Elements of Olfactory Reception in Adult *Drosophila melanogaster*

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ABSTRACT

The olfactory system of *Drosophila* has become an attractive and simple model to investigate olfaction because it follows the same organizational principles of vertebrates, and the results can be directly applied to other insects with economic and sanitary relevance. Here, we review the structural elements of the Drosophila olfactory reception organs at the level of the cells and molecules involved. This article is intended to reflect the structural basis underlying the functional variability of the detection of an olfactory universe composed of thousands of odors. At the genetic level, we further detail the genes and transcription factors (TF) that determine the structural variability. The fly's olfactory receptor organs are the third antennal segments and the maxillary palps, which are covered with sensory hairs called sensilla. These sensilla house the odorant receptor neurons (ORNs) that express one or few odorant receptors in a stereotyped pattern regulated by combinations of TF. In addition, perireceptor events, such as odor molecules transport to their receptors, are carried out by odorant binding proteins. Also, the rapid odorant inactivation to preclude saturation of the system occurs by biotransformation and detoxification enzymes. These additional events take place in the lymph that surrounds the ORNs. We include some data on ionotropic and metabotropic olfactory transduction, although this issue is still under debate in Drosophila. Anat Rec, 00:000-000, 2013. © 2013 Wiley Periodicals, Inc.

Key words: olfactory receptor organs; antenna; maxillary palps; olfactory reception; drosophila; odorant receptors; odorant binding proteins; olfactory transduction

Drosophila melanogaster is one of the most important model organisms in genetic and neurobiological studies. The olfactory system of Drosophila allows the flies to detect a wide variety of volatile chemicals that are

important for finding food, mates and oviposition sites. Despite being simpler that the olfactory system of vertebrates, the *Drosophila* olfactory system follows the same organizational principles (Stocker, 2001; Vosshall and

Grant sponsor: Spanish Ministry of Education and Science; Grant number: BFU2005–04525; Grant sponsors: Spanish Ministry of Science and Innovation and FEDER Funds; Grant number: BFU2008-01256; Grant sponsor: PCTI (Asturias regional government); Grant number: POST07–28 (F.M.); T.B. is a predoctoral FPU fellow sponsored by Spanish Ministry of Education and Science.

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Received 5 June 2013; Accepted 18 June 2013.

DOI 10.1002/ar.22747

Published online 00 Month 2013 in Wiley Online Library (wiley onlinelibrary.com).

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In recent years, important progress in the study of the olfactory system of *Drosophila* has been achieved by combining several neurogenetic tools with neurophysiological, anatomical, and behavioral assays. Thus, the sequencing of the whole genome of *Drosophila* allowed researchers to identify the main family of odorant receptor genes, the ORs (Clyne et al., 1999b; Gao and Chess, 1999; Vosshall et al., 1999). The investigation of OR expression patterns (Gao et al., 2000; Vosshall et al., 2000; Couto et al., 2005) and odorant response profiles, obtained either by the ectopic expression in an empty neuron (Hallem et al., 2004; Hallem and Carlson, 2006) or directly in the native ORNs by electrophysiological assays (Clyne et al., 1997; de Bruyne et al., 2001) has produced a large amount of information about the elements of olfactory reception in *Drosophila*.

In this review, we will focus on the anatomy of the adult olfactory system of *Drosophila* at the receptor level. We will describe the olfactory receptor organs and the olfactory sensilla types, components and distribution. Then, we will summarize the classes of olfactory receptor neurons as defined by the molecular receptors that they express. We will also introduce the transcription factors (TF) that have been implicated in their expression. Finally, the expression of other elements that are involved in olfactory reception will be discussed. We will distinguish the elements that are involved in perireceptor events, that is, the events that are involved in the making the odors accessible to the molecular receptors and the receptor events that follow detection of the odors.

GENERAL ANATOMY OF THE ADULT OLFACTORY RECEPTOR ORGANS IN DROSOPHILA

The olfactory receptor organs in *Drosophila* (Shanbhag et al., 1999) are situated in the anterior part of the head as in all other higher animals. There are two couples of bilateral olfactory organs, the third antennal segments and the maxillary palps (Fig. 1). The antenna has three segments: the first segment that joins it to the head, a second segment that houses the Johnston's organ with auditory and mechanosensory functions, and the third segment, or funiculus, that is, the main olfactory receptor organ. The third segment has a multichambered cavity that opens to the posterior surface, the sacculus, and near the lateral edge, a feathered

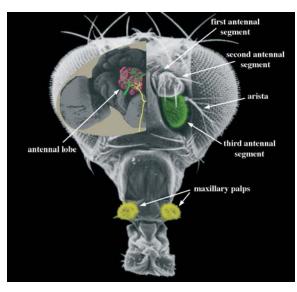


Fig. 1. The olfactory receptor organs in *Drosophila*. The third antennal segments (green) and the maxillary palps (yellow) are the olfactory organs in *Drosophila*. The ORNs of these two organs send their axons to glomeruli in the AL (magenta).

arista with a triangular section (Fig. 1). The maxillary palps have a club shape; they insert into the base of the proboscis and are hidden between the head and the proboscis at rest and during flight (Fig. 1; Shanbhag et al., 1999).

Both olfactory organs, the third antennal segments and the maxillary palps, are covered by special innervated hairs with porous walls, called sensilla, along with other noninnervated hairs, called spinules (Fig. 2A) There are ~400 sensilla in each antenna and 60 in each maxillary palp, and each sensillum houses between 1 and 4 ORNs. Hence, there are ~1200 ORNs in each antenna and 120 in each palp (Vosshall and Stocker, 2007). From the functional point of view, it has been proposed that antennae and maxillary palps mediate 90% and 10% of the olfactory information, respectively (Charro and Alcorta, 1994).

In the antenna, the axons of the ORNs join together into three principal fasciae and project, along with auditory fibers, from the second antennal segment and hydro- and thermo-sensorial fibers from the arista in the antennal nerve. These olfactory fibers are wrapped with two types of glia, central and peripheral; these glia have different origins, either migrating into the antenna from the brain or from a sensory lineage, respectively. The central glia tightly ensheathes the olfactory fascicles and the peripheral glia form a second layer on top and also wrap the ORN bodies (Sen et al., 2005). The antennal olfactory neurons' axons project into the glomerulus of the AL in the brain. The maxillary palp ORNs also terminate in the AL following the labial nerve and projecting there through the sub esophageal ganglion (Vosshall and Stocker, 2007).

SENSILLA TYPES AND COMPONENTS

As we stated above, *Drosophila* ORNs are located in the bases of special hairs called sensilla. In these

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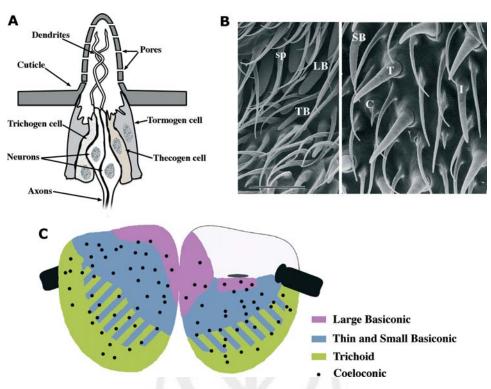


Fig. 2. Sensilla structure, morphological types and distribution. **A**: Structure and components of typical sensilla. **B**: Morphological types of sensilla. LB: Large basiconic. TB: Thin basiconic. SB: Small basiconic. T: Trichoid. C: Coeloconic. I: Intermedia. sp: spinules. **C**: Sensilla distribution in the anterior (left) and posterior (right) part of the third antennal segment.

sensilla (Fig. 2A), the cuticle is porous to allow the odors to enter a central cavity that is full of aqueous lymph. Each sensillum contains one to four ORNs. Their dendritic branching is embedded in this lymph. Three auxiliary cells surround the ORN bodies. The outermost, or tormogen, cell is in contact with the cuticle and the epidermal cells, while the other two, the trichogen and the thecogen cells, are in close contact with the neurons. These three cells form the border of the sensillum cavity and display a large number of microvilli (Shanbhag et al., 2000).

The sensilla in Drosophila can be classified into three major groups based on morphology (Fig. 2B). The first group, the basiconic sensilla, are club-shaped sensilla; they have a thin cuticle and contain between 2 and 4 ORNs in their base. There are 3 subtypes of basiconic sensilla in the antenna that are based on their length and thickness: large, thin, and small. A fourth subtype of basiconic sensilla is present exclusively in the maxillary palps. The second group is composed of the trichoid sensilla; they have a needle shape, thick walls, and contain between 1 and 3 neurons. The third major group is the coeloconic sensilla; they are small, fin-shaped, double-walled, and contain 2 or 3 ORNs (Shanbhag et al., 1999). There is a fourth group with only 10-20 sensilla per antenna, the intermedia sensilla; their shape is between that of the basiconic and trichoid sensilla, and they have two or three neurons. Only basiconic sensilla are present in the maxillary palp. Every sensillum in the palp houses two different neurons that are always

paired together in three distinct functional sensilla classes (de Bruyne et al., 1999).

In the antenna, the large, small, and thin basiconic and trichoid sensilla are arranged in a stereotyped and symmetric stripped pattern (Fig. 2C). The large basiconic sensilla are clustered in the dorsomedial part, the small and thin basiconic sensilla are clustered in the central part, and the trichoid sensilla are clustered in the ventrodistal part of the antenna. The coeloconic sensilla are distributed along the whole antennal segment (Shanbhag et al., 1999). It is known that, during antenna development, the morphological sensilla classes arise in the pupae from the eye-antenna imaginal disc due to the action of a combination of proneural and helix-loop-helix TF (Fuss and Ray, 2009). Thus, the atonal TF is necessary for the development of the antennal coeloconic and palp basiconic sensilla (Gupta and Rodrigues, 1997), and amos is required for antennal basiconic and trichoid sensilla (Goulding et al., 2000; zur Lage et al., 2003).

OLFACTORY RECEPTOR NEURONS

Genetic, functional and expression studies performed in *Drosophila* have identified all the different ORN classes present in adults. Extracellular recording in single sensilla has revealed that the ORNs in the palps fall into six functional classes (de Bruyne et al., 1999).

Similar studies that have been performed in the basiconic and coeloconic sensilla in the antenna have MARTIN ET AL.

established several functional classes of ORNs (de Bruyne et al., 2001; Yao et al., 2005). However, it was the discovery of the odorant receptors and analyses of their function and expression that revealed all the ORN classes.

The odorant receptors in Drosophila can be divided into two main families with different molecular structures, expression patterns, and odorant reception profiles. These receptors follow the rule that only one or few of them are expressed in a given ORN (Vosshall et al., 2000), similar to what is observed in vertebrates (Buck, 2000). The first family (ORs) has seven transmembrane domains and is distantly related to the G protein-coupled receptor (GPCR) family, as are the odorant receptors of vertebrates (Clyne et al., 1999b; Gao and Chess, 1999; Vosshall et al., 1999). However, these Drosophila odorant receptors have an inverted topology relative to other GPCRs (Benton et al., 2006). There are 60 genes of this class in the genome of Drosophila that encode for 62 receptors, 45 of which are expressed in the adult antenna and palp (Couto et al., 2005). One of these OR genes, orco, is coexpressed with the rest of the members of the family (forming an heterodimer odorant receptor) and is essential to their subcellular expression and function (Larsson et al., 2004). Transgenic expression of these OR genes in the so-called "empty neuron" expression system allowed assignment of many of them to a particular functional group of ORNs (Hallem and Carlson, 2006). Expression studies of these genes have shown that the members of this family are expressed mainly in basiconic and trichoid sensilla, with the exception of one that is expressed in coeloconic sensilla (Couto et al., 2005).

In summary (Table 1), 45 members of this family and 3 members of the related family of gustatory receptors (GR) have been mapped to 39 ORN classes that innervate 19 distinct and stereotyped sensilla (Couto et al., 2005; Ronderos and Smith, 2009). The sensillum subtypes inferred from these expression studies comprise 3 large antennal basiconic (ab1 to ab3), 3 thin antennal basiconic (ab4 to ab6), 4 small antennal basiconic (ab7 to ab10), 3 thin palp basiconic (pb1 to pb3) and 4 trichoid (at1 to at4) sensilla subtypes. Every basiconic sensillum is innervated by 2 ORNs (a and b), except ab1, which houses 4 ORNs (ab1a, ab1b, ab1c and ab1d). ab1c neurons express 2 GRs, Gr21a, and Gr63a, and are involved in CO₂ sensing (Jones et al., 2007; Kwon et al., 2007). By contrast, in the trichoid sensilla, at 1 is innervated by only 1, at2 by 2, and at3 and at4 by 3 ORNs. One member of this family, Or13a, is expressed in one of the neurons of the intermediate sensilla. Or35a is the only ORgene that is expressed in the coeloconic sensilla of the ac2b neuron (Couto et al., 2005; Yao et al., 2005).

A second family of odorant receptors, the ionotropic receptors (IR), which are related to the ionotropic glutamate receptor (iGluRs) family, was recently found in *Drosophila* (Benton et al., 2009). This family is composed of 61 different genes, but only 14 of them are present in the antennal coeloconic sensilla (Benton et al., 2009; Abuin et al., 2011; Silbering et al., 2011). Confirming previous functional data (Yao et al., 2005), a study of the expression of these genes has resolved four distinct coeloconic classes (ac1 to ac4; Benton et al., 2009; Silbering et al., 2011) each housed by three ORNs, except for ac2, that only contains two ORNs.

Taking the expression data from both odorant receptor families in the adult receptor organs together, there are 22 sensilla subtypes, 19 in the antenna and 3 in the palp that are innervated by 49 ORN classes that express one or a few specific odorant receptors.

The expression studies carried out on both types of receptors have permitted the generation of a complete ORN projection map in the 49 glomeruli of the AL. Every ORN that expresses a particular odorant receptor projects to the same glomerulus (Couto et al., 2005; Silbering et al., 2011; Table 1). There is a spatial organization in which the afferents from the ORNs innervating each sensilla class project to glomeruli in the same location in the AL. Thus, ORNs in the antennal basiconic sensilla project to the medial region of the AL, palp basiconic sensilla project to the central-medial region, antennal trichoid sensilla project to the lateral anterior region, and antennal coeloconic sensilla project to the posterior region (Couto et al., 2005).

The control of this stereotyped OR expression in the ORNs is still under study. Several TF have been implicated in the control of the expression of OR family members in adult olfactory organs (Table 2). Regarding the ORs expressed in the palps, five TFs have been implicated in their regulation, thus far (Clyne et al., 1999a; Ray et al. 2007; Tichy et al., 2008; Song et al., 2012). Two recent studies in the antennae have involved nine TFs in the control of OR expression (Jafari et al., 2012, Song et al., 2012). In both studies, the combination of the TFs expressed in a particular ORN determines the expression of ORs. Thus, TFs may be related to the type of sensilla. For example, none of the receptors expressed in the large basiconic sensilla are regulated by E93 and dachshund. The same is true for the regulation by onecut of the ORs expressed in the thin basiconic sensilla and the regulation of the ORs expressed in the trichoid sensilla by dachshund.

PERIRECEPTOR EVENTS

As mentioned above, the odorant receptors are located in the membrane of the dendrites of the ORNs. These dendrites are embedded in lymph that is in contact with the air through the pores in the cuticle of the sensilla. Thus, the odor molecules need to enter into the aqueous lymph to interact with the odorant receptors. Although some odors are soluble in water, many are hydrophobic; therefore, some mechanism is required to allow the odorants to reach their receptors. In most animals, soluble proteins called odorant-binding proteins (OBPs) have been described, although their roles are not yet well understood. Some of these roles are to solubilize odors and transport them through the lymph, protect the odors from enzymatic degradation and produce a complex with the odor that activates the odorant receptors (Laughlin et al., 2008).

In *Drosophila*, there is a large family of OBPs composed of 51 genes (Hekmat-Scafe et al., 2002), and the expression of 35 of these genes has been described in the adult olfactory system (Table 3). The OBPs are located in the sensilla lymph, and they are secreted by the 3 non-neuronal support cells of the sensilla (Shanbhag et al., 2001). Some OBPs are expressed exclusively in the olfactory system, and their expression is further restricted to a particular sensillum class. Thus, Obp19d

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TABLE 1. Organization of the Drosophila olfactory system

Sensillum class	Sensillum subtype	Neuron	Receptor	Coreceptor	Glomerulus
Large Basiconic	ab1	ab1a	Or92a	orco	VA2
_		ab1b	Or42a	orco	DM1
		ab1c	Gr21a, Gr63a		V
		ab1d	Or10a, Gr10a	orco	DL1
	ab2	ab2a	Or59b	orco	DM4
		ab2b	Or33b, Or85a	orco	DM5
	ab3	ab3a	Or22a, Or22b	orco	DM2
		ab3b	Or85b	orco	VM5d
Thin Basiconic	ab4	ab4a	Or7a	orco	DL5
		ab4b	Or33a, Or56a	orco	DA2
	ab5	ab5a	Or82a	orco	VA6
		ab5b	Or33b, Or47a	orco	DM3
	ab6	ab6a	Or85b, Or98b ^a	orco	VM5d
		ab6b	Or49b	orco	VA5
Small Basiconic	ab7	ab7a	Or98a	orco	VM5v
		ab7b	Or67c	orco	VC4
	ab8	ab8a	Or43b	orco	VM2
		ab8b	Or9a	orco	VM3
	ab9	ab9a	Or69aA, Or69aB	orco	D
		ab9b	Or67b	orco	VA3
	ab10	ab10a	Or49a, Or85f	orco	$\mathrm{DL4}$
		ab10b	Or67a	orco	DM6
Intermedia	ai1	ai1	Or13a	orco	DC2
m · 1 · 1			-	_	_
Trichoid	at1	at1	Or67d	orco	DA1
	at2	at2a	Or23a	orco	DA3
		at2b	Or83c	orco	DC3
	at3	at3a	Or2a	orco	DA4m
		at3b	Or19a, Or19b	orco	DC1
	. 4	at3c	Or43a	orco	DA4I
	at4	at4a	Or47b	orco	VA1v
		at4b	Or65a, Or65b, Or65c	orco	DL3
~ .		at4c	Or88a	orco	VA1d
Coeloconic	ac1	ac1a	Ir31a	Ir8a	VL2p
		ac1b	Ir75d	Ir25a	VL1
		ac1c	Ir92a	Ir76b	VM1
	ac2	ac2a	Ir75a	Ir8a	DP1I
		ac2b	Ir75d	Ir25a	VL1
		ac2c	Ir41a	Ir76b	VC5
	ac3	ac3a	Ir75a, Ir75b, Ir75c	Ir8a	$\mathrm{DL}2$
		ac3b	Or35a	orco, Ir76b	VC3
	ac4	ac4a	Ir84a	Ir8a	VL2a
		ac4b	Ir75d	Ir25a	VL2a
		ac4c	Ir76a	Ir76b	VL1
Palp Basiconic	pb1	pb1a	Or42a	orco	VM7
	_	pb1b	Or71a	orco	VC2
	pb2	pb2a	Or33c, Or85e	orco	VC1
		pb2b	Or46aA	orco	VA7I
	pb3	pb3a	Or59c	orco	1
		pb3b	Or85d	orco	VA4

^a: The coexpression of these two OR in ab6a is not yet confirmed.

is expressed in coeloconic sensilla, Obp28a in basiconic sensilla, Obp83a, and Obp83b are expressed both in trichoid and intermedia sensilla, and Obp76a (LUSH) is only expressed in trichoid sensilla (Shanbhag et al., 2001). These OBPs display distinct-odorant-binding specificities, and their deficiency affects the response to specific odorants (Kim et al., 1998, Swarup et al., 2011). For example, LUSH is involved in the reception of alcohols in the trichoid sensilla (Kim et al., 1998) and the cVA pheromone by Or67d in the at1 sensilla (Ronderos and Smith, 2009). There is another element, SNMP, a member of the CD36 family of lipid binding receptors, that

has been implicated in the reception of cVA in *Drosophila* (Benton et al., 2007; Jin et al., 2008). However, there must be additional unknown elements involved in cVA reception, as the expression of Or67d, LUSH, and SNMP in the empty neuron system fail to recapitulate the cVA response in the at1 sensilla (Laughlin et al., 2008).

Recently, an extracellular carboxyl esterase, esterase-6 (est-6), has been implicated in the cVA response (Chertemps et al., 2012). Carboxyl esterases are members of another group of components that are important for olfactory function, the biotransformation or degradation enzymes, which include the cytochrome P-450

^{-:} Data not known.

TABLE 2. TF that regulate the OR expression	TF	Acj6 (Clyne et al., 1999b; E93 Fer1 onecut Sim xbp1 zf30c en dac lozenge pdm3 2007; Jafari Jafa			× ××		
TABLE 2. TI			×× ××	****)r P	100	
		OR	0r92a 0r42b Gr21a Or10a Or59b Or85a Or22a	$egin{array}{c} \mathrm{Ur85b} \\ \mathrm{Or7a} \\ \mathrm{Or56a} \\ \mathrm{Or82a} \\ \mathrm{Or47a} \\ \mathrm{Or85b}^{\mathrm{a}} \end{array}$	Or49b Or98a Or67c Or43a Or69a Or67b Or87c	Or674 Or23a Or23a Or2a Or19a/b Or43a Or47b	Or42a Or71a Or33c, 85e Or46aA Or59c
		Neuron	ab1a ab1b ab1c ab1d ab2a ab2b ab2b	ab3b ab4a ab5a ab5a ab6b	ab6b ab7a ab8a ab8b ab9a ab9b	at1a at2a at2b at3a at3b at3c at4a at4b	pb1a pb1b pb2a pb3a pb3a
		Sensilla type	Large basiconic	Thin basiconic	Small basiconic	Trichoid	Palp Basiconic

 \mathbf{X} : Involvement of the TF in the OR expression. $\vec{-}$: Data not determinated. $^{\mathrm{a}}$: The expression of or85b in ab6a is not yet confirmed. Pink: Negative relationship between a TF and a sensilla type.

TABLE 3. Odorant Binding Proteins expressed in adult olfactory organs

Name	Synonym	Position	Expression	References
Obp19a		19D2	A (Some sensilla)	Galindo and Smith, 2001
Obp19d	Pbrp-2	19D2	A (Some coeloconic), M, O	Pikielny et al., 1994; Galindo and Smith, 2001; Shanbhag et al., 2001
Obp28a	Pbrp-5	28A1	A (Some basiconic)	Pikielny et al., 1994; Galindo and Smith,
				2001; Shanbhag et al., 2001; Anholt and
Obp44a		44A8	A^{b}	Willians, 2010 Anholt and Willians, 2010
Obp44a Obp46a		46F11	A, O ^a	Zhou et al., 2004
Obp40a Obp47b		47E5	A, O ^a	Zhou et al., 2004 Zhou et al., 2004; Anholt and Willians, 2010
Obp49a		49B9	A, O ^a	Zhou et al., 2004, 74moit and Williams, 2010
Obp50a		50F6	A, O ^a	Zhou et al., 2004 Zhou et al., 2004
Obp50b		50F6	A, O ^a	Zhou et al., 2004 Zhou et al., 2004
Obp50c		50F6	A, O ^a	Zhou et al., 2004
Obp50d		50F6	A, O ^a	Zhou et al., 2004
Obp50e		50F6	A O ^a	Zhou et al., 2004
Obp56a		56E2	A, O ^a A ^b	Anholt and Willians, 2010
Obp56c		56E2	A(Some sensilla), O	Galindo and Smith, 2001
Obp56d		56E2	A (All sens), M (all sens), O	Galindo and Smith, 2001; Shanbhag et al., 2001; Hekmat-Scafe et al., 2002; Anholt
01 70		K ATTO	1/G 371 \ O	and Williams, 2010
Obp56e		56E2	A(Some sensilla), O	Galindo and Smith, 2001; Anholt and Willians, 2010
Obp56h		56E4	A(Some sensilla), O	Galindo and Smith, 2001
Obp57a		57A4	A (Some sens), M (Some sens)	Galindo and Smith, 2001
Obp57b		57A4	A (Some sens), M (Some sens), O	Galindo and Smith, 2001
Obp57c		57A4	A (All sens), M (all sens), O	Galindo and Smith, 2001
Obp58b		59A3	A, O ^a	Zhou et al., 2004
Obp58c		59A3	A	Zhou et al., 2004
Obp59a		59A3	A^{b}	Anholt and Willians, 2010
Obp69a	Pbprp-1	69B2	A (Some sensilla)	Pikielny et al., 1994; Galindo and Smith, 2001; Anholt and Willians, 2010
Obp76a	LUSH	76B9-C1	A (trichoid)	Kim et al., 1998; Galindo and Smith, 2001;
•				Shanbhag et al., 2001; Zhou et al., 2004; Anholt and Willians, 2010
Obp83a	OS-F, Pbrp-3	83C8-D1	A(Trichoid., intermediate)	Pikielny et al., 1994; McKenna et al., 1994; Shanbhag et al., 2001; Anholt and Willians, 2010
Obp83b	OS-E	83D1	A(Trichoid., intermediate)	McKenna et al., 1994; Shanbhag et al., 2001; Anholt and Willians, 2010
Obp83cd		83D4	A, O ^a	Zhou et al., 2004
Obp83ef		83D4	A, O ^a	Zhou et al., 2004
Obp84a	Pbprp-4	84C7	A (Some sensilla)	Pikielny et al., 1994; Galindo and Smith, 2001; Anholt and Willians, 2010
Obp85a		85A1	A, O ^a	Zhou et al., 2004
Obp93a		93C1	A, O ^a	Zhou et al., 2004
Obp99b		99B10	A (Some sens), M (Some sens)	Galindo and Smith, 2001; Anholt and Willians, 2010
Obp99c		99B11	A^{b}	Anholt and Willians, 2010
Obp99b		99C1	A^{b}	Anholt and Williams, 2010

A: expression in the antenna; M: expression in the maxillary palp; O: other chemosensory organs.

monooxygenases, the UDP-glucuronosyltransferases, and the glutathione-S-transferases. These enzymes have been described in the mucus surrounding the olfactory neuron cilia in vertebrates (Breer, 2003) and in the sensillum lymph of invertebrates (Rogers et al., 2001). The function of these enzymes is the rapid inactivation of odorants to preclude saturation of the olfactory system. In *Drosophila*, several studies have reported the preferential expression of these enzymes in olfactory organs (Wang et al., 1999; Anholt and Williams, 2010; Chertemps et al., 2012).

OLFACTORY TRANSDUCTION

Once the odor joins an odorant receptor, the chemical signal is transformed into an electrical signal in the ORN and transmitted to the second order neurons in the AL. In the case of the IR family of odorant receptors, (which are themselves ionic channels), binding of the odorant produces a conformational change that opens the channel, which triggers the electric signaling. However, there is still controversy about the transduction pathway of the OR family. As shown above, the ORs

<sup>a: may include maxillary palps.
b: only antennal expression was investigated.</sup>

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have seven transmembrane domains, as do other metabotropic receptors including the odorant receptors of vertebrates. However, fly's ORs form a heterodimer with the Orco coreceptor and have an inverted topology relative to other GPRCs, that is, the N-terminus is on the inside of the cell, and the C-terminus is on the outside (Benton et al., 2006, Lundin et al., 2007). Furthermore, several studies have reported that OR-Orco heterodimers transfected into heterologous systems can act as ionotropic channels (Sato et al., 2008; Smart et al., 2008; Wicher et al., 2008, 2009). However, one of these studies also reported a metabotropic component that is dependent on G proteins (Wicher et al., 2008). This metabotropic component in the function of the OR-Orco heterodimers has been either supported (Kain et al., 2008; Chatterjee et al., 2009; Deng et al., 2011) or argued against (Yao and Carlson, 2010) in several studies of genetically modified flies with mutated G proteins. Recently, it has been reported that the activity of Orco is regulated by phosphorylation via protein kinase C (PKC), which is activated by the inositol 1,4,5-triphosphate/diacyl glycerol (IP3/DAG) transduction cascade (Sargsyan et al., 2011 commented in Martin and Alcorta, 2011). Two hypotheses have been proposed to explain these results: (A) it is possible that the insect ORs may be mixed ionotropic-metabotropic receptors (Wicher, 2010), or (B) alternatively, insect ORs may be metabotropically modulated ionotropic receptors (Nakagawa and Vosshall, 2009).

Despite their disputed implication in the olfactory function, many elements of the two metabotropic transduction cascades, IP3/DAG and cyclic adenosine monophosphate (cAMP), have been reported to be expressed in the olfactory organs of *Drosophila*. A systematic study of the expression of all known variants of each G-protein subunit in *Drosophila* showed that almost all of variants are expressed in the olfactory organs in a generalized F3 pattern (Boto et al., 2010; Fig. 3). Nevertheless, the G proteins are expressed in the ORNs, as observed by the double labeling of Gs or Gi with Orco, which is expressed in basiconic and trichoid sensilla, or Or47b, which is expressed in one of the trichoid sensilla (at4). Further, the presence of both Gs and Gi has been observed in the dendrites of the ORNs.

Related to the cAMP transduction cascade there are functional studies that support the involvement of Gs in olfactory reception in Drosophila (Wicher et al., 2008; Deng et al., 2011; Sargsyan et al., 2011). In addition to the G alpha units (Gs and Gi) that control the cAMP cascade, (Boto et al., 2010), there are additional components expressed in the olfactory organs. Thus, the expressions of an adenylyl cyclase (rut) and a cAMP phosphodiesterase (dnc), the enzymes that produce and degrade cAMP, have been reported in the antenna (Martin et al., 2001). Mutations of rut and dnc produce defective behavioral and electrophysiological olfactory phenotypes (Martin et al., 2001; Gomez-Diaz et al., 2004). Furthermore, a cyclic nucleotide-gated channel (cng) activated by cAMP has been described in Drosophila olfactory organs (Baumann et al., 1994).

Likewise, there is evidence of the expression and functional significance of several elements of the IP3/DAG transduction cascade in the olfactory reception of *Drosophila*. The expression of Gq (the alpha subunit that activates this pathway) has been reported (Talluri et al.,

1995; Kalidas and Smith, 2002; Boto et al., 2010), and mutants of this gene exhibit a reduced odor response (Kain et al., 2008). Two different phospholipase-C-βs (PLC\u00eds), the enzymes that break down phosphoinositol 4,5 bisphosphate (PIP2) and produce IP3 and DAG, are expressed and have functional relevance in the antenna (Plc21c; Kain et al., 2008) and the maxillary palp (norpA; Riesgo-Escovar et al., 1995). Additionally, elements that are activated by IP3 or DAG are expressed in the olfactory receptor organs. For example, there is a receptor of IP3 expressed in the antenna (itpr; Hasan and Rosbash, 1992; Yoshikawa et al., 1992) that is required for olfactory adaptation (Deshpande et al., 2000). Furthermore, as we discussed above, DAG activated PKC affects the activity of Orco (Sargsyan et al., 2011). Proteins of this pathway involved in the inactivation of IP3 and DAG are also involved in Drosophila olfaction. For example, the over-expression of an IP3 kinase (IP3K1) in the antenna produces altered olfactory behavior (Gomez-Diaz et al., 2006). The expression of IP3K1 was studied using in situ hybridization with mRNA probes, which showed that it is expressed in a generalize pattern in the antenna (Fig. 4). IP3K1 is present in the ORNs as demonstrated by colocalization with antiorco probes, but it is also present in many nonneuronal cells in the antenna. Similarly, a DAG kinase (rdgA) has been shown to be involved in olfactory reception (Kain et al., 2008) and the visual system of the fruit fly (Hardie et al., 2002). This DAG kinase is one of the five variants $(rdgA, Dgk\epsilon, DgkD, Dgk, and DgkT)$ described in the Drosophila genome. The expression of these five genes was studied using RT-PCR to examine the expression of their mRNAs in the antenna, maxillary palp, and retina (Fig. 5). As shown in Fig. 5, rdgA and $Dgk\varepsilon$ are expressed in the three organs (the same is true for Dgk and DgkT, not shown), while DgkD is expressed in the antenna and retina but not in the maxillary palps. Finally, another element of this transduction pathway, a phosphatidylinositol transferase (rdgB) that participates in the regeneration of PIP2, is involved in the olfactory system (Woodard et al., 1992). Together, these data show the important role that the metabotropic transduction pathways have in the olfactory function of Drosophila, although the extent of their mechanisms has yet to be determined.

CONCLUDING REMARKS

The olfactory system of *Drosophila melanogaster* is capable of detecting a wide variety of volatile chemicals that are important for finding food, mates, and oviposition sites. Despite being simpler than the olfactory systems of vertebrates, the fly olfactory system follows the same organizational principles. At the receptor level, the olfactory system consists of specific elements and other common elements that capture chemical signals and transform them into electrical signals that are sent to the brain.

Two molecular olfactory receptor families are known in *Drosophila*, the ORs and IRs. Each receptor has specificity for a subgroup of odors; some are fine-tuned for a few odorants, and others are broadly tuned for many odorants but all of them contribute to the combinatorial coding (de Bruyne et al., 2001; Hallem and Carlson, 2006; Silbering et al., 2011). Although absolute

F4

F5

AQ1

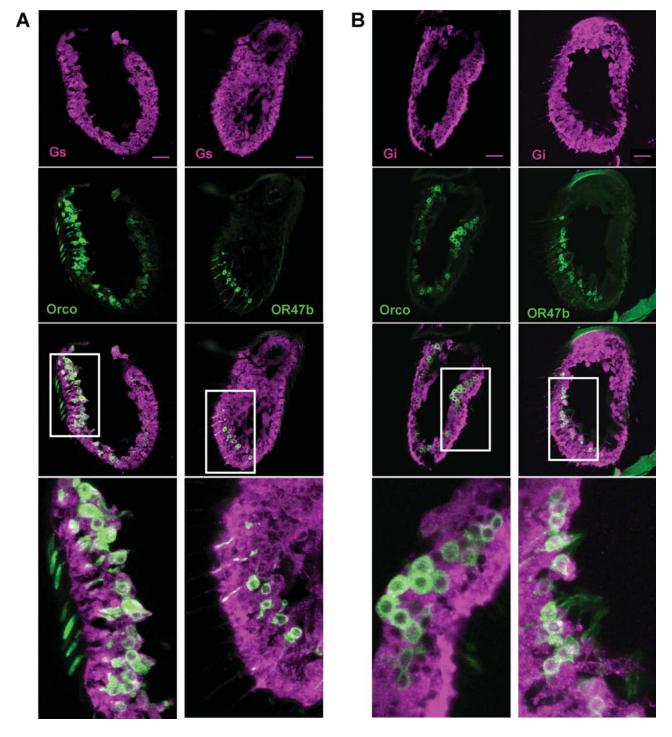


Fig. 3. Immunostaining of several G proteins in third anntenal segments. Magenta corresponds to the Galpha subunits and green staining represents GFP expression in different ORN types. **A**: left, immunolocalization of Gs and Orco; right: immunolocalization of Gs and OR47b (ORN in trichoid sensillum at4). **B**: left, immunolocalization of Gi and OR47b. Complete colocalization of the G proteins and each odorant receptor is highlighted in the details. Scale bars: 20 μm.

specificity does not occur, except in the case of pheromone receptors, these receptors have a high level of specificity. Other elements of the receptor system, such as the OBPS, show some specificity but also seem to follow a combinatorial model (see for example, Swarup et al., 2011).

In this review, we also mentioned elements of the system that seem to show a more general pattern of

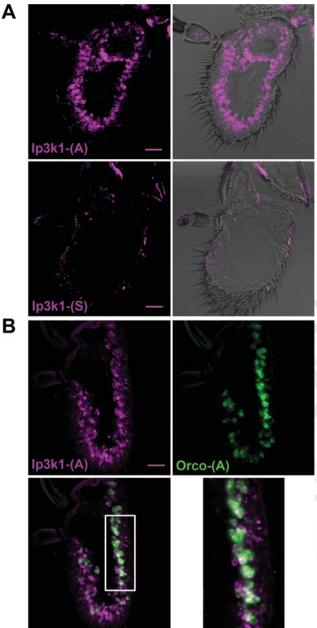


Fig. 4. Ip3k1 mRNA expression in third antennal segments of *Drosophila*. **A**: *In situ* hybridization with antisense (A) and sense (S) Ip3k1 mRNA probe (magenta). **B**: Double *in situ* hybridization with antisense Ip3k1 (magenta) and Orco (green) mRNA probes. Inset shows colocalization examples. Scale bars: 20 μ m.

expression because they appear not only in the olfactory receptor organs but also in other parts of the body and in nonolfactory cell types of the receptor organs. These types of elements include the detoxification enzymes involved in the inactivation and decomposition of odor molecules, for example, P-450 or the glutathione-Stransferases. These molecules appear throughout the evolutionary scale, both in plant and animal species (Wang et al., 1999; Rogers et al., 2001; Anholt and Willians, 2010; Chertemps et al., 2012). Additionally, the



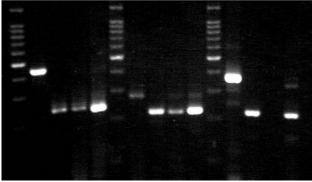


Fig. 5. Expression of three DAG kinase genes in *Drosophila*. RT-PCR expression study of rdgA, $Dgk\varepsilon$, and DgkD. L: Ladder 100 size marker. G: Genomic DNA. A: Antenna. M: Maxillary palp. R: Retina.

intermediate elements of the transduction cascades, including G proteins, show a widespread pattern of expression (Boto et al., 2010).

The use of common elements for different tasks is a common standard in biological systems to spare resources. Thus, the generalized expression of different items cannot be considered by itself as a proof of the nonparticipation in olfactory reception or of a small contribution. Compartmentalization of different tasks inside a cell has been extensively reported. Restriction of signaling molecules within "raft domains" of the plasma membrane has been suggested for GPCRs, G proteins, and effectors (Cooper, 2005) and cyclic nucleotide signaling (Baillie, 2009).

Through functional testing, modification or specific deletion of these items, one can measure the importance of different elements in olfactory reception. Thus, the tools provided by *Drosophila* make this species a particularly suitable model to resolve these issues.

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