

Neuronal organization of the main olfactory bulb revisited

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Abstract The main olfactory bulb is now one of the most interesting parts of the brain; firstly as an excellent model for understanding the neural mechanisms of sensory information processing, and secondly as one of the most prominent sites whose interneurons are generated continuously in the postnatal and adult periods. The neuronal organization of the main olfactory bulb is fundamentally important as the basis of ongoing and future studies. In this review we focus on four issues, some of which appear not to have been recognized previously: (1) axons of periglomerular cells, (2) the heterogeneity and peculiarity of dopamine-GABAergic juxtglomerular cells, (3) neurons participating in the interglomerular connections, and (4) newly found transglomerular cells.

Keywords Olfactory bulb · Glomerulus · Interneuron · Axon · Dendrite

Introduction

The main olfactory bulbs are one of the most interesting parts of the brain for at least two reasons. First, the epoch-making study of Buck and Axel (1991) makes the main olfactory bulb—the first station of olfaction—an excellent model for understanding the neural mechanisms of sensory information processing. Second, some pioneering studies

(Altman and Das 1966; Altman 1969; Hinds 1968a, b; Luskin 1993; Lois and Alvarez-Buylla 1994) and numerous recent studies (Lepousez et al. 2013) have revealed that the main olfactory bulb is one of the most prominent sites where intrinsic neurons are generated continuously in the postnatal and adult periods from progenitor cells located in the subventricular zone of the lateral ventricle that migrate through the rostral migratory stream.

Recently, several reviews on the organization of the main olfactory bulb have been published (Kosaka and Kosaka 2009b, 2011, 2014; Imai 2014; Nagayama et al. 2014; Ennis et al. 2015). In our previous reviews (Kosaka et al. 1998; K. Kosaka and T. Kosaka 2005; Kosaka and Kosaka 2009b, 2011, 2014) we also described some aspects of the organization of the main olfactory bulb, focusing mainly on our own data; that is, (1) chemically defined neuron groups of the juxtglomerular or periglomerular cells (Kosaka et al. 1995; Kosaka and Kosaka 2007a), (2) the compartmental organization of the glomerulus, i.e., the olfactory nerve (ON) zone and non-ON zone (Kosaka et al. 1997, 1998), (3) the classification of periglomerular cells into type 1 and type 2 periglomerular cells (Kosaka et al. 1997, 1998, 2001), (4) parvalbumin positive anaxonic external plexiform layer (EPL) multipolar cells with multiple dendritic hot spots displaying the molecular markers for node of Ranvier (NR) and axon initial segments (AISs) such as ankyrin G, β IV-spectrin, sodium channel clusters (Kosaka and Kosaka 2008a; Kosaka et al. 2008), (5) non-principal neurons projecting to the extrabulbar regions, NPP neurons (Kosaka and Kosaka 2007b, 2010; Eyre et al. 2008), (6) the intraglomerular and extraglomerular dendritic links via chemical synapses and gap junctions (Kosaka and Kosaka 2003, 2004b; T. Kosaka and K. Kosaka 2005; Kosaka et al. 2005b), (7) comparative aspects of the main olfactory bulb neuronal organization

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(Kosaka and Hama 1982–1983; Kosaka and Kosaka 1999, 2001, 2004a, Kosaka et al. 2005a). Thus, in this review, to avoid the duplication we discuss only some fundamental issues that are rarely ever referred to but which we have encountered in the course of our morphological analysis and hope to solve in future.

Periglomerular cells; axonic and/or anaxonic, uniglomerular and/or multiglomerular?

Three types of local circuit neurons are generally considered present in the olfactory bulb: granule cells, periglomerular cells, and short-axon cells. Of these, granule cells are anaxonic, whereas both periglomerular cells and short-axon cells have been regarded to bear axons. Regarding periglomerular cells, the textbook of Ramón y Cajal (1995) contains the following description: “Their perikarya give rise to one or more thin dendrites that arborize within the depths or near the periphery of the glomeruli. In addition, they give rise to a very thin axon that courses more or less tangentially between glomeruli and then ends by ramifying within one of them”. Figures 414 and 416 in this latter textbook (Ramón y Cajal 1995; also shown here in Figs. 1 and 2, respectively, with modification) clearly depict the structural characteristics of this description. In Cajal’s figure 414 (Fig. 1 in this review) some cells (cells E, F, H and I) display apparent axonal processes, while others (cells A, B, C, D and G) do not. It is also noteworthy that, as Fig. 1 (Cajal’s figure 414) shows, periglomerular cells are rather heterogeneous in their dendritic arborization; cells C, E, H and I in Fig. 1 extend their dendritic tufts into a nearby single glomerulus, whereas cells A, B, D, F in Fig. 1 extend two or three dendritic tufts into two neighboring glomeruli, and cell G in Fig. 1 extends two dendritic tufts into one nearby glomerulus and another glomerulus somewhat distant from

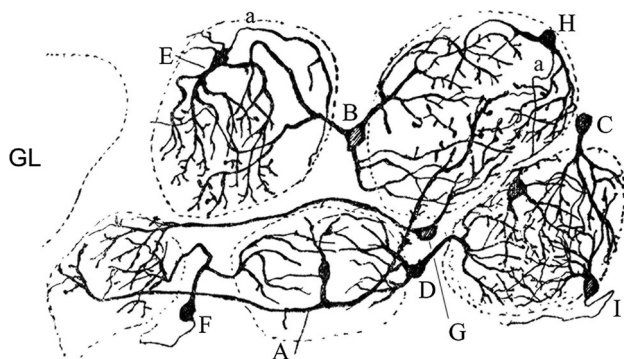


Fig. 1 Drawing of Golgi impregnated periglomerular cells. Modified from Figure 414 of the French edition of Ramón y Cajal’s textbook, Ramón y Cajal S (1911) *Histologie du Système Nerveux de l’homme et des Vertébrés. Tome II* (see Ramón y Cajal 1995)

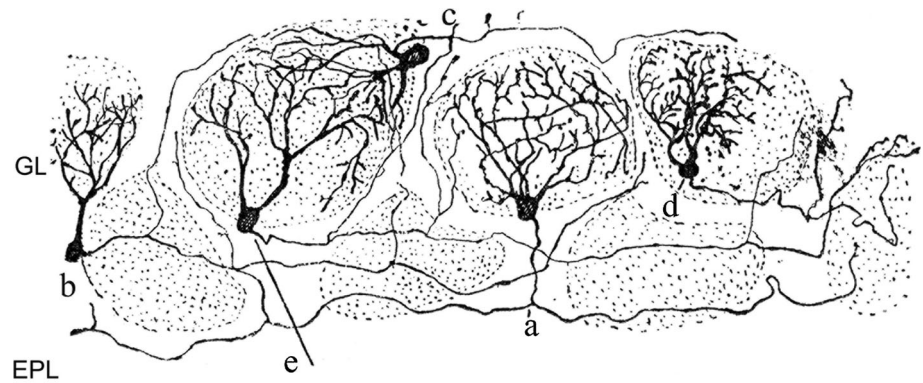
its soma. Similarly, Valverde (1965) also reported a periglomerular cell (cell k in Fig. 25 in Valverde 1965) possessing “three main dendritic branches forming part of the three glomeruli”. These reports indicate that periglomerular cells are not necessarily uniglomerular and some are apparently multiglomerular.

In their landmark series of morphological analyses on the rat main olfactory bulbs (Price and Powell 1970a, b, c, 1971a, b, c, d, 1972a, b, c), Price and Powell (1970a) and Pinching and Powell (1971b) described the structural features of the granule cells and periglomerular cells, respectively, confirming classical studies, but also added some comments on the presence of axons of periglomerular cells: “The axons of the periglomerular cells are not always evident in Golgi-stained material, even after repeated impregnations, a fact also noted by Blanes, who considered this to be impregnation defect. In view of the difficulty of staining these cells at all, and indeed of impregnating the axons of any of the cell types of the glomerular layer, such an explanation would seem fair; however, the absence of an axon in the granule cells, to which the periglomerular cells are in many ways analogous, suggests the possibility that some periglomerular cells may be entirely lacking in an axonal process (Pinching and Powell 1971b).”

Later Golgi studies (Schneider and Macrides 1978; López-Mascaraque et al. 1990) also showed clearly some periglomerular cells bearing and extending apparent axons. As far as we know, the camera lucida drawings of Golgi-impregnated periglomerular cells of the hedgehog main olfactory bulb shown in Figures 4 and 8 of López-Mascaraque et al. (1990) display most clearly the details of periglomerular cell axons, although the authors’ description is as follows, “The axons of periglomerular cells were difficult to trace and we could only follow their paths between different glomeruli in tangential sections. The difficulty resides not only in their extremely fine caliber but also in their complex and twisting paths between several rows of glomeruli”. It is also noteworthy that some periglomerular cells (cell h in Fig. 4 of López-Mascaraque et al. 1990) extend an axonal process into the internal plexiform layer (IPL) after extending some collaterals in the border between the glomerular layer (GL) and the EPL.

The immunocytochemical studies from the 1970s revealed the heterogeneity of juxtglomerular neurons including periglomerular cells in their chemical properties, i.e., neurons containing calretinin (CR), calbindin (CB), parvalbumin (PV), secretagogin (SCGN), nitric oxide synthase (NOS), tyrosine hydroxylase (TH), and various peptides (Alonso et al. 1993, 2001; Briñón et al. 1999, 2001; Crespo et al. 2003; Gutiérrez-Mecinas et al. 2005; Kosaka et al. 1995, 1997, 1998; Kosaka and Kosaka 2007a, b, 2008a, 2013; Mulder et al. 2009). So far, we have encountered only a few chemically defined periglomerular cells with possible

Fig. 2 Drawing of Golgi impregnated periglomerular cells. Modified from Figure 416 of Ramón y Cajal S (1911) *Histologie du Système Nerveux de l'homme et des Vertébrés. Tome II* (see Ramón y Cajal 1995)

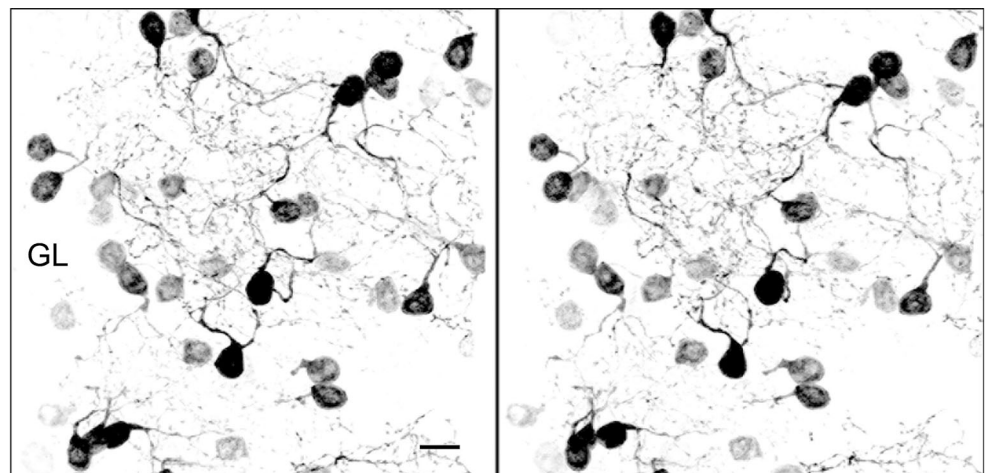


axonal processes. For example, as Fig. 3 shows, CB-positive periglomerular cells, one of the type 2 periglomerular cells, appear to have no axonal processes (Kosaka and Kosaka 2010). On the other hand, NOS positive periglomerular cells (Kosaka and Kosaka 2007b), PV positive periglomerular cells (Kosaka and Kosaka 2008a) and SCGN positive juxtglomerular cells (Kosaka and Kosaka 2013) sometimes displayed thin axon-like processes that we could follow to some extent. Somewhat different from these periglomerular cells whose individual processes could be occasionally traced, TH positive processes clustered compactly in glomeruli and it was usually difficult to trace their individual processes in immunocytochemically stained sections of normal wild type animals. However, in sensory-deprived olfactory bulbs we could occasionally trace individual TH-positive perikarya and their processes and observe some details of TH-positive juxtglomerular neurons. As is well known, when the sensory input is reduced/deprived by, e.g., unilateral naris occlusion, TH-positive somata and processes are reduced in number, but they survive and their TH immunoreactivities recover soon after removal of the occlusion (Baker et al. 1983, 1984; Kosaka et al. 1987b). We encountered some small- to medium-sized TH-positive

neurons displaying the characteristics of so-called classical periglomerular cells, that is, tuft-like intraglomerular dendrites and thin axon-like processes (Figs. 4; 5; Fig. 6a, c).

Recently we applied immunostaining of molecular markers for the nodes of Ranvier and axon initial segments (NR/AIS molecular markers), i.e., ankyrin G, sodium channel clusters, β IV-spectrin and phospho-I κ B α , to further examine the possible presence of axonal processes of those chemically identified neurons (Kosaka and Kosaka 2008a, 2010, 2011; Kosaka et al. 2008). As expected, mitral cells, tufted cells and short-axon cells (short-axon cells defined with some chemical markers such as NOS, CB and PV) displayed these NR/AIS molecular markers on the proximal portions of their apparent axonal processes (Kosaka and Kosaka 2008a, 2010, 2011; Kosaka et al. 2008). Among juxtglomerular neurons, external tufted cells (BDA-labeled and/or NOS-positive tufted cells), superficial short-axon cells (NOS- or CB- or PV-positive cells) and the larger type of dopamine (DA)-GABAergic neurons (Figs. 7, 8, 9) clearly showed axonal segments positive for NR/AIS molecular markers (Kosaka and Kosaka 2008a, 2010, 2011). Interestingly, we encountered a few larger type DA-GABAergic neurons with two AISs positive for NR/AIS

Fig. 3 Stereo pair of confocal laser scanning microscope projection images of calbindin (CB)-immunostained periglomerular cells in a 50 μ m-thick section of mouse olfactory bulb. Bar 10 μ m



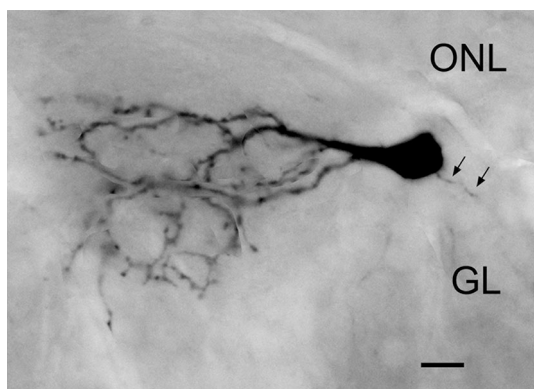


Fig. 4 Photomontage of a small TH positive cell in the GL of a rat olfactory bulb whose olfactory input was deprived for 5 weeks before fixation. *Arrows* Axon-like process arising from the soma of a presumed periglomerular cell. *Bar* 10 μ m

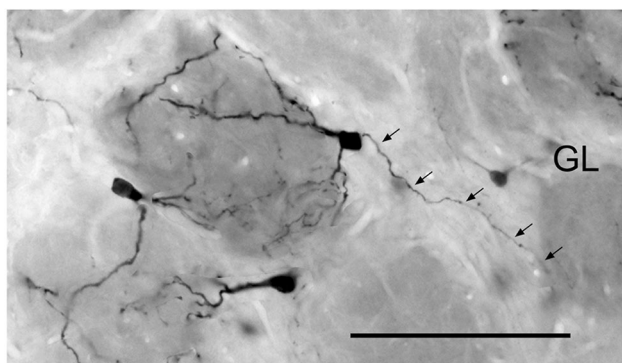


Fig. 5 Photomontage of TH positive cells in the GL of a rat olfactory bulb whose olfactory input was deprived for 5 weeks before fixation. *Arrows* An axon-like process arising from the soma of a presumed periglomerular cell. *Bar* 100 μ m

molecular markers (Fig. 8). Other juxtglomerular neurons, presumed periglomerular cells, i.e., CB, CR, NOS, SCGN and smaller TH-positive neurons, appeared to have no axonal processes positive for these NR/AIS molecular markers so far examined. Interestingly, we encountered a “dendritic hot spot”—short segments positive for these NR/AIS molecular markers—on the intraglomerular dendrites of NOS-positive, presumed periglomerular, cells, whereas axon-like thin processes of those NOS-positive periglomerular cells were negative for NR/AIS molecular markers (Kosaka et al. 2008). Thus, we cannot simply regard such thin axon-like processes as typical axons with the AIS displaying the molecular organization for spike initiation. These observations indicate that some of the chemically defined periglomerular cells are anaxonic, or at least bear no typical axons. Whether some other chemically defined periglomerular cells correspond to classical periglomerular cells with apparent axonal processes remains to be determined.

In recent electrophysiological studies, juxtglomerular neurons in slice preparations were labeled intracellularly with biocytin or fluorescent dyes (McQuiston and Katz 2001; Zhou et al. 2006; Gire and Schoppa 2009); some cells identified as periglomerular cells displayed axons whereas others did not. Based on the study of the dissociated culture of rat and mouse olfactory bulbs immunostained for ankyrin G, Chand et al. (2015) showed that there were two different types of dopaminergic neurons, one possessing an AIS and the other without an AIS, and that those AIS-positive cells were morphologically and functionally distinct from their AIS-negative counterparts; the authors assumed that the former corresponds to the larger type of DA-GABAergic juxtglomerular neurons and the latter to the smaller type of DA-GABAergic juxtglomerular neurons. Thus, so far, among chemically defined juxtglomerular neurons other than tufted cells, only the larger type of DA-GABAergic juxtglomerular neurons were confirmed to bear typical axonal processes. Do they then correspond to the classical axon-bearing periglomerular cells? As described in the next section, this is not the case.

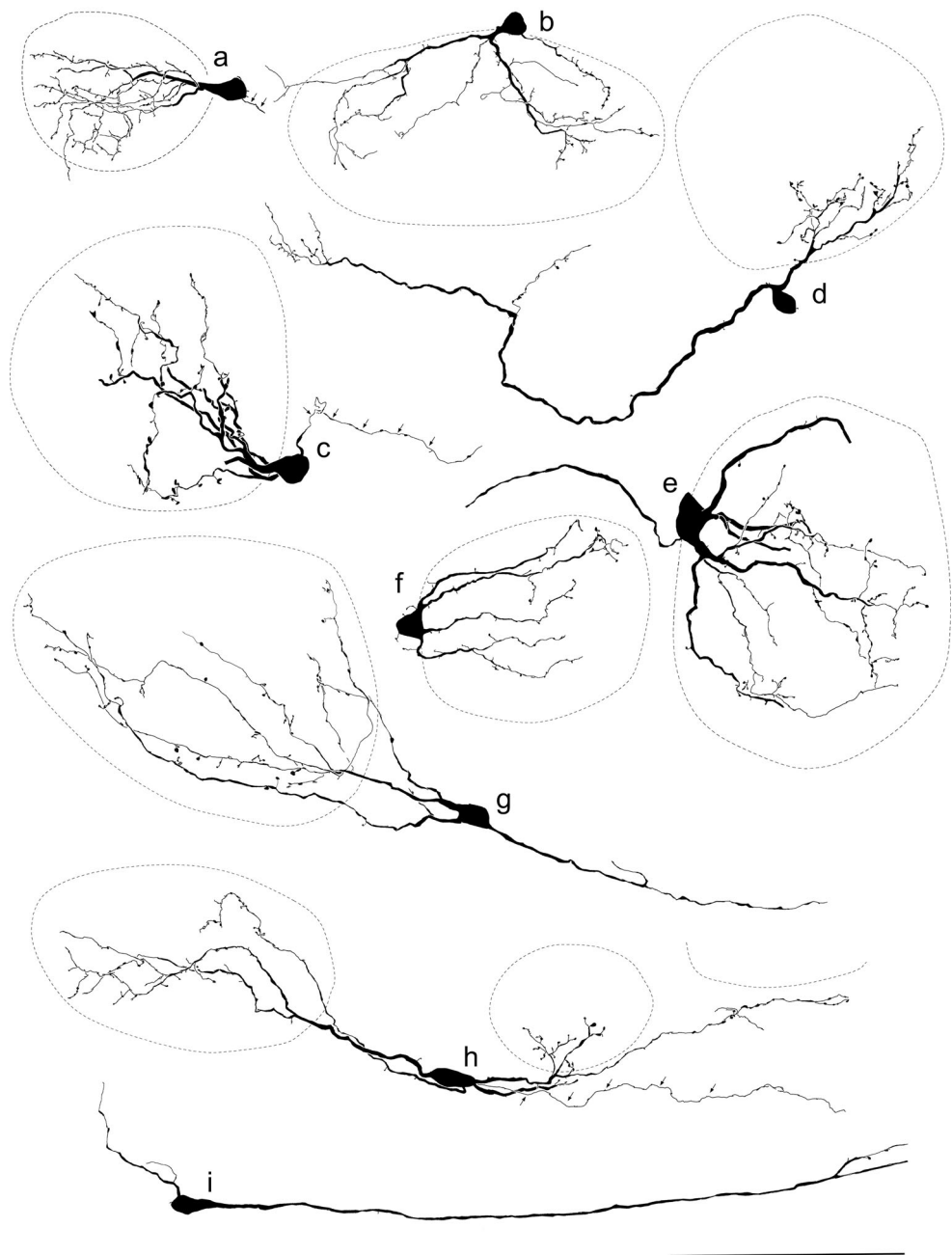
At any rate the accumulating data indicate that we have not yet identified conclusively the chemical properties of those classical axonic periglomerular cells characterized with the Golgi-impregnation method.

Dopaminergic juxtglomerular cells; periglomerular cells, external tufted cells, short-axon cells or something else?

Among chemically defined juxtglomerular neurons, dopaminergic neurons are somewhat peculiar. Dopaminergic neurons have been identified mostly by their immunocytochemistry for TH (Halász et al. 1981). TH-positive neurons in the juxtglomerular region were considered to consist of two populations, based on structural features such as somal location, size and intraglomerular dendritic arborizations. The larger type of TH-positive juxtglomerular neurons were formerly regarded as a type of external tufted cell, whereas the smaller type are a type of periglomerular cell (Halász et al. 1981; Davis and Macrides 1983). For example, Davis and Macrides (1983) described them as follows; “Based on their somal sizes and the association of their dendrites with glomeruli, most of the larger THLI (TH-like immunoreactive) neurons in the glomerular layer can be identified as external tufted cells, whereas the smaller and less common THLI neurons can be classified as periglomerular cells...”.

On the other hand, some periglomerular cells were shown to be GABAergic on the basis of the immunocytochemistry for the GABA synthesizing enzyme, glutamic acid decarboxylase (GAD; Ribak et al. 1977). Later, with

Fig. 6 Camera lucida drawings of TH positive cells in the GL of a rat olfactory bulb whose olfactory input was deprived for 5 weeks before fixation. Cell **a** is the cell shown in Fig. 4. *Broken lines* indicate the outlines of individual glomeruli. In cells **a**, **c** and **h** *arrows* indicate axon-like processes. Cells **a–h** show the tuft-like intraglomerular dendritic branches. Cell **i** is located at the border between the GL and external plexiform layer (EPL), extending a short process into a glomerulus and a long process in the border zone parallel to layers. *Scale bar* is 100 μm



two-color immunocytochemistry using a sheep anti-GAD and a rabbit anti-TH, Mugnaini et al. (1984) reported that “The two labels are never seen in the same cell” and “GABA and dopamine periglomerular cells are separate populations”. However, surprisingly, we revealed that GAD and TH immunoreactivities frequently colocalized in the same neurons in the juxtglomerular region of the rat main olfactory bulb (Kosaka et al. 1985); in the rat main olfactory bulb, 70–85 % of TH-positive neurons have been shown to be GAD and/or GABA-like immunoreactive (Kosaka et al. 1987a, c, d, 1995; Gall et al. 1987). In the mouse main olfactory bulb, our immunocytochemical

studies on wild-type mice (Kosaka and Kosaka 2007a) as well as other studies on the GAD-GFP mice (Parrish-Aungst et al. 2007; Panzanelli et al. 2007) showed that nearly all TH-positive juxtglomerular neurons were GABAergic. Thus, these studies revealed that almost of dopaminergic juxtglomerular neurons were included into GABAergic juxtglomerular neurons and that both the smaller type and larger type of dopaminergic neurons could be regarded as “DA-GABAergic juxtglomerular cells”.

In the olfactory bulbs of other mammals and submammals, the presumed colocalization of these two classical transmitters was confirmed and is thus supposed to be

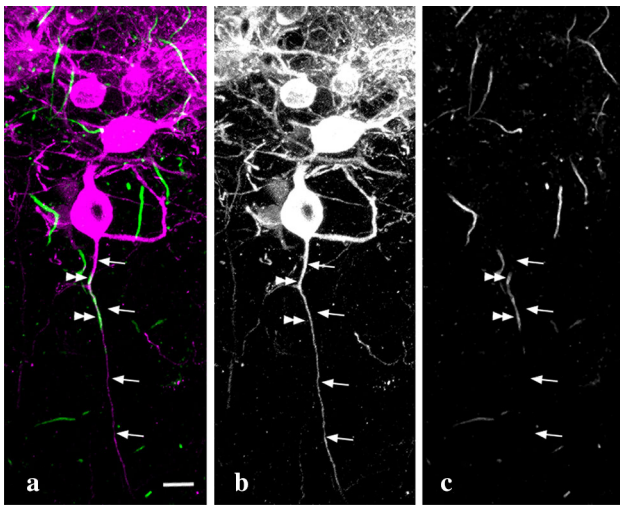


Fig. 7 CLSM partial projection images. Mouse main olfactory bulb. **a** Pseudo-colored CLSM partial projection image double-immunostained for tyrosine hydroxylase (TH; *magenta*) and β IV-spectrin (*green*). **b**, **c** show individual channels shown in **a**, i.e., *magenta* (**b**) and *green* (**c**) channels. One TH-positive cell displays a β IV-spectrin positive axon initial segments (AIS; *arrows*) descending in the EPL. *Bar* 10 μ m

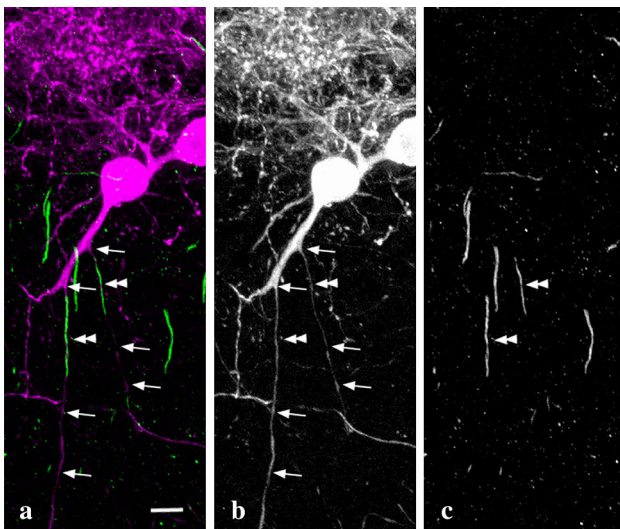


Fig. 8 CLSM partial projection images. Mouse main olfactory bulb. **a** Pseudo-colored CLSM partial projection image double-immunostained for TH (*magenta*) and β IV-spectrin (*green*). **b**, **c** Individual channels shown in **a**, i.e., *magenta* (**b**) and *green* (**c**) channels. One TH-positive cell displays a dendrite from which two β IV-spectrin-positive AISs (*arrows*) originate and descend in the EPL. *Bar* 10 μ m

general in the olfactory bulbs of various species and conserved phylogenetically; that is, in hamsters (Kosaka et al. 1988), musk shrews (Kosaka and Kosaka 1999, 2001, 2004a), moles (Kosaka and Kosaka 2004a), hedgehogs (Kosaka and Kosaka 2004a), tree shrews (Kosaka and Kosaka 2004a), bats (Kosaka and Kosaka 2004a), lesser hedgehog tenrecs (Kosaka et al. 2005a), snakes (Kosaka

et al. 1991), frogs (our unpublished observations), goldfish (our unpublished observations), zebrafishes (Zhu et al. 2013), sharks (our unpublished observations), and lamprey (Barreiro-Iglesias et al. 2009).

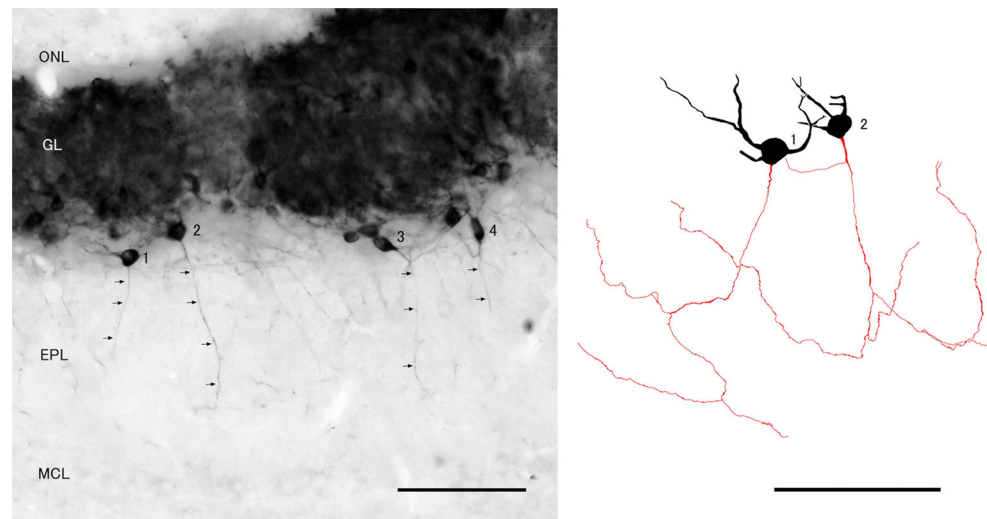
Recent physiological studies on transgenic mice reported that both dopamine and GABA were released from TH-expressing juxtglomerular cells, indicating the functional significance of dopamine-GABA colocalization (Maher and Westbrook 2008; Borisovska et al. 2013; Liu et al. 2013).

As previously described, TH-expressing neurons are known to be heterogeneous regarding soma sizes. Pignatelli et al. (2005) showed clearly that the distribution of soma sizes (diameter) of TH-expressing juxtglomerular neurons in TH-GFP mice was not normal and could be best fitted with two Gaussian curves, which we also confirmed in our own materials from wild type mice (Kosaka and Kosaka 2007a), indicating at least two populations of TH-expressing juxtglomerular neurons differing in soma size. Our recent experiments clearly showed the prominent differences between the larger and smaller types of DA-GABAergic juxtglomerular neurons (Kosaka and Kosaka 2008b, 2009a) in two aspects, i.e., (1) participation in long-range interglomerular connections, and (2) time of origin.

Firstly, our tracer experiments using a retrograde tracer, fluorogold (FG), or retro- and antero-grade tracer, cholera toxin B subunit (CTB), revealed that the larger type of TH-positive juxtglomerular neurons are the main source of long-range interglomerular connections. When the injections were restricted to the GL, tracer-labeled cells were encountered in the GL and the superficial part of the EPL, not only near the injection sites but also more than 500 μ m distant from the injection sites. Most, but not all, of the tracer-labeled neurons distant from the injection sites were large TH-positive juxtglomerular neurons (Kosaka and Kosaka 2008b). When CTB was injected and restricted to the GL, in addition to retrogradely CTB-labeled TH positive somata, anterogradely CTB-labeled TH-positive puncta were encountered in glomeruli (mainly in the ON zone of the glomerular compartments), indicating that the large DA-GABAergic juxtglomerular neurons near the injection site extended their axons into glomeruli located distantly (Kosaka and Kosaka 2011).

Recently, Kiyokage et al. (2010) reported that, on the basis of their analyses of TH-GFP mice, TH-expressing juxtglomerular neurons extended processes distantly and thus confirmed our conclusion, although they did not consider the somal sizes but divided TH-expressing juxtglomerular neurons into oligglomerular and polyglomerular types. Kiyokage et al. (2010) insisted that all DA-GABAergic juxtglomerular neurons are “short-axon cells” and none are periglomerular cells. However, as described above, some DA-GABAergic juxtglomerular neurons are now shown to be anaxonic (Chand et al.

Fig. 9 Photomontage of a TH-immunostained section of mouse main olfactory bulb. Horizontal section. Cells 1–4 are the larger type of TH-positive juxtglomerular neurons extending axonal processes (arrows) into the EPL. Camera lucida drawings of cells 1 and 2 are also shown. Bars 100 μm



2015), and thus cannot be “short-axon cells”. Furthermore, as shown in Figs. 4–6, at least some of DA-GABAergic juxtglomerular neurons are regarded as periglomerular cells. As discussed in detail in our previous review (Kosaka and Kosaka 2011), “the superficial short-axon cells are characterized by the entirely periglomerular distribution of their dendrites (Pinching and Powell 1971b) with no or few intraglomerular dendrites”. However, apparent spiny dendritic processes of biocytin labelled DA-GABAergic juxtglomerular neurons (Fig. 4 in Kiyokage et al. 2010) were located in glomeruli. Thus we do not think that the DA-GABAergic juxtglomerular neurons shown in Kiyokage et al. (2010) are superficial short-axon cells.

On the other hand, the larger type of DA-GABAergic juxtglomerular neurons might be somewhat difficult to characterize as typical periglomerular cells. In addition, as we reported in our previous review (Kosaka and Kosaka 2011), “a few DA-GABAergic cells with relatively large somata scattered in the EPL and extended some smooth dendritic processes into glomeruli. They were also frequently labeled retrogradely when tracer was injected into the GL”. Thus, we suggested that they could be regarded as “displaced DA-GABAergic juxtglomerular neurons”, further indicating that the large, as well as the displaced, DA-GABAergic juxtglomerular neurons might separate from the typical periglomerular cells or the typical short-axon cells. We tentatively named these large DA-GABAergic cells “inhibitory juxtglomerular association neurons (IJGA neurons)”. The details of structural features of these DA-GABAergic cells participating in long-range interglomerular connections, i.e., IJGA neurons, remain to be revealed. Regarding the interglomerular connections, in the next

section we would like to discuss further some confusion induced by the data published by Shipley’s group.

Secondly, DA-GABAergic juxtglomerular neurons are known to be one of the major groups of adult generated juxtglomerular neurons (De Marchis et al. 2007; Merkle et al. 2007; Whitman and Greer 2007). That being the case, are both the larger and smaller types of DA-GABAergic juxtglomerular neurons included in those adult generated juxtglomerular neurons? We examined the time of origin of DA-GABAergic juxtglomerular neurons using the thymidine analog 5-bromo-2'-deoxyuridine (BrdU) and showed that the time of origin of these large DA-GABAergic juxtglomerular neurons is mainly pre- and peri-natal, with none arising in adult periods so far as we examined, whereas the smaller type of DA-GABAergic juxtglomerular neurons are produced even in adult periods (Kosaka and Kosaka 2009a). Thus, the large DA-GABAergic juxtglomerular neurons participating in interglomerular connections differ from adult-generated DA-GABAergic juxtglomerular neurons; the adult-born DA-GABAergic juxtglomerular neurons should be included in the smaller type of DA-GABAergic juxtglomerular neurons.

So far, we have divided DA-GABAergic juxtglomerular neurons into two categories—smaller and larger types (Kosaka and Kosaka 2007a)—and other group into oligglomerular and polyglomerular types (Kiyokage et al. 2010). Taking the apparent heterogeneity of the DA-GABAergic juxtglomerular neurons in their structural features into consideration (Fig. 6), this categorization into two groups seems oversimplified and there is a need to analyze details of the structural features, including the differentiation between axons and dendrites, before classifying DA-GABAergic juxtglomerular neurons.

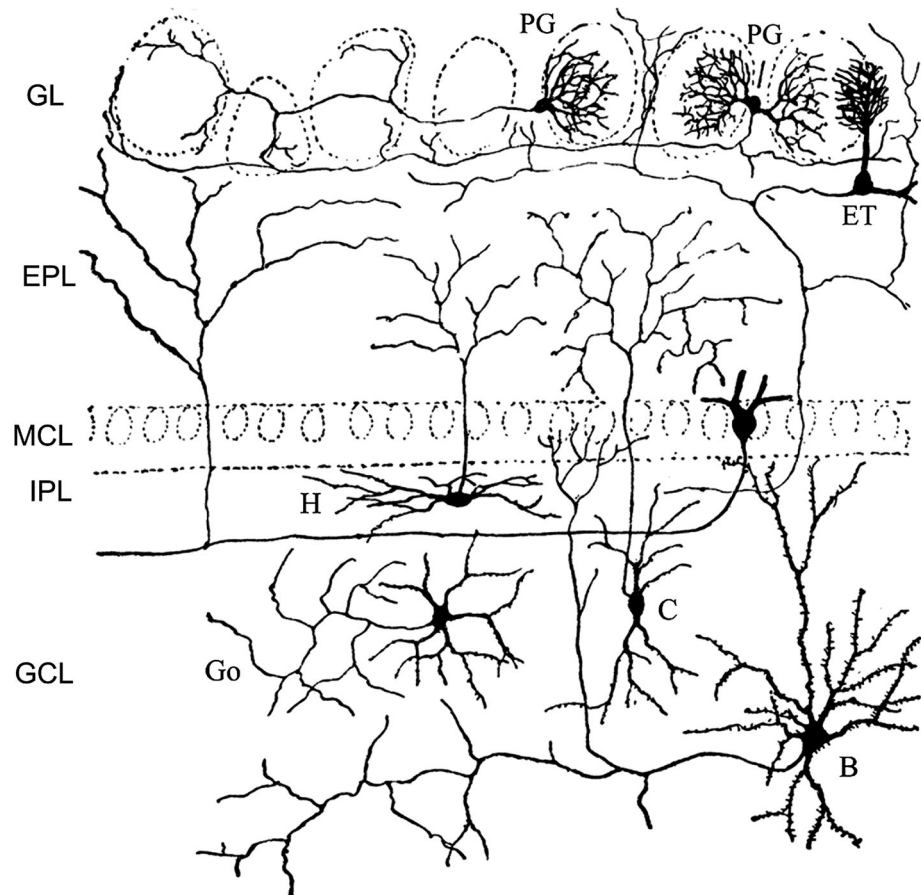
Neurons participating in interglomerular connections

Classical Golgi studies showed that the periglomerular cells and tufted cells of the main olfactory bulb extend their axons laterally in the GL to make interglomerular connections (Figure 415 in Ramón y Cajal 1995, which is also shown in Fig. 10 with modification). In addition, after their finding of superficial short-axon cells, Pinching and Powell (1971b, 1972c) revealed that these cells also extended axonal collaterals in the GL. Pinching and Powell (1972c) applied small lesions to the superficial layers of the dorsal surface of the rat olfactory bulb and examined the resulting axonal degeneration with light- and electron-microscopy. They revealed that the external tufted cells, periglomerular cells and superficial short-axon cells extended axonal collaterals to various extents in the GL, and interconnected the glomeruli and periglomerular regions. In their paper, Pinching and Powell (1972c) summarized as follows: “Accepting the limitations and provisos imposed on a study in which several types of axon have been interrupted, this method has provided evidence of the axonal distribution of the different cells in the glomerular layer of the bulb: the tufted cell collaterals extend farthest (6–12

glomeruli), periglomerular cells less far (4–5 glomeruli), and superficial short-axon cells least far (2–3 glomeruli); these estimates are consistent with those obtained from Golgi-impregnation but provide more substantial evidence”.

However, based on their morphological and physiological analyses on the slices from transgenic mice (GAD65-GFP mice), Aungst et al. (2003) proposed that the main source of long interglomerular connections was the “glutamatergic excitatory short-axon cells”, which they stressed as a newly found type of neurons, rather than the GABAergic periglomerular cells or GABAergic superficial short-axon cells or glutamatergic external tufted cells. They supply the following description: “To investigate the role of GABAergic neurons in interglomerular projections, we made DiI injections in transgenic mice in which the promoter for glutamic acid decarboxylase 65 (GAD65...) drives the expression of green fluorescent protein..., the contribution of GABAergic cells to interglomerular connections is minor. Furthermore, none of the labelled cells had prominent dendritic tufts characteristic of DiI-labelled ET (*external tufted) cells, suggesting that ET cells do not contribute substantially to the interglomerular network”. In their paper in *Nature* (Aungst et al. 2003) they made

Fig. 10 Neurons in the periglomerular region and deep short-axon cells. Modified from Figure 415 in Ramón y Cajal S (1911) *Histologie du Système Nerveux de l'homme et des Vertébrés. Tome II* (see Ramón y Cajal 1995). *B* Blanes cell, *C* Cajal cell, *ET* external tufted cell, *Go* Golgi cell, *H* horizontal cell, *PG* periglomerular cell



“whole cell recordings from JG (*juxtglomerular) cells 3 or 4 glomeruli away from the site of focal glomerular stimulation in main olfactory bulb slice” in order to “exclude some contribution of long-range inhibitory connections”. Then they concluded that “These results further support the conclusion that most interglomerular connections are excitatory and glutamatergic”.

The proposal by Aungst et al. (2003) apparently conflicted with previous classical observations and our own recent data showing the larger type of DA-GABAergic juxtglomerular neurons as the main source of long-range interglomerular connections described in the previous section. But, as described above, the same group reported recently that DA-GABAergic juxtglomerular neurons are the main source of interglomerular connections on the basis of their analyses of TH-GFP mice (Kiyokage et al. 2010) and thus confirmed our conclusions, which seems to us to deny their own previous conclusion. In a recent textbook article, they showed a figure including DA-GABAergic juxtglomerular neurons with interglomerular connections (Fig. 3 in Ennis et al. 2015), which appeared to replace the “glutamatergic excitatory short-axon cells” shown in their original article (Fig. 6 in Aungst et al. 2003), although they cited their own paper published in *Nature* (Aungst et al. 2003) as follows (Ennis et al. 2015): “These DA-GABAergic cells and a few neurons that express GAD67, but lack TH contact multiple glomeruli over distances up to 1–2 mm to form extensive interglomerular circuits (Kiyokage et al. 2010; Aungst et al. 2003)”. It seems that they cited their paper in 2003 as if it proposed that the DA-GABAergic juxtglomerular neurons, instead of their “glutamatergic excitatory short-axon cells”, were the main source of interglomerular connections. Then, where have the “glutamatergic excitatory short-axon cells” gone? Are there no “glutamatergic excitatory short-axon cells”? Although the authors never discuss this theme, we think there might be other possible interpretations of their previous data (Aungst et al. 2003). If neurons with interglomerular connections shown by Aungst et al. (2003) are really glutamatergic in nature, then those neurons cannot be the large DA-GABAergic juxtglomerular neurons. Although they described “none of the labeled cells had prominent dendritic tufts characteristic of DiI-labeled ET cells, suggesting that ET cells do not contribute substantially to the interglomerular network”, one of the most plausible interpretations is that those neurons were a type of “external tufted cell” rather than the newly discovered glutamatergic “short-axon cells”. In fact the cell shown in Fig. 2g of Aungst et al. (2003) extended a tuft-like dendritic branch into a glomerulus and several secondary dendrite-like branches in the juxtglomerular region. External tufted cells are heterogeneous (Macrides and Schneider 1982) and, as well known, some have been shown to extend axonal branches in the GL-EPL (Ramón y Cajal 1995; Macrides and Schneider

1982; López-Mascaraque et al. 1990), and to participate in interglomerular connections (Pinching and Powell 1972c). Macrides and Schneider (1982) described the structural details of Golgi-impregnated tufted cells and divided them into several types on the basis of their soma locations and dendritic branches. Among them their “external tufted cells with sparsely branched secondary dendrites” are especially interesting for “approximately one-third of the external tufted cells with sparsely branched secondary dendrites and 30 % of those in our sample have multiglomerular arborizations”, which could be misinterpreted as “short-axon cells” by Aungst et al. (2003). Schoenfeld et al. (1985) revealed the heterogeneity of external tufted cells in their axonal projections and suggested three types of external tufted cells, which were summarized by Halász (1990) as follows: (1) conventional projection-type external tufted cells; (2) external tufted cells with the associational pathway between the opposing regions of the medial and lateral olfactory bulb; and (3) interneuron-like external tufted cells. As our observations (Kosaka and Kosaka 2008b) indicated, as also confirmed by Kiyokage et al. (2010), “there might be some additional minor group of neurons contributing to the long interglomerular connections (Kosaka and Kosaka 2008b)” other than the large DA-GABAergic juxtglomerular neurons. One of the candidates for non DA-GABAergic neurons contributing to the long interglomerular connections must be a type of external tufted cells. Thus, it is most plausible to think that the results shown by Aungst et al. (2003) confirmed the previous results obtained by Pinching and Powell (1972c).

In the classical experimental study of Pinching and Powell (1972c), did they encounter the neurons corresponding to the large DA-GABAergic juxtglomerular neurons, the major source of the long-range interglomerular connections? In their study, the depth of the lesion appears to be restricted to the surface of the olfactory bulb, presumably including the ONL, GL and only the superficial portion of the EPL. Our preliminary studies indicated that the axons arising from the large DA-GABAergic juxtglomerular neurons frequently descended into the EPL rather than extended laterally in the GL (Figs. 7–9), occasionally close to the mitral cell layer MCL (Kosaka and Kosaka 2011), then branched and extended laterally in the EPL and their collaterals ascended to the GL. Those axons might then not be lesioned in the experiments by Pinching and Powell (1972c), and thus could be undetected in their study. Similarly, in the study of Aungst et al. (2003), the cut through the deep bulb layer including the EPL might lesion the axonal processes of those large DA-GABAergic juxtglomerular neurons and thus preclude detection of their contribution to the interglomerular connections, with the excitatory interglomerular

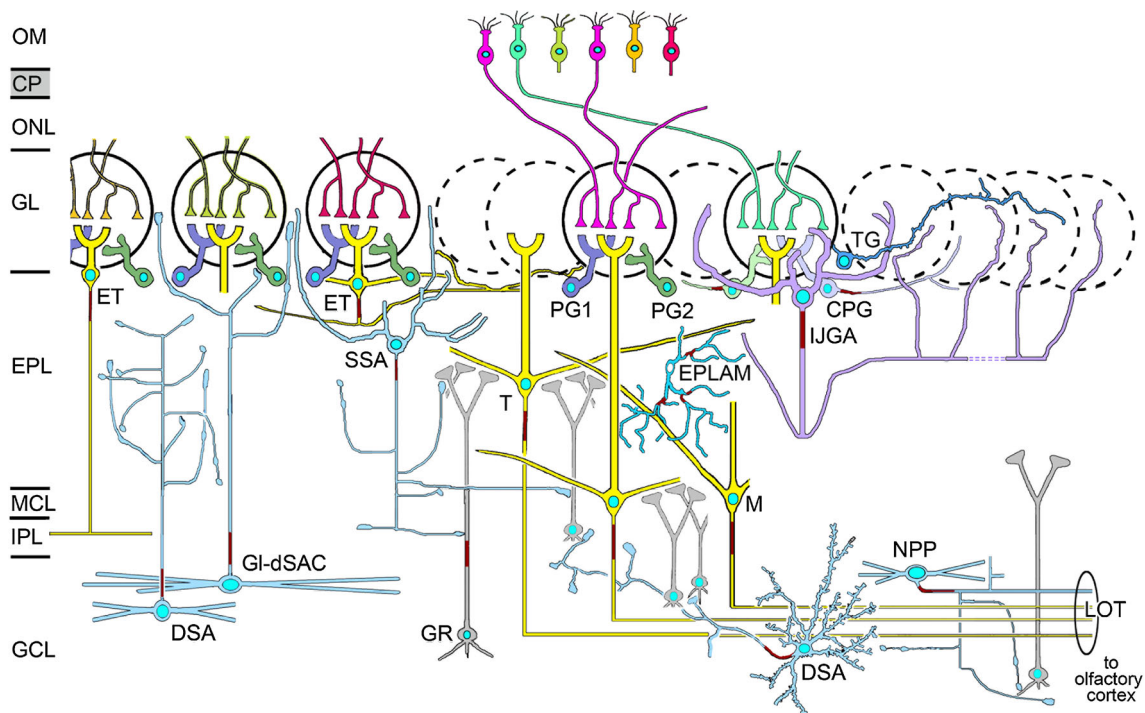


Fig. 11 Scheme of the neuronal organization of the main olfactory bulb in rodents. *CPG* Classical periglomerular cell with axon, *DSA* deep short-axon cell, *EPL* external plexiform layer, *EPLAM* EPL anaxonic multipolar neuron, *ET* external tufted cell, *GCL* granule cell layer, *Gl-dSAC* deep short-axon cell with axonal ramification in the GL, *GR* granule cell, *IJGA* inhibitory

juxtglomerular association neuron, *IPL* internal plexiform layer, *LOT* lateral olfactory tract, *M* mitral cell, *MCL* mitral cell layer, *NPP* nonprincipal projection neuron, *OM* olfactory mucosa, *ONL* olfactory nerve layer, *PG1* and *PG2* type 1 and type 2 periglomerular cell, *SSA* superficial short-axon cell, *T* tufted cell, *TG* transglomerular cell

connections of external tufted cells presumably remaining intact.

At any rate we had better go back to the classical descriptions, i.e., that different types of neurons near the GL participate in interglomerular connections: external tufted cells, periglomerular cells and superficial short-axon cells (Pinching and Powell 1972c). The larger type of DA-GABAergic juxtglomerular neurons might be the fourth cell group participating in interglomerular connections; presumably they perform a major role in long-range interglomerular connections, whereas other types participate mainly in medium- to short-range interglomerular connections. Details of the structural features of each of those juxtglomerular neurons participating in interglomerular connections remain to be revealed.

Transglomerular cells

It has been generally considered that the juxtglomerular neurons consist of three types of neurons, periglomerular cells, external tufted cells and superficial short-axon cells. As described above, the larger type of DA-GABAergic neurons

can be another type of juxtglomerular neurons. In addition “transglomerular cells (TG cells)” have been recognized recently as another type of juxtglomerular neurons. Transglomerular cells were found among SCGN-positive juxtglomerular neurons (Kosaka and Kosaka 2013).

SCGN-positive juxtglomerular neurons are heterogeneous in their structural features including apparent periglomerular cells. Among SCGN-positive neurons some extended slender dendritic processes into a glomerulus that penetrated into another nearby glomeruli, spanning two or three glomeruli. Thus, we tentatively named them “transglomerular cells (TG cells)”. Our preliminary dye-labelling studies indicated that there are possible SCGN-negative transglomerular cells, indicating that transglomerular cells are also heterogeneous in their chemical properties. The details of transglomerular cells remain to be revealed.

Conclusion

The main olfactory bulb is occasionally compared to the retina (Shepherd 2004). In the retina there are only five major classes of neurons, photoreceptors, horizontal cells,

bipolar cells, amacrine cells and ganglion cells, but each class is very diverse and mammalian retinas contain more than 60 distinct cell types (Masland 2012). In contrast, we still do not know how many types (or classes) of neurons are contained in the main olfactory bulb. Moreover, it seems that we lack distinct definitions of cell type such as short-axon cells, periglomerular cells, etc. Although many aspects of the main olfactory bulb circuit remain unknown or uncharacterized, we show a tentative scheme of the neuronal organization of the main olfactory bulb, which, although incomplete, incorporates some recent findings (Fig. 11).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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