Leslie Vosshall

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Danger
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Rodent taste


Fly taste

J. Carlson, R. Axel, K. Scott, H. Amrein, T. Takei, C. Montell, M. Walsh, and others

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Problems the nose has to solve

- What compound(s)?
- What concentration?
- How does it change over time?

Gas chromatogram

>200 volatile compounds = Lemon
Early theories of olfaction:
Ferroelectric transduction


Early theories of olfaction: vibration

Vibrations

Wright

Dyson

Turin

Rotation
Early theories of olfaction: shape

Fig. 1. Empirical, structural and stereochemical formulae of d-camphor, hexachloroethane and trinitroacetonitrile (reproduced by permission of the Toilet Goods Association).

Fig. 2. The human olfactory receptor sites, corresponding with the seven primary odours: A, ethereal; B, camphoraceous; C, musky; D, floral; E, pepperminty; F, pungent; G, putrid (reproduced by permission of the Perfumer and Essential Oil Record).

Amoore, Nature 198, 28 (1963)

Pace et al., Nature 316, 29 (1985)
Vertebrate OR signal transduction

Vertebrate odorant receptors are G protein-coupled 7 transmembrane domain receptors


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A combinatorial code for odor perception?

Malnic et al., Cell 96:713, 1999

Organization of the vertebrate olfactory system


1 odorant receptor: 1 olfactory neuron
1 olfactory neuron type: 1 glomerulus
Zones on olfactory epithelium
Chemotopy in olfactory bulb

Johnson and Leon, J. Comp. Neurol. 422:496, 2000

rostral caudal

Johnson and Leon, J. Comp. Neurol. 422:496, 2000

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Carvone
Fenchone
2-heptanol


Enantiomers “smell” different to the olfactory bulb


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Smell in insects

Malaria
- Mosquito-borne disease
- Infects 400 million people per year
- Kills 1.5 million people per year
- Children younger than 4 most vulnerable

Insect vectors choose human hosts primarily through their sense of smell

Fruit flies (Drosophila melanogaster)
- Genome sequenced 1999
- All odorant receptors cloned 1999-2000
- Wiring pattern of these neurons into the brain 2000-2005
- Odor response profiles of most are known 2006
- Identification of volatile pheromones - still to be done
- Understanding how the brain processes odors - still to be done (!)
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- Multi-transmembrane domain proteins
- Multi-gene family
- Enriched in olfactory neurons

J. Carlson, R. Axel, A. Chess 1999

Drosophila odorant receptors

Food odor
CO₂
Pheromones

J. Carlson, R. Axel, L. Vosshall, B. Dickson, D. Smith and others

Hallem et al., 2006

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Expression of odorant receptors

An olfactory map in the fly brain

Adapted from Heisenberg, 2003

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Maxillary Pulp DrX ➔ Gal4
UAS-synaptobrevin-GFP

Fishilevich & Vosshall, Current Biology 2005

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Fishilevich & Vosshall, Current Biology 2005

Lin et al., Cell 128:1205-1217, 2007

Jefferis et al., Cell 128:1187-1203, 2007

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Spatial (identity) coding

Distributed coding

Experiment 1: only VA7I ORNs stimulated
Experiment 2: only VM7 ORNs stimulated

Conventional odorant receptor gene expression

Or43a Or22a
**Or83b** is broadly expressed

**Or83b** is co-expressed with conventional odorant receptors

Rapid evolution of conventional insect odorant receptors

**Or83b Or22a Merge**

Mosquito specific

24% Identical

77% Identical

Hill et al. 2002

77% Identical

24% Identical

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Or83b homologues are also broadly expressed in most olfactory neurons

Fruit fly
D. melanogaster

Medfly
C. capitata

Mosquito
A. gambiae

Moth
H. zea

Or83b is strongly conserved in different insect species

Or83b is conserved across 450 million years
Unique properties of Or83b

- Highly conserved across millions of years of evolution
- Broadly expressed in most olfactory neurons
- Co-expressed with conventional odorant receptors

Models of Or83b function

- Receptor for an important universal odorant
- Modulator of odorant receptor function
- Co-receptor for conventional odorant receptors

Wild type Or83b mutant

Larsson et al. Neuron 2004
Electroantennograms record the activity of multiple olfactory neurons simultaneously.

Or83b\(^{-}\) mutant antennae do not respond to odors.

Single sensillum recordings reveal responses of 1-4 olfactory neurons in one sensillum.
Odor-sensitive olfactory neurons are silent in Or83b−/− flies

Normal fly larva

Or83b mutant fly larva

Conventional odorant receptors fail to localize in the absence of Or83b

OR22a immunostaining
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Models of OR83b function

- Receptor for an important universal odorant
- Modulator of OR function
- Co-receptor for typical ORs

Or83b orthologues are interchangeable across insect species

Or83b orthologues are interchangeable across insect species
Fly odorant receptors are divergent membrane proteins unrelated to G protein-coupled receptors

Benton et al., PLoS Biol. 2006

Insect odorant receptors are seven transmembrane proteins with atypical membrane topology

Benton et al., PLoS Biol. 2006

Mapping odorant receptor topology with antibody epitopes

Benton et al., PLoS Biol. 2006
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Confirming topology prediction by immuno-electron microscopy

Benton et al., PLoS 2006

Olfactory signal transduction strategies

Mammals

Nematodes

Insects

Reconstituting insect smell in *Xenopus* oocytes
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**Drosophila odorant receptors generate ligand-dependent inward cation currents**

- OR47a
- OR83b
- OR47a
- OR83b

- Cyclohexanol 1 mM
- Pentyl acetate 1 mM

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**Odor-evoked cation currents are ligand- and odorant receptor specific**

- GPROR1/GPROR7
- GPROR2/GPROR7

- 4-MP 0.1 µM
- 4-MP 1 µM
- 4-MP 10 µM
- 2-MP 0.1 µM
- 2-MP 1 µM
- 2-MP 10 µM

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**Models of insect olfactory signal transduction**

- Second messenger cascade gates ion channels
- Receptor coupled directly with ion channels
- Direct odor-gated ion channels
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