REVIEW

Eur J Anat, 11 (2): 123-147 (2007)

Chemical heterogeneity of the periglomerular neurons in the olfactory bulb. A review

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SUMMARY

Periglomerular cells are interneurones that modulate the primary sensory information in the olfactory bulb. It was originally assumed that periglomerular cells constituted a homogeneous GABAergic population in the rat olfactory bulb, but in other species studies addressing this are scarce. However, several authors have shown that this neuronal type exhibits extraordinarily heterogeneous neurochemical features. The aim of this review is to compile and describe in detail the expression patterns of neuronal markers in the rat olfactory bulb, in particular in periglomerular cells, and to compare such information with previous data on other macrosmatic and microsmatic animals. Interspecies differences in the neurochemical composition of periglomerular cells could indicate different modes in the modulation of olfactory information.

Key words: Olfactory bulb – Periglomerular cells – Neurochemical heterogeneity

INTRODUCTION

Smell and taste are the most ancient senses from the phylogenetic point of view (Ache, 1987). Smell is the primary mode of communication for most animals. Nevertheless, both unicellular and multicellular organisms are able to detect and distinguish thousands of chemical compounds at very low concentrations (Macrides and Davis, 1983; Switzer et al., 1985; Shipley and Ennis, 1996). Based on this sensory capacity, animals detect and locate food, mates, predators and prey (Freeman et al., 1999).

Organisms are exposed to a continuous flow of olfactory sensory information. Depending on the chemical signal detected, olfactory information can be processed by at least two different subsystems: the main and the accessory olfactory systems (Allison, 1953; Hoffman, 1963; Moulton and Beidler, 1967). The main olfactory system is involved in general behavioral processes, while the accessory olfactory system is implicated in reproductive signals. Both take part in emotional, social and other adaptative processes (Halász, 1990).

The sensory pathway of the main olfactory system can be summarized as follows: Odorants are detected by sensory receptor neurons located in the olfactory epithelium. Depending on the molecular composition of the odorants, these neurons may be activated in different ways. The stimulus is then transmitted and released from the olfactory nerve (ON)

Submitted: December 20, 2006
Accepted: April 30, 2007

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axons to the olfactory bulb (OB), the first relay synaptic station. The OB comprises *input fibers*, derived from olfactory receptor axons and centrifugal fibers; *interneurons* such as PG, granule cells, and short-axon (SA) cells, and *principal neurons* or *projection neurons*, such as mitral cells and tufted cells. The input fibers, interneurons, and principal neurons constitute the *triad of neuronal elements* (Shepherd and Koch, 1998). The sensory stimulus activates projection neurons, both mitral cells and tufted cells (Allison, 1953). Olfactory information is modulated and refined by interneurons, mainly periglomerular cells (PG) and granule cells, both of which affect the processing of this relay. Then, the sensory signal is transmitted via the lateral olfactory tract from axons of mitral/tufted cells to different regions collectively referred to as secondary olfactory structures (Cleland and Linster, 2003), although formerly known as "primary olfactory cortices" (De Olmos et al., 1978; Haberly, 2001). Finally, without direct synapses in the thalamus, the olfactory information is processed and integrated in non-exclusively olfactory structures (Ngai et al., 1993; Mori and Yoshihara, 1995; Mori et al., 1999).

The OBs are paired, ovoid-shaped structures usually constituting the rostral part of the brain, although in other species such as primates they are located under the ventral surface of the frontal lobes. Based on the size of the OB in comparison with the size of the brain, animals have been classified as macrosmatic, microsmatic or anosmatic (Turner, 1891). Macrosmatic species such as rodents have large OBs as compared to their brains. Microsmatic animals such as primates have proportionately smaller OBs in comparison with most other mammals (Smith and Bhatnagar, 2004). Anosmatic animals such as cetaceans have no or only vestigial OBs (Johnson et al., 1994).

The OB is characterized by a laminar organization constituted by seven concentric layers that from the surface to the inner parts are:

- Olfactory nerve layer (ONL)
- Glomerular layer (GL)
- External plexiform layer (EPL)
- Mitral cell layer (MCL)
- Internal plexiform layer (IPL)
- Granule cell layer (GCL)
- White matter (WM)

One of the most distinctive structures of the OB is the olfactory glomerulus. Olfactory glomeruli are complex spherical structures of highly organized neuropil, surrounded by glial cells and different types of interneurons (Pinching and Powell, 1971a). Depending on the species, glomeruli vary from 30 to 200 μm in diameter (Kratskin and Belluzzi, 2003) and they are aligned in one or several rows, forming the GL of the OB. In the glomeruli, ON axons make synapses with the dendrites of projection neurons and intrinsic neurons. The glomeruli are functional units in the processing and transmission of olfactory information (Shepherd and Firestein, 1991; Kauer and Cinelli, 1993; Friedrich and Korsching, 1998; Mori et al., 1999). The interneurons that surround the glomeruli are commonly called juxtaglomerular neurons (Pinching and Powell, 1971a) which, based on morphological criteria by Golgi impregnation, have been classified into three types: PG, superficial SA cells and external tufted cells.

Based on the synaptic contacts inside the glomeruli, each glomerulus can be divided into two zones: an ON zone and a non-ON zone. The ON zone comprises preterminals and terminals of the ON axons, which establish excitatory synapses with the dendrites of both interneurons and projection neurons (Kosaka et al., 1995, 1997). The non-ON zone is occupied by dendritic processes of interneurons that establish inhibitory synapses with the mitral/tufted cells and among interneurons (Kosaka et al., 1995, 1997, 1998). PG interneurons mainly establish synapses with projection neurons and other interneurons in the glomeruli.

The aim of this review is to carry out a detailed description of the main characteristics of PG, the most numerous population of juxtaglomerular neurons (Pinching and Powell, 1971a; Halász, 1990) and, in particular, their neurochemical composition.

Periglomerular cells

Initially, Golgi (1875) described PG as glial elements, but in 1892 Kölliker identified them as neurons, naming them "external granular cells". Pinching and Powell (1971a) changed this denomination because it may be confused with the most abundant neurons of the OB, the granule cells; accordingly, they were renamed "periglomerular cells".

Development

In the mouse, OB development begins around embryonic day 12 (E12) (Farbman,

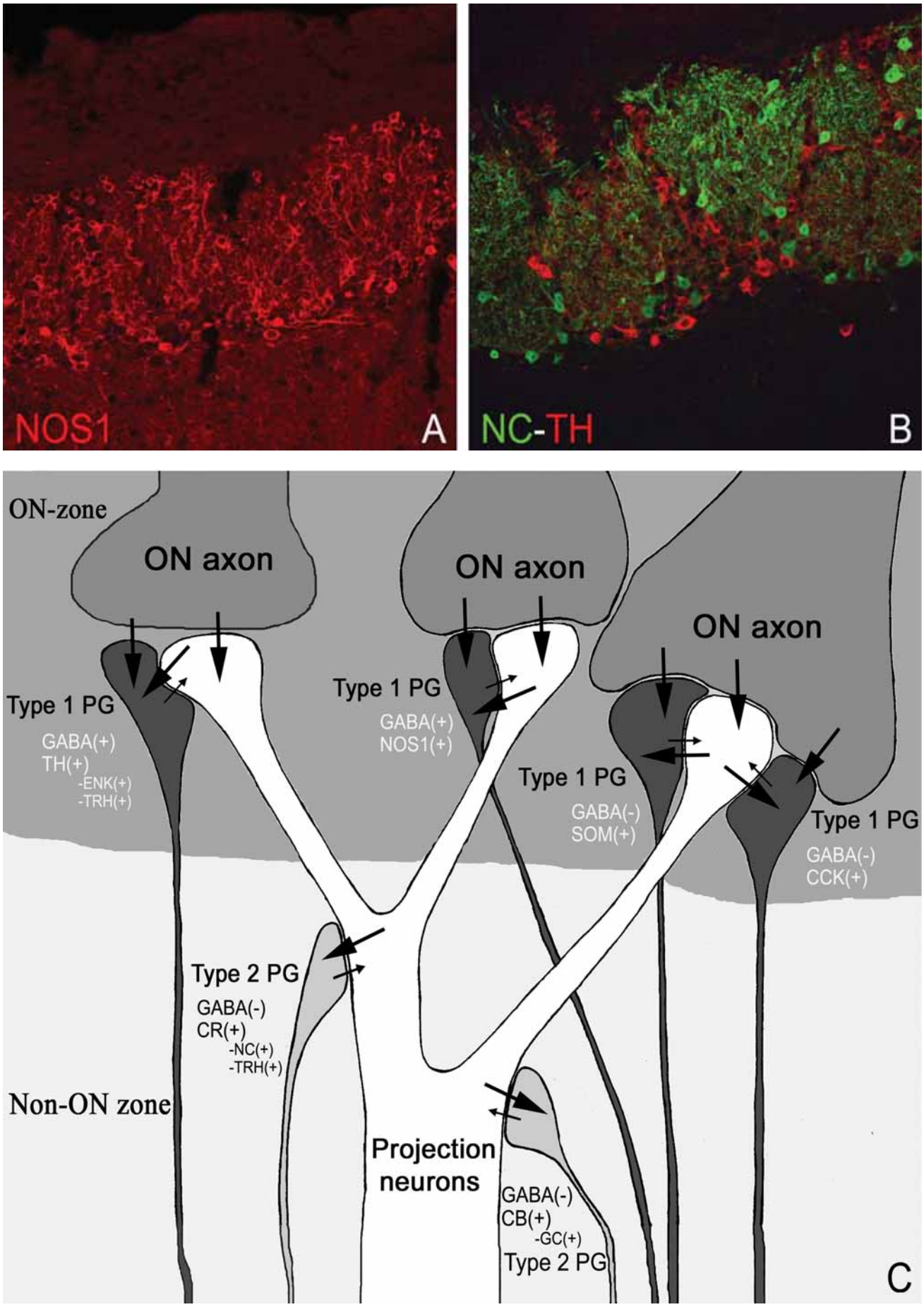

Fig. 1. The figure shows NOS1-stained PG (A), and double immunohistochemistry (B) for NC (green) and TH (red) where mouse PG do not coexpress both markers. In C, we represent a scheme (modified from Gutièrrez-Mecinas et al., 2005b) of the rat olfactory glomerulus. Large arrows indicate excitatory synapses and short arrows those inhibitory.

1992; Gong and Shipley, 1995). The first neurons developed are mitral cells (E13), after which tufted cells are formed by about E15 (Hinds, 1968). Finally, interneurons, including PG, appear at around E18 and their development continues during the first three postnatal weeks (Hinds, 1968; Rosselli-Austin and Altman, 1979; Bayer, 1983). The postnatal addition of interneurons from the subventricular zone to the OB produces an increase of about 80% in the size of the OB (Farbman, 1992). During adulthood, PG are continuously added. Newly generated neuroblasts migrate tangentially from the subventricular zone to the OB (Lois et al., 1996; Peretto et al., 1997). Within the OB, neuroblasts migrate radially towards both the GCL and the GL, differentiating and giving rise to granule cells and PG (Altman, 1969; Lois and Álvarez-Buylla, 1994; Carleton et al., 2003).

Structural features

Pinching and Powell (1971a) made a detailed study of the morphology of these interneurons. They generally have small and round or oval somata, from 5 to 8 μm in diameter (Pinching and Powell, 1971a), although this morphology is not the same in other species. The size of PG in the frog *Xenopus laevis* is much bigger (10-16 μm) than that of other species analyzed (Nezlin et al., 2003). The soma is sometimes enveloped by a glial covering of lamellae (Brightman, 1968). Electron microscopy studies of the soma disclose an electron-dense nucleus surrounded by a thin band of dark cytoplasm. Many organelles are located in the initial region of the primary dendrites (Pinching and Powell, 1971a). PG dendrites branch into one or, more rarely, two glomeruli. Two different types of dendrites have been described: large and thin (Pinching and Powell, 1971a).

Owing to the similar morphology of PG and granule cells, it was originally proposed that PG would lack an axon, since granule cells clearly lack this process (Blanes, 1898). However, later studies demonstrated the presence of axonal processes in the PG (Pinching and Powell, 1971a). They extend along three-five neighboring glomeruli and rarely branch. The axons run along the interstices between individual glomeruli, and between these glomeruli and the ONL and EPL (Pinching and Powell, 1971a; Buck and Axel, 1991; Ressler et al., 1994; Vassar et al., 1994; Mombaerts et al., 1996).

It has been suggested that the PG axon establishes synaptic contacts with other PG and other juxtaglomerular neurons (Pinching and Powell, 1971b). Apart from the already known existence of these chemical synapses, Pinching and Powell (1971a) proposed the existence of gap junctions in PG. These intercellular channels allow an electrical coupling between neurons, and they participate in the synchronization of neuronal activities (Korn and Farber, 1979; Christie et al., 2005). Kosaka and Kosaka (2003) also demonstrated the existence of gap junctions in intraglomerular dendritic processes, but they were unable to confirm that these processes belong to PG. Based on all these characteristics, PG can be differentiated from other juxtaglomerular neurons in electron microscopy studies (Pinching and Powell, 1971a, b).

Function

PG are involved in the initial processing of sensory information in the OB. Through inhibitory synapses, these neurons modulate the transmission of sensory information coming from ON axons to mitral and tufted cells (Kosaka et al., 1998). Three types of inhibitory synapses are established by the PG. First, they make reciprocal dendrodendritic synapses in the glomeruli with the apical dendrites of projection neurons (Pinching and Powell, 1971b; Bischofberger and Jonas, 1997). These synapses are regulated by postsynaptic $GABA_A$-receptors. The synapses via GABA release from PG to projection neurons are inhibitory, although the contacts from mitral/tufted cells to PG are excitatory (Halász, 1990). Second, ON axons are regulated by GABAergic PG via presynaptic contacts involving $GABA_B$- and D_2-receptor activation (Lledo et al., 2004). Third, the release of GABA from PG produces a retrograde inhibition on neighboring PG (Murphy et al., 2005). In addition, when the sensory stimulation arriving from ON axons is intense, GABA-mediated self-inhibition is carried out by PG (Smith and Jahr, 2002). Interestingly, PG dendrites are able to accumulate high concentrations of Cl^- (Siklos et al., 1995), thus providing the basis for excitatory actions mediated by GABA (Rhoades and Freeman, 1990).

Neurochemical composition of periglomerular cells

The OB is an attractive structure for studying the neurochemistry of the central nervous system owing to its layered structure, its well-

known neuronal types, and its richness in neuroactive compounds (Halász and Shepherd, 1983). It was originally assumed that PG formed a homogeneous population of cells immunopositive for GABA (Shepherd and Greer, 1998). However, this has been refuted in numerous studies that have shown that this neuronal type constitutes a population that is extraordinarily heterogeneous in its neurochemical features (Kosaka et al., 1995, 1998; Briñón et al., 1997, 1999; Toida et al., 1998; Gutièrrez-Mecinas et al., 2005a, b). In this review, we shall focus on the neurochemical variability of these neurons. The interspecies differences in the neurochemical composition of the PG suggest the existence of different routes of actions in the modulation of sensory information.

Many neurochemical markers have been employed to characterize different PG subpopulations. Calcium-binding proteins, neurotransmitters and enzymes, among others, are useful tools for the characterization of neuronal populations. Here, we compile and describe the expression patterns of these markers in the rat OB, especially in the PG, and compare these observations with previous data on other macrosmatic and microsmatic animals.

Calcium-binding proteins

Calcium-binding proteins (CaBPs) form a small group of molecules that are divided into three groups: the EF-hand family, annexins and protein kinase C family (Persechini et al., 1989; Kasai, 1993; Dedman and Kaetzel, 1995). CaBPs shuttle and buffer Ca^{2+}, modifying neuronal excitability to synaptic inputs (Baimbridge et al., 1992; Bellido et al., 2000; Berggård et al., 2002; Zimmermann and Schwaller, 2002). In addition, these proteins are involved in the development of the rat OB (Philpot et al., 1997).

Several CaBPs of the EF-hand family have been used as neuroanatomical tools for the characterization of PG (Jande et al., 1981; Baimbridge and Miller, 1982; Celio, 1989). Below we review the expression patterns of four CaBPs in the OB: calbindin D-28k, calretinin, neurocalcin and parvalbumin.

Calretinin

Calretinin (CR) is widely distributed in both the central and the peripheral nervous systems (García-Segura et al., 1984; Celio, 1990; Résibois and Rogers, 1992), and it is mainly expressed in neurons belonging to sensory pathways (Dechesne et al., 1991; Résibois and Rogers, 1992; Rogers and Résibois, 1992; Arévalo et al., 1995; Porteros et al., 1997). It regulates intracellular Ca^{2+} concentrations (Rogers, 1987). Since neurons containing this protein are often resistant to neurodegenerative processes (Hof et al., 1993; Philpot et al., 1997), a neuroprotective role for CR has been proposed (Pike and Cotman, 1995; Vogt-Weisenhorn et al., 1996). In particular, in the olfactory system CR-immunopositive PG are unaffected by neurodegenerative processes that cause the losses of other PG subpopulations (Dellovade et al., 1998) or losses of peripheral afferent inputs (Philpot et al., 1997). However, this does not hold in all pathological conditions. The expression of this protein in neurons of other olfactory areas such as the piriform cortex is markedly reduced following bulbectomy (Kinzie et al., 1997; Lim and Brunjes, 1999).

The distribution pattern of this protein in the rat OB can be summarized as follows: all bulbar layers display a high number of CR-immunoreactive elements and even the ONL is strongly stained. The highest density of CR-immunopositive neurons is observed in the GL. These CR-reactive neurons surround the glomeruli, and they are more numerous at the limit with the EPL (Briñón et al., 1997; Crespo et al., 1997). This population constitutes 20% of the total rat PG (Kosaka et al., 1995) and these immunoreactive PG decrease as from 1 year of age (Hwang et al., 2006).

The pattern of CR expression in the OB is similar in several mammals such as the hedgehog (*Erinaceus europaeus*; Briñón et al., 2001b), the gray short-tailed opossum (*Monodelphis domestica*; Jia and Halpern, 2004), the musk shrew (*Suncus murinus*; Kakuta et al., 2001), the tree shrew (*Tupaia belangeri*; Malz et al., 2000), and the mouse (*Mus musculus*; Kimura and Furukawa, 1998). Even microsmatic mammalians such as the macaque monkeys *Macaca fascicularis*, *M. mulatta* and, *M. nemestrina* (Alonso et al., 2001), or primitive mammals such as the shortbeaked echidna (*Tachyglossus aculeatus*) and the platypus (*Ornithorhynchus anatinus*) contain CR-immunopositive PG (Ashwell, 2005). Additionally, the presence of high numbers of CR-containing PG has been reported in other vertebrate groups, such as birds (*Gallus domesticus*; Rogers, 1989) or prim-

itive chordates such as the lamprey (*Lampetra fluviatilis*), which show a similar distribution (Pombal et al., 2002). Nevertheless, this is not a universal expression pattern since in the zebrafish (*Danio rerio*), CR is not expressed by the PG (Castro et al., 2006).

The relative similarity in the expression pattern of CR-immunopositive PG in both mammals and non-mammals indicates that this protein is phylogenetically conserved in the PG of the OB.

Calbindin D-28k

Calbindin D28-k (CB) is a soluble intracellular CaBP homologue of CR (Rogers, 1987; Parmentier, 1990; Jacobowitz and Winsky, 1991). It is detected in both the peripheral and in the central nervous system. CB has also been proposed as a neuroprotective molecule (Hof and Morrison, 1991). However, in the olfactory system this function is remarkably different from that exerted by CR, since PG expressing CB are affected following naris closure whereas those expressing CR remain intact (Philpot et al., 1997). Moreover, in the piriform cortex, CB immunoexpression is increased following bulbectomy whereas CR-immunoexpression decreases (Lim and Brunjes, 1999).

In the rat OB, CB is expressed in all layers, except the ONL and the MCL (García-Segura et al., 1984; Celio, 1990; Briñón et al., 1992). The highest number of CB-immunopositive neurons is located in the GL; most of them can be identified as PG and a few as SA cells (Seroogy et al., 1989; Briñón et al., 1992; Toida et al., 1998; Kosaka and Kosaka, 2004). PG neuronal bodies appear strongly labeled, although variations in the intensity of their staining can be observed. This variation suggests the possibility of divergences in their afferent activity (Philpot et al., 1997). García-Segura et al. (1984) found that 26% of rat PG were immunoreactive for CB. However, later quantitative analyses have established that only 10% of PG appear to be immunopositive for CB (Kosaka et al., 1995). The number of rat CB-immunoreactive PG increases significantly from postnatal month 1 to postnatal month 6 (Hwang et al., 2002). This number is preserved at later ages, although other age-related changes do occur: these neurons show a tendency to be smaller and to have fewer dendrites. Such changes may be involved in age-related functional restrictions (Hwang et al., 2002).

The CB-immunostaining pattern described for the rat GL is very similar to that reported for most macrosmatic mammals (Yamagishi et al., 1993; Vallejo et al., 2000; Kakuta et al., 2001; Hwang et al., 2003; Jia and Halpern, 2004; Kosaka and Kosaka, 2004), except the hedgehog (*E. europaeus*) and the monotreme (*Z. bruijni*), where only a few PG express this protein or where it is completely absent (Alonso et al., 1995; Ashwell, 2005). In addition, the chick (*G. domesticus*) contains numerous CB-stained PG (Rogers, 1989). However, in microsmatic mammals such as the macaque monkey (*M. fascicularis*, *M. mulatta* and *M. nemestrina*) or humans, the expression pattern is different from that seen in macrosmatic animals: a few PG contain CB and they exhibit only a very weak immunoreactivity (Ohm et al., 1991; Alonso et al., 2001). It seems that a functional relationship between the expression of this protein and the importance of olfactory sense in the species analyzed can be assumed. The presence of this protein in the PG is higher in macrosmatic mammals than in microsmatic species.

Neurocalcin

Neurocalcin (NC) belongs to the group of neural calcium-sensor proteins. Neurochemical studies have shown it to be widely distributed in the central nervous system (Okazaki et al., 1992, 1994; Terasawa et al., 1992; Hidaka and Okazaki, 1993; Briñón et al., 1998a). NC is expressed in both the main and the accessory OBs (Porteros et al., 1996b). This protein modulates signal transduction events (Ikura, 1996; Haynes et al., 2006). In addition, proteins with a high homology to recoverin carry out adaptive processes in the olfactory receptors (Kramer and Siegelbaum, 1992). Interestingly, NC shares some similarities with recoverin (Ikura, 1996). In this sense, in previous studies we have proposed that the presence of NC in the interneurons of the OB could be involved in olfactory sensory adaptation mechanisms (Briñón et al., 1998a). Other mechanisms in which NC could be involved are those proposed for CaBPs, including short-term Ca^{2+} buffering, the redistribution of Ca^{2+} within the neuron, and cellular protection against the damaging effects of excessive Ca^{2+} influxes (Andressen et al., 1993).

The rat OB contains NC-immunopositive elements in all its layers, except in the ONL (Briñón et al., 1998a, 1999). The bulbar layer with most NC-containing neurons is the GL, where two different populations can be distin-

guished. The first consists of strongly immunostained neurons that are mostly located in the superficial zone of the EPL and around the glomeruli. Morphological features and the location of the somata indicate that these neurons are external tufted cells (Crespo et al., 1997; Briñón et al., 1998a). The second population consists of neurons identified as PG (Crespo et al., 1997; Briñón et al., 1998a). NC-immunopositive PG show a weak immunostaining, although their cell bodies and many of their dendrites can be observed.

The expression pattern of this protein in the mouse OB is similar to that described for the rat (Murias, 2003). However, in species such as the hedgehog (*E. europaeus*) or the macaque monkey (*M. fascicularis*, *M. mulatta* and, *M. nemestrina*), the NC-immunopositive neurons situated in the GL have been typified only as external tufted cells and no NC-immunopositive PG can be observed (Alonso et al., 2001; Briñón et al., 2001b). Although the expression pattern of this protein has been studied in only a limited number of species, the results suggest that the expression pattern of this CaBP in rodents differs from those described for insectivores and primates.

Parvalbumin

Parvalbumin (PV) was first isolated from hake muscle (Pechère et al., 1971a, b) and along the past few decades many different functions have been attributed to it. Its function in the nervous system is poorly understood, although several roles -including control of Ca^{2+} concentrations and participation in neuroprotection mechanisms- have been suggested (Celio and Heizmann, 1981; Heizmann, 1984; Satoh et al., 1991; Tortosa and Ferrer, 1994; Appel et al., 1996).

PV-immunostaining in the rat reveals labeled neurons in all layers but the ONL (Kosaka et al., 1994), although the number and degree of immunoreactivity of the elements varies, depending on the layer. The location of PV-immunopositive interneurons is almost entirely restricted to the EPL. In addition, a few PV-immunopositive neurons are located in the GL, MCL and IPL (Briñón et al., 1997).

In the GL, most PV-immunostained interneurons are identified as PG, although immunopositive superficial SA cells located at the limit between the GL and the EPL can be observed. In most cases, PV-positive PG surround glomeruli in the dorsomedial and ventrolateral areas (Kosaka et al., 1994; Crespo et al., 1997). They exhibit a weak immunostaining that only permits the observation of their neuronal bodies and, occasionally, their primary dendrites.

Macrosmatic species such as the hedgehog or the house musk shrew (*S. murinus*) display a similar PV-expression pattern (Kakuta et al., 1998; Briñón et al., 2001b); an exception is the guinea pig (*Cavia porcellus*), whose OB does not contain PV-immunostained elements (Yamagishi et al., 1993). Additionally, in other species such as the human, the macaque monkey, the gray short-tailed opossum (*M. domestica*) and the echidna (*T. aculeatus*) PV is not expressed by any PG (Ohm et al., 1990; Alonso et al., 2001; Jia and Halpern, 2004; Ashwell, 2005).

It may be concluded that the distribution of CaBPs in the PG of the macrosmatic mammals studied shows a higher degree of complexity than those reported for microsmatic mammals. Exceptionally, CR appears to be highly preserved in PG along the phylogenetic scale. These results can be interpreted as a lower capability in modulatory processes carried out by CaBPs in the PG of the microsmatic OB (Alonso et al., 2001).

Neurotransmitters

Neurotransmitters are a group of molecules that are synthesized and released by presynaptic cells to stimulate postsynaptic neurons. Classically, neurotransmitters have been divided into three categories: monoamines, acetylcholine and aminoacids. Currently, five different types of neurotransmitters are envisaged:

1) Monoamines
2) Acetylcholine
3) Aminoacids, including γ-aminobutyric acid (GABA)

} Classical neurotransmitters

4) Neuropeptides
5) Gases such as nitric oxide

} New neurotransmitters

The distribution and function of neurotransmitters such as acetylcholine, glutamate, GABA, nitric oxide and dopamine have been particularly well analyzed in the nervous system, and accurately so in the olfactory system. Below we describe the expression pattern of these neurotransmitters in the OB.

Monoamines

Dopamine

Dopamine (DA) is the most important catecholamine owing to its high expression in the

nervous system. In the olfactory system, DA seems to play an important role in sensory modulation due to the high number of dopaminergic neurons in the OB of all vertebrates.

The presence of DA in the rat OB has been reported (Versteeg et al., 1976; Halász et al., 1977) and it is one of the most abundant neurotransmitters in that organ. One function suggested for it in the glomerular circuitry is the inhibition at presynaptic level, via D_2-receptor activation, of ON axons. More recently, it has been proposed that this type of receptor has intrinsic activity, causing a tonic dopaminergic release that modulates the sensitivity of the olfactory system during odor detection (Koster et al., 1999; Ennis et al., 2001; Puopolo et al., 2005). The magnitude and varied locations of the modulatory capabilities of DA in the OB suggest an important role for it in odorant processing.

There is a subpopulation of PG that expresses tyrosine hydroxylase (the rate-limiting enzyme in the DA synthesis pathway), suggesting that such cell would be dopaminergic neurons. PG expressing TH are present prenatally and their number increases sharply during early postnatal development (Biffo et al., 1992). The expression of this enzyme in PG depends on peripheral stimulation (Baker et al., 1983, 1990). Loss of functional input due to pathological or experimental processes such as deprivation or deafferentation results in a profound decrease in TH expression by PG (Nadi et al., 1981; Baker et al., 1984, 1990; Weruaga et al., 2000; Briñón et al., 2001a). Since other markers of PG, such as GABA, remain unchanged following this manipulation, a shift in cellular phenotype rather than cell death can be suggested (Baker et al., 1984). When the functional inputs to the OB are restored, TH-immunoexpression is recovered (Baker et al., 1990; Weruaga et al., 2000; Briñón et al., 2001a). Therefore, peripheral afferent innervation is necessary for the maintenance of TH activity in PG. Nevertheless, in contrast to the results described for other brain dopaminergic systems and for other subpopulations of PG, such as CR-immunopositive cells, the expression level of TH in PG is preserved in the aging olfactory bulb (Baker et al., 1995).

The expression pattern of TH in the rat OB is almost wholly restricted to the GL, although a low number of weakly immunostained neurons, identified as tufted cells and deep SA cells, can be detected in the rest of the layers (Halász et al., 1977, 1981; Jaffe and Cuello, 1980; Toida et al., 2000). TH-immunoreactive neurons located in the GL were initially identified as external tufted cells (Baker, 1986b). However, electron microscopy studies allowed the typification of most TH-immunopositive cells of the GL as PG.

Studies carried out in other mammals have also demonstrated the greater density of TH-IR neurons in the GL (Baker et al., 1983, 1986a, b; Kream et al., 1984; Kosaka et al., 1985, 1994; Tillet et al., 1987; Phelix and Krause, 1990; Brunjes et al., 1992; Toida et al., 1994, 2000; Hoogland and Huisman, 1999; Vallejo et al., 2000; Kosaka and Kosaka, 2001; Jeong et al., 2003; Ashwell, 2005). Most immunostained interneurons correspond to PG, except in some hamsters (*Mesocricetus auratus* and *Cricetulus griseus*), where TH-immunopositive external tufted cells are more numerous than TH-stained PG (Davis and Macrides, 1983; Baker, 1986b; Halász, 1990). The expression pattern of this enzyme in the macaque monkey and human OB is comparable to those previously described for other mammals, although the number of TH-positive juxtaglomerular neurons is lower than in macrosmatic species (Smith et al., 1991). As in mammals, most TH-immunopositive elements in the OB of birds and reptiles such as some snakes (*Python regius* and *Elaphe quadrivirgata*), the lizard (*Gekko gecko*), or the turtle (*Pseudemys scripta elegans*) are located in the GL (Halász et al., 1982; Smeets et al., 1986, 1987; Smeets, 1988; Kosaka et al., 1991; Reiner et al., 1994).

In amphibians, differences are seen in the expression pattern depending on the species. In urodele species such as *Triturus cristatus*, *Pleurodeles waltl*, *Typhlonectes compressicauda*, and *Ambystoma mexicanum* immunohistochemical studies have shown that TH-positive neurons located in the GL are PG (Franzoni et al., 1986; González and Smeets, 1991, 1994; González et al., 1993; Beltramo et al., 1998). By contrast, anuran amphibians such as *Rana catesbiana*, *R. pipiens* and *X. laevis* exhibit a few TH-stained neurons in the GL, and these have been typified as external tufted cells rather than PG (Inagaki et al., 1981; Nezlin et al., 2003). Most fish analyzed do not contain TH-immunopositive PG (Northcutt et al., 1988; Alonso et al., 1989a; Meek et al., 1989; Roberts et al., 1989; Ekström et al., 1990; Reiner and Northcutt, 1992; Pierre et al., 1997; Rodríguez-Gómez et al., 2000; Adrio et

al., 2002), although exceptionally some fish species do have TH-immunopositive neurons located in the GL, generally designated juxtaglomerular neurons, whose morphology appears to be that of PG (Meredith and Smeets, 1987; Sas et al., 1990; Edwards and Michel, 2002; Castro et al., 2006).

Dopaminergic expression in the PG is preserved in mammals, reptiles, and urodele amphibians, while there are no TH-containing PG in most fish and anuran amphibians. In conclusion, an increase in the complexity of the modulation carried out by dopaminergic interneurons in the GL can be detected in the olfactory system throughout the phylogenetic scale.

Acetylcholine

Acetylcholine (ACh) is one of the neurotransmitters first identified and is widely distributed throughout the brain. In the olfactory system it is involved in mechanisms of plasticity and is associated with olfactory learning and the ability of animals to discriminate between closely related odors (Kaba and Keverne, 1988). Another function in the OB is to modulate the transmission of olfactory information by the release of GABA and dopamine through nicotinic and muscarinic receptors respectively (Nickell and Shipley, 1988; Elaagouby et al., 1991; Crespo et al., 2000). Attempts to map the cholinergic elements have normally been carried out using histochemistry for acetylcholinesterase (AChE) and immunohistochemistry against choline acetyltransferase (ChAT). The coexpression of both markers identifies cholinergic elements while the detection of AchE alone typifies cholinoceptive elements.

There are discrepancies in the results obtained for AChE histochemistry in the rat OB. Several authors have described the presence of a few stained PG in the rat OB (Nickell and Shipley, 1988; Le Jeune and Jourdan, 1994; Crespo et al., 1995), and a similar distribution pattern has been described for the mouse (Carson and Burd, 1980). In contrast, other authors refute the existence of cholinoceptive PG in the rat OB (Kása et al., 1996). A few PG can be detected with AChE histochemistry in the macaque monkey OB (Porteros et al., 2007) whereas they are not present in the hedgehog OB (Crespo et al., 1999).

In the case of ChAT-immunohistochemistry, very few rat bulbar neurons have been detected using this technique. Based on their morphology and their location, some of these neurons have been identified as PG (Phelps et al., 1992). By contrast, there are no ChAT-containing PG in the OB of other groups of vertebrates such as fish (Ekström, 1987; Brantley and Bass, 1988; Villani et al., 1994, Adrio et al., 2000; Anadón et al., 2000; Pérez et al., 2000; Pombal et al., 2001; Clemente et al., 2004), amphibians (Marín et al., 1997; González et al., 2002), reptiles (Hoogland and Vermeulen-VanderZee, 1990; Medina et al., 1993), birds (Medina and Reiner, 1994) and other mammalian species different from the rat, both macrosmatic and microsmatic (Ichikawa et al., 1997; Kovacs et al., 1998; Crespo et al.,1999; Kratskin and Belluzzi, 2003; Porteros et al., 2007). This suggests that there is a differential cholinergic modulation exerted by the PG in the rodent olfactory system as compared to that of other animals analyzed.

Aminoacids

γ-aminobutyric acid

γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system. In the OB, this aminoacid modulates the transmission of sensory information through its inhibitory effect, carried out by interneurons located in the GL and GCL to the projection neurons (Shipley and Ennis, 1996; Kratskin and Belluzzi, 2003).

In the rat OB, GABA is present in all layers except the ONL. The main GABAergic population in the rat OB comprises granule cells (Ribak et al., 1977). In addition, there are large numbers of GABAergic PG (Halász et al., 1979; Jaffe et al., 1983; Mugnaini et al., 1984a, b). The percentage of GABAergic PG in the rat OB is about 20% of the total number of PG (Kosaka et al., 1995). Immunohistochemical analyses have shown that high concentrations of this neurotransmitter are present in both presynaptic dendrites and in the neuronal bodies of the PG (Ribak et al., 1977). The distribution pattern of GABA-IR PG is similar in all mammals (Ribak et al., 1977; Kosaka et al., 1985, 1988; Ohm et al., 1990; Kosaka and Kosaka, 2001), birds (Veenman and Reiner, 1994), amphibians (Franzoni and Morino, 1989; Kratskin et al.,

1989; Hamilton, 1992) and fish (Medina et al., 1994; Meléndez-Ferro et al., 2001) studied. Nevertheless, the OBs of several fish species such as the goldfish (*Carassius auratus*) or the zebrafish (*D. rerio*) do not contain GABA-immunoreactive PG (Martinoli et al., 1990; Kim et al., 2004). All these data indicate the high rate of conservation of this neurotransmitter in the interneurons of the OB.

Neuropeptides

Neuropeptides are a group of neuromodulator substances that in recent years have been raised to the status of neurotransmitters or neurohormones. However, they exhibit several characteristics that differentiate them from classical neurotransmitters. Thus, neuropeptides are present in lower concentrations and their actions are more powerful than those of the former. They are very abundant in the nervous system and they participate in the regulation of adaptative, autonomic, and endocrine functions.

In the complex neurochemistry of the OB, specific neuronal subpopulations express different neuropeptides such as cholecystokinin (CCK), somatostatin (SOM), neuropeptide Y, enkephalin (ENK) and vasoactive intestinal peptide (VIP; Kosaka et al., 1998). Antibodies against these neuropeptides can be used as neurochemical markers. We summarize the expression pattern of these neuropeptides in the OB of different species.

Cholecystokinin

Cholecystokinin (CCK) was first isolated from the brain of vertebrates (Vanderhaeghen et al., 1975). In the nervous system, CCK is located in the hippocampus, cortex, thalamus, the amigdaloid nucleus and OB, among other regions (Larsson and Rehfeld, 1979; Seroogy et al., 1985; Seroogy and Fallon, 1989; Smith et al., 1993). As a neurotransmitter, CCK is involved in the mechanisms of pain perception and in the modulation of emotions (Weller and Feldman, 2003; Panksepp et al., 2004). In addition, it has been demonstrated that in different regions of the central nervous system CCK is involved in the modulation of inhibitory synaptic transmission through GABA and dopamine release acting on presynaptic $GABA_A$- and $GABA_B$-receptors (Rakovska, 1995a, b; Miller et al., 1997; Kombian et al., 2005; Deng and Lei, 2006). However, no specific physiological functions of CCK in the OB have yet been described.

Regarding CCK-immunoreactivity in the rat OB, immunohistochemical analysis reveals positive neurons in all bulbar layers, except the ONL (Seroogy et al., 1985; Gutièrrez-Mecinas et al., 2005b). The highest number of CCK-immunopositive elements is located in the superficial zone of the EPL, limiting with the GL. Two types of interneurons have been identified in this region. According to their morphology, they have been typified as external tufted cells and PG, the latter showing weaker immunoreactivity (Gutièrrez-Mecinas et al., 2005b). The estimated number of CCK-immunopositive PG is about 40 per glomerulus (Gutièrrez-Mecinas et al., 2005b). Since the gemmules of CCK-positive PG are in close contact with ON axons containing dopamine D_2-receptors, Gutièrrez-Mecinas et al. (2005) have suggested that CCK-containing PG could exert an inhibitory modulation of these receptors in the same way as those described by Tanganelli et al. (2001) in the nucleus accumbens.

In mammals such as the sheep (*Ovis aries*) or the hedgehog (*E. europaeus*), CCK-immunoreactive neurons have been described in the OB, although the specific neuronal types have not been identified (Antonopoulos et al., 1987). In addition, immunohistochemical analyses performed in a large variety of species including humans, the cat (*Felis catus*), the opossum (*M. domestica*), the guinea pig (*C. porcellus*), and the chameleon (*Chameleo chameleon chameleon*) have demonstrated that there are no CCK-immunoreactive neuronal bodies in their OB, but only fibers (Matsutani et al., 1989; Fox et al., 1991; Smith et al., 1993; Bennis et al., 1997; Won et al., 1997).

Somatostatin

This neuropeptide was originally isolated from the hypothalamus (Burgus et al., 1973; Sarantakis and McKinley, 1973; Brazeau et al., 1974) and was identified as a neurotransmitter in the nervous system. Immunohistochemical and radioimmunoassay studies have revealed SOM-immunopositive elements in different zones of the nervous system, including the limbic area, neocortex, amygdaloid complex, anterior periventricular area, and OB, among others (Pelletier et al., 1975; Epelbaum et al., 1977; Johansson et al., 1984; Takami et al., 1990). It has been described

that SOM modulates excitatory, but not inhibitory, synapses in the hippocampus (Tallent and Siggins, 1997). Thus, in rat olfactory glomeruli this neuropeptide may exert an inhibitory modulation of glutamatergic transmission from the axons of receptor neurons to the dendrites of mitral and tufted cells (Gutièrrez-Mecinas et al., 2005b).

SOM-immunopositive neurons are distributed in the rat OB, particularly in the GL, GCL and WM (Brownstein et al., 1975; Serogy et al., 1989; Takami et al., 1990; Gutièrrez-Mecinas et al., 2005b). In the GL, SOM immunostaining reveals a scarce population of PG and superficial SA cells, while in the GCL deep SA cells and fibers running along the GCL can be observed (Scott et al., 1987; Takami et al., 1990; Gutièrrez-Mecinas et al., 2005b). The estimated number of SOM-containing PG is about 25 per glomerulus (Gutièrrez-Mecinas et al., 2005b). The distribution pattern of SOM elements in the GL varies, depending on species. Human and frog (*R. catesbiana*) OBs contain SOM-positive PG (Inagaki et al., 1981; Ohm et al., 1988a; Smith et al., 1993), although in low numbers. By contrast, other species that do not contain SOM-positive PG include mammals such as the guinea pig (*C. porcellus*), hamster, garden dormouse (*Eliomys quercinus*), the hedgehog or the sheep (*O. aries)* (Richoux and Dubois, 1980; Davis et al., 1982; Papadopoulos et al., 1986; Matsutani et al., 1989); birds such as the warbling grass parakeet (*Melopsittacus undulatus*; Takatsuki et al., 1981); reptiles such as the turtle (*Testudo hermanni*) or the lizard (*Ctenosauria pectinata*; Goossens et al., 1980; Weindl et al., 1984), and the electric fish (*Apteronotus leptorhynchus*; Sas and Maler, 1991). The reduced number of PG containing SOM in several species and their absence in others suggest that this neuropeptide is not essential in the modulatory function carried out by the PG of the OB.

Vasoactive intestinal neuropeptide

Vasoactive intestinal neuropeptide (VIP) is a neurotransmitter formed by 28 aminoacids. Its best documented function in the central nervous system is to activate the neurons of the hypothalamus in order to increase the release of prolactin. Even though its presence in the olfactory system has been reported (Gall et al., 1986; Gracia-Llanes et al., 2003), its function is still unknown, although it has been proposed that in the OB VIP-containing neurons would exert a modulatory function of the inhibitory circuits (Gracia-Llanes et al., 2003).

In the rat OB, VIP-immunoreactive neurons are located in all bulbar layers except the ONL and the GL and are exclusively SA cells (Gall et al., 1986; Gracia-Llanes et al., 2003). In addition, other mammals such as the golden hamster (*M. auratus*), the sheep (*O. aries*), or the bat (*Myotis lucifugus*), and birds and fish do not contain VIP-immunoreactive cell bodies (Antonopoulos et al., 1987; Laemle and Cotter, 1988; Alonso et al., 1989b, 1990; Batten et al., 1990; Aste et al., 1995; Nakajima et al., 1996; Mathieu et al., 2001).

López-Mascaraque and co-workers (1989) described the distribution pattern of VIP-immunoreactive elements in the hedgehog (*E. europaeus*). They found highly VIP-immunostained PG. Likewise, a similar pattern of expression to that described for the hedgehog (*E. europaeus*) is found in the cat (*F. catus*) and the common marmoset monkey (*Callithrix jacchus*), where VIP-IR neurons located in the GL were identified as PG (Sanides-Kohlrausch and Wahle, 1990a, b).

Neuropeptide Y

This neuropeptide was isolated from porcine brain (Tatemoto, 1982). The immunoexpression of neuropeptide Y (NPY) is widespread in the brain, and it is present in the basal ganglia, amygdala, nucleus accumbens, caudate and putamen, hypothalamus and OB, among others (Adrian et al., 1983; Pelletier et al., 1984; Gaikwad et al., 2004).

Recently, the function of this neuropeptide in the OB has been described: NPY modulates excitatory synaptic transmission in the OB via a presynaptic effect on excitatory neurotransmitter (glutamate) release (Blakemore et al., 2006). In the OB, the immunoexpression of this neuropeptide has been analyzed, with the finding that in all species studied (both mammalian and non-mammalian) PG do not contain this neuropeptide (Danger et al., 1985; Scott et al., 1987; Kuenzel and McMurtry, 1988; Ohm et al., 1988b; Matsutani et al., 1989; Bonn, 1990; Sanides-Kohlrausch and Wahle, 1990a; Reiner and Northcutt, 1992; Cepriano and Schreibman, 1993; Byrd and Brunjes, 1995; Nakajima et al., 1996; Subhedar et al., 1996; Castro et al., 1999; Chiba, 1999, 2005; Gould et al., 2001; Gaikmad et al., 2004; Ashwell, 2005; Sakharkar et al., 2005). Only the existence of NPY-

immunopositive olfactory interneurons surrounding the glomeruli in one species of Insecta has been reported (Settembrini et al., 2003). Therefore, NPY must be involved in the modulation of the olfactory sensory information exerted by interneurons other than PG.

Enkephalin

Enkephalin (ENK) is an opioid peptide. Two different enkephalins can be distinguished, depending on the last amino acid of their sequences; i.e. Met-ENK or Leu-ENK. These opioid neuropeptides were first isolated from the pig brain (Hughes et al., 1975).

The presence of ENK in the rat OB was initially studied using RIA measurements. These studies revealed that the OB has a low concentration of ENK (Hong et al., 1977). In contrast, receptor-binding (Hirsch and Margolis, 1980; Nadi et al., 1980), immunocytochemical (Finley et al., 1981) and immunohistochemical studies (Bogan et al., 1982) have revealed the widespread presence of ENK in the OB. ENK-immunopositive neurons are located in the GL, EPL and GCL of the rat OB. In the GL, the number of interneurons exhibiting ENK-immunoreactivity is high. These interneurons have been identified as PG and superficial SA cells (Bogan et al., 1982; Merchenthaler et al., 1986). Other rodents such as the guinea pig (*C. porcellus*) also contain ENK in their PG (Matsutani et al., 1989). In the hamster, ENK-IR elements located in the GL have not been clearly identified since these interneurons were initially typified as PG (Davis et al., 1982), although a more recent study has suggested that they would be external tufted cells (Holt and Newman, 2004).

Birds, reptiles and fish do not contain ENK-immunoreactive PG in their OB (Blahser and Dubois, 1980; Brauth, 1984; Northcutt et al., 1988; Reiner and Northcutt, 1992).

Nitric Oxide

Nitric oxide (NO) is an unconventional messenger in the nervous system. This gas is one of the latest additions to the list of neurotransmitter candidates, and it appears to be involved in the development of sensory processing in the visual and olfactory systems (Cramer et al., 1998; Chen et al., 2004; Eldred and Blute, 2005; Matsumoto et al., 2006). Nitric oxide synthase (NOS) enzyme catalyzes the stepwise conversion of the amino acid L-arginine to nitric oxide and L -citrulline. (Marletta, 1989, 1993; Förstermann et al., 1991; Moncada et al., 1991; Bredt and Snyder, 1994). There are at least three different isoforms of NOS, designated according to their activity or the tissue type in which they were first described: the neural isoform (NOS1), the inducible isoform (NOS2) and the endothelial isoform (NOS3; Knowles and Moncada, 1994; Griffith and Stuehr, 1995). NOS1 is widely distributed in the brain, including the cerebellum, cortex, the hippocampus and the OB, among many other areas (Bredt et al., 1990, 1991; Roskams et al., 1994). NO acts as a physiological inhibitor of neurogenesis in the OB (Moreno-López et al., 2004).

Identification of the nitrergic population has usually been carried out with two different techniques: NADPH-diaphorase histochemistry, and immunohistochemistry against NOS. The former allows the detection of the activity of NOS enzyme, whereas the second one detects its location (Morris et al., 1997; Weruaga et al., 1998, 2000).

Regarding immunoreactivity for NOS1 or NADPH-diaphorase activity in the PG of the OB, the distribution pattern of nitrergic PG differs among vertebrates. For example, all mammals analyzed, except the dog (*Canis familiaris*; Nakajima et al., 1998), contain NOS1 in their PG (Davis, 1991; Kishimoto et al., 1993; Weruaga et al., 1998; Vallejo et al., 2000; Kosaka and Kosaka, 2001; Singru et al., 2003; Ashwell 2005), although the distribution throughout the OB is not the same. While in the mouse (*M. musculus*), the rat, the hamster, the mouse and the musk shrew (*S. murinus*) numerous nitrergic PG can be detected (Davis, 1991; Kishimoto et al., 1993; Weruaga et al., 1998; Vallejo et al., 2000; Kosaka and Kosaka, 2001, 2006), in other mammals such as the macaque monkey, humans, sheep (*O. aries*) and primitive mammals such as monotremes the nitrergic PG subpopulation is rare (Kendrick et al., 1997; Alonso et al., 1998; Briñón et al., 1998b; Ashwell, 2005). In addition, in birds (chicken), reptiles such as some snakes (*Trimeresurus flavoviridis*) and both anuran (*Rana perezi*, *R. esculenta*) and urodele amphibians (*Triturus marmoratus* and *P. waltl*), NOS1-containing PG do not exist in the OB (Bruning et al., 1994; Jiang and Terashima, 1996; Muñoz et

al., 1996; Porteros et al., 1996a; Lázár and Losonczy, 1999; Moreno et al., 2002). Finally, the presence of NOS1-immunostained interneurons has been reported in the GL of fish, although the specific neuronal types have not been identified (Lema and Nevitt, 2001; Singru et al., 2003; Ando et al., 2004). It may be concluded that nitrergic modulation in the OB is very variable across the phylogenetic scale and that it is apparently more complex in macrosmatic animals.

In conclusion, here we have seen of summary of the different distribution patterns of active molecules in the PG of the OB. In addition, we have seen divergences along the phylogenetic scale that in some cases (i.e. CCK, SOM, ACh) have become more complex with the increase in the physiological advances of the olfactory system whereas for other substances there is no clear explanation to account for interspecies differences. Furthermore, the distribution pattern of CaBPs, the neuropeptides CCK and SOM, and the nitrergic system is simpler in both microsmatic animals and ancestral species, and is more complex in species where olfaction is crucial for survival.

Neurochemical classification of periglomerular cells

Early studies based on light microscope morphological observations described PG as inhibitory interneurons with a similar morphology and connectivity (Halász, 1990). Later, immunocytochemical and immunohistochemical work has shown that chemical variability differs widely in PG, which based upon their neurochemical, hodological and physiological features comprise different subsets (Kosaka et al., 1995; Briñón et al., 1997, 1999; Gutièrrez-Mecinas et al., 2005 a, b). Most analyses have been carried out in rats, although other species of mammals and other classes of vertebrates have also been studied, providing a wider perspective.

A classification for the rat PG has been proposed (Kosaka et al., 1995). This sorting is based on the synapses from ON axons onto these interneurons. Two different types of PG have been described: type 1 PG and type 2 PG. Type 1 PG receive synapses from ON axons while type 2 establish few or no synaptic contacts with them. In addition, each type can be divided into different subtypes, depending on its neurochemical profile.

Type 1 periglomerular cells

The classification criterion for type 1 PG is that their dendrites establish asymmetric synapses with the ON axons in the ON zone of the glomeruli (Kosaka and Kosaka, 2004). Furthermore, type 1 PG show dendrodendritic connections with projection neurons, mitral cells and tufted cells. These connections may be excitatory, when presynaptic neurons are the principal neurons, or inhibitory, if the presynaptic element is a PG. Regarding their neurochemical features, two subtypes of type 1 PG have been identified: GABAergic and non-GABAergic cells.

GABAergic type 1 PG

GABAergic PG have been mainly typified as type 1 PG. However, it should be noted that the GABAergic PG subpopulation is heterogeneous, and some of these neurons could also confine their dendrites within the non-ON zone and hence should be included as type 2 PG (Kosaka and Kosaka, 2005). GABAergic type 1 PG can be divided into two groups again:

Group I is composed of dopaminergic neurons, characterized by the expression of TH (Gall et al., 1987; Kosaka et al., 1997; Toida et al., 2000).

Group II is constituted by non-dopaminergic PG (Crespo et al., 2003).

Group I forms a subpopulation of PG that has been widely analyzed and that is well typified. Different neurochemical subsets can be differentiated in the GABA/TH subpopulation: 1) the presence of ENK in many PG suggests that this neuropeptide coexists with GABA or TH in the PG. The coexistence of ENK with GABA and/or TH has been confirmed, but in low percentages (Kosaka et al., 1987). 2) Fifty percent of GABA/TH PG contain thyrotropin-releasing hormone (TRH; Kosaka et al., 1995). Thus, this group contains other neurochemical compounds, forming different subgroups such as GABA/TH/TRH, GABA/TH/ENK, and even GABA/TH/TRH/ENK (Tsuruo et al., 1988; Kosaka et al., 1995). TH-positive PG containing GABA comprise about 65% of total of dopaminergic PG. The coexistence of taurine and TH in rat PG has been reported (Sakai et al., 1987) and taurine has been postulated as an inhibitory neurotransmitter in the rat OB (Belluzzi et al., 2004). It may therefore be proposed that non-GABAergic but dopamin-

ergic PG could contain other inhibitory neurotransmitters such as taurine, although the inclusion of this group within type 1 PG remains uncertain. In other cases, in rodents such as hamsters, insectivores such as the tenrec and in reptiles such as the snake (*E. quadrivirgata*), dopaminergic PG are also GABAergic (Kosaka et al., 1988, 1991, 2005). These data are consistent with those obtained in the rat (Kosaka et al., 1995). However, in amphibians (*R. pipiens* and *X. laevis*) the coexistence of these markers has been checked and they have found to form non-overlapping populations (Boyd and Delaney, 2002).

Group II of GABAergic type 1 PG comprise non-dopaminergic neurons. This group is characterized by the expression of NOS1, and these PG are therefore nitrergic (Crespo et al., 2003). This group is less abundant than the first and no reports of the existence of further subgroups have been made (Crespo et al., 1995, 2003; Briñón et al., 1997).

Non-GABAergic type 1 PG

Recently, a second subtype of type 1 PG has been described (Gutièrrez-Mecinas et al., 2005b). These non-GABAergic neurons can be divided into two groups: (i) CCK-immunopositive cells, and (ii) SOM-containing cells (Gutièrrez-Mecinas et al., 2005b). In addition, immunohistochemical analyses have revealed that SOM-immunopositive PG do not express TRH (Tsuruo et al., 1988) or NPY (Seroogy et al., 1989). In addition, it has been demonstrated that rat cholinoceptive PG do not belong to GABAergic type 1 PG (Le Jeune and Jourdan, 1994; Crespo et al., 1995).

Type 2 periglomerular cells

Type 2 PG restrict their dendrites to the non-ON zone and receive few or no synapses from ON axons. They only establish dendrodendritic synapses with projection neurons. The main neurochemical characteristic of this type is that they do not contain GABA. PG exert their functions through inhibitory synapses, and since type 2 PG do not contain the principal inhibitory neurotransmitter, GABA, other inhibitory substances should be invoked to account for the modulation exerted by these PG. Substances such as glycine or taurine have been proposed to participate as inhibitory neurotransmitters in the OB (Trombley and Shepherd, 1994; Belluzzi et al., 2004). However, this possible expression by type 2 PG awaits confirmation. This type of PG can be subdivided into two groups (Kosaka et al., 1995):

- Group (a): CB-immunopositive PG.
- Group (b): CR-immunoreactive PG.

Later studies characterized the different neurochemical subgroups of each group. Recently, it has been shown that a high percentage of Group (a) PG is guanylate cyclase-immunopositive (Gutièrrez-Mecinas et al., 2005a). In addition, different subpopulations of Group (b) PG have been established. Quantitative studies have shown that TRH is expressed by 24% of the CR-immunoreactive PG subpopulation and that ENK is expressed by a similar percentage of CR-positive PG (Kosaka et al., 1995). The percentage of cells colocalizing ENK and TRH (52%) suggests the existence of a PG subpopulation identified as CR/ENK/TRH (Kosaka et al., 1995). Furthermore, Briñón and co-workers demonstrated the coexpression (15%) in the PG of CR with NC, another CaBP (Briñón et al., 1999).

There are other PG subpopulations whose neurochemical profiles cannot be used to determine whether they belong to type 1 or 2, or, by contrast, whether they constitute a new type of PG. One of these subpopulations comprises PG expressing PV. PV-containing PG do not express GABA, TH, or NADPH-diaphorase/NOS1 (Kosaka et al., 1987; Briñón et al., 1999). Accordingly, they do not belong to GABAergic type 1 PG. Furthermore, no colocalization studies of PV with CB/CR/SOM or CCK have yet been conducted. However, the partial coexistence of PV with NC, or with the Neuron specific Calcium Sensor 1 (NCS-1) has been described, although in low percentages in both cases (Treloar et al., 2005). These data, together with the fact that only 15% of CR-immunoreactive PG contain NC (Briñón et al., 1999), do not allow us to conclude whether the PV/NC subpopulation belongs to CR-immunopositive PG or not.

Interspecies comparison

As described above, the structural organization of the rat glomerulus is defined by two different compartments innervated by two well-characterized neurochemical types of PG (Kosaka and Kosaka, 2005). This compart-

mentalized organization of the glomeruli and the division of PG into two types is seen in different mammalian species such as the musk shrew (*S. Murinus*), the mole (*Mogera wogura*), the hedgehog (*E. europaeus*), the tree shrew (*Tupaia glis*), the bat (*Miniopterus fuliginosus*) and the mouse (*M. musculus*; Kosaka and Kosaka, 2001, 2004; Crespo et al., 2002).

There are three insectivorous mammals - the laboratory musk shrew (*S. murinus*), the lesser hedgehog tenrec (*Echinops telfairi*), and the hedgehog (*E. europaeus*)- for which extensive analyses (synaptologic and neurochemical) of their PG have been carried out. All the studies revealed the type 1 and the type 2 PG sending their dendritic processes into the ON zone or the non-ON zone, respectively, as has been described in the rat (Kosaka and Kosaka, 1999, 2001; Crespo et al., 2002; Kosaka et al., 2005). Moreover, similar to the rat, the dendrites of CB-immunoreactive PG in *S. murinus* and *E. telfairi* branch into the non-ON zone, and hence they should be included in type 2 PG. These data indicate that the glomerular compartments and the different types of PG in *S. murinus* and *E. telfairi* are similar to those described in the rat (Kosaka and Kosaka, 1999, 2001; Kosaka et al., 2005). In *E. europaeus*, only the synaptology of VIP-immunopositive PG has been studied, while it is unknown for other neurochemical populations in that species. In particular, Crespo and co-workers (2002) found that hedgehog VIP-containing PG project their dendrites into the non-ON zone. Therefore, this subpopulation should be classified as type 2 PG. However, the neurochemical composition of the PG types described for the rat is not necessarily the same as in other species. Neurochemical studies have confirmed that in *S. murinus* and *E. telfairi* most CB-positive PG are GABAergic, differing widely from those in the rat (Kosaka and Kosaka, 1999, 2001, 2004). In addition, it has been described in *M. musculus* that most CB-positive PG are GABAergic (Baltanás, 2005). Moreover, in the rat, there are not nitrergic PG that contain CR (Crespo et al., 2003), however, in *M. musculus*, about 70% of nitrergic PG coexpress CR (Kosaka and Kosaka, 2006).

Regarding the neurochemical features of *E. europaeus* PG, CR-, NC-, PV-, CB-, VIP-, and NOS1-containing PG have been identified, whereas there are no cholinergic PG (López-Mascaraque et al., 1989; Alonso et al., 1995; Crespo et al., 1999; Briñón et al., 2001b). The presence of GABAergic or dopaminergic PG has not yet been analyzed. In addition, as in the rat and the mouse, CB-immunopositive PG do not express NADPH-diaphorase activity (Alonso et al., 1995; Kosaka and Kosaka, 2006).

Conclusion

The present review offers a compilation of the data obtained from a broad array of neurochemical studies. They can be summarized in the following points: 1) Many studies performed in different groups of vertebrates have revealed the extraordinary neurochemical heterogeneity of this neuronal type, 2) The expression pattern of diverse neurochemical markers in the rat PG shows important differences with those of other mammals and other vertebrate groups, 3) The chemoarchitecture of PG exhibits considerable interspecies variability for certain neurotransmitters and neuroactive substances whereas other neurochemically-identified PG are remarkably constant between microsmatic and macrosmatic mammals, 4) Both the compartmentalized organization of the glomeruli and the two types of PG innervation inside them are consistent in rodents and in other groups of mammals, 5) the neurochemical composition of PG innervating the same compartment of the glomeruli differs between the rat and other rodents. All these results suggest different types of modulation exerted by the PG in the sensory information relayed within the olfactory glomeruli.

Acknowledgements

The authors express their gratitude to N. Skinner for revising the English version of the manuscript. This work was supported by Ministerio de Educación y Ciencia (SAF2006-05705), Fundación FMM, and Junta de Castilla y León.

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