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Review

# Satellite glial cells in sympathetic and parasympathetic ganglia: In search of function

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ABSTRACT

Glial cells are established as essential for many functions of the central nervous system, and this seems to hold also for glial cells in the peripheral nervous system. The main type of glial cells in most types of peripheral ganglia – sensory, sympathetic, and parasympathetic – is satellite glial cells (SGCs). These cells usually form envelopes around single neurons, which create a distinct functional unit consisting of a neuron and its attending SGCs. This review presents the knowledge on the morphology of SGCs in sympathetic and parasympathetic ganglia, and the (limited) available information on their physiology and pharmacology. It appears that SGCs carry receptors for ATP and can thus respond to the release of this neurotransmitter by the neurons. There is evidence that SGCs have an uptake mechanism for GABA, and possibly other neurotransmitters, which enables them to control the neuronal microenvironment. Damage to post- or preganglionic nerve fibers influences both the ganglionic neurons and the SGCs. One major consequence of postganglionic nerve section is the detachment of preganglionic nerve terminals, resulting in decline of synaptic transmission. It appears that, at least in sympathetic ganglia, SGCs participate in the detachment process, and possibly in the subsequent recovery of the synaptic connections. Unlike sensory neurons, neurons in autonomic ganglia receive synaptic inputs, and SGCs are in very close contact with synaptic boutons. This places the SGCs in a position to influence synaptic transmission and information processing in autonomic ganglia, but this topic requires much further work.



## Contents



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*Abbreviations:* apoD, apolipoprotein D; BDNF, brain derived neurotrophic factor; GFAP, glial fibrillary acidic protein; EM, electron-microscopy; ECM, extracellular matrix; HRP, horseradish peroxidase; HSP, heat-shock protein; 6-OHDA, 6-hydroxydopamine; IL-6, interleukin-6; LIF, leukemia inhibitory factor; LTP, long term potentiation; MMP, matrix metalloproteinase; MCP-1, monocyte chemoattractant protein-1; NGF, nerve growth factor; N-CAM, neural cell adhesion molecule; SGC, satellite glial cell

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## 1. Introduction: what do we know about glial cells?

It is now beyond question that glial cells play an essential role in most aspects of the nervous system. They control the neuronal microenvironment and participate in the regulation of synaptic transmission (Haydon and Carmignoto, 2006; Perea et al., 2009; Simard and Nedergaard, 2004). Glial cells are able to transmit signals over long distances in the form of $Ca^{2+}$ waves (Scemes and Giaume, 2006) and are also important for the development of the nervous system and for the formation of synaptic contacts (Barres, 2008). Glia have a central position in neurological disorders, inflammation and pain (Giaume et al., 2007; Milligan and Watkins, 2009). Numerous reviews on glial cells, mostly those in the central nervous system (CNS), have been published recently, (e.g., Barres, 2008; Haydon et al., 2009; Takano et al., 2009; Wang and Bordey, 2008). For recent books on glia see Kettenmann and Ransom (2005), Verkhratsky and Butt (2007), and Parpura and Haydon (2009). In this introduction, only selected topics, which are directly relevant to glial cells in autonomic ganglia, will be highlighted. Another important type of peripheral glial cells, Schwann cells, will be only briefly dealt with here (see Section 5); for a review on these cells see Griffin and Thompson (2008).

The vast majority of glial studies have focused on the CNS, covering astrocytes, oligodendrocytes, retinal Müller cells, Bergmann cells, and microglia. When glial cells in the peripheral nervous system (PNS) are discussed, usually only Schwann cells are mentioned. However, the PNS consists not only of nerve fibers, but includes a large number of ganglia containing neuronal cells bodies and also specialized glial cells, which are distinct from Schwann cells. Ganglia in the PNS can be divided into sensory and autonomic. The main type of glial cells in sensory ganglia and in parasympathetic and sympathetic ganglia is satellite glia cells (SGCs). The third division of the autonomic nervous system, the enteric nervous system, contains specialized glial cells termed ‘enteric glia’, which will briefly described in Section 5. A survey of the literature revealed that a large body of research touched upon SGCs in autonomic ganglia, but there have been no attempts for a systematic characterization of these cells. In many studies, where SGCs were encountered, the authors provided experimental data on them, but did not pursue the subject to any depth. The main objective of this review is to start laying the foundation for a methodical investigation of SGCs in autonomic ganglia, which should lead to the understanding of the function of these cells under normal and pathological conditions.

### 1.1. *Some characteristics of CNS glia*

Glial cells in the CNS, and astrocytes in particular, have been studied extensively for many years, and much more is known about them compared with SGCs. The brief outline below, which is mostly on astrocytes, is meant to facilitate a comparative discussion of SGCs.

#### 1.1.1. *Morphology*

Astrocytes are highly ramified, with fine processes extending from the main cellular processes, which give the cells a characteristic bushy appearance. Some astrocyte processes contact blood vessels by structures called endfeet, whereas other processes enclose synapses. Astrocytes and also Bergmann glia make close contact with neuronal dendrites, forming microdomains (Grosche et al., 1999). Individual astrocytes establish non-overlapping territories, in which each astrocyte contacts numerous neurons (Bushong et al., 2002). Microglia are mobile cells functioning as the macrophages of the CNS. They are ramified in the resting state, but upon activation (see below) they lose much of their ramified structure and become ameboid (Raivich et al., 1999).

#### 1.1.2. *Glial communications*

There is strong evidence that glial cells of all types are endowed with a variety of receptors for neurotransmitters, hormones and other bioactive molecules (Kettenmann and Steinhäuser, 2005). Glial cells can release numerous messenger molecules such as ATP, glutamate and cytokines (Montana et al., 2006). Thus, these cells can maintain chemical communications among themselves and with other cell types, in particular neurons and cells in blood vessels.

Intercellular connection of adjacent cells by gap junctions is one of the hallmarks of astrocytes (Ransom and Ye, 2005). This allows these cells to transport ions and metabolites over long distances. This ability, combined with the presence of special potassium channels and neurotransmitter transporters, enables astrocytes to actively control the chemical content of the extracellular space. There accumulated evidence on the profound influence of astrocytes on synaptic transmission led to the formulation of the concept of the "tripartite synapse", which consists of the pre- and postsynaptic elements and an astrocyte (Haydon and Carmignoto, 2006). Calcium waves are believed to be an important means for transmission of signals in the astrocytic network, and are mediated by both ATP and gap junctions (Scemes and Giaume, 2006).

#### 1.1.3. *Glial activation*

Any brain insult (trauma, infection, ischemia, autoimmune disease, etc.) triggers a complex response in glial cells, known as 'activation' or 'reactive gliosis'. Activation is the most prominent pathologic response of glial cells, and has been studied extensively in astrocytes and microglia. This process consists of several stages and depends on the distance of the cells from the site of injury (for reviews see Aldskogius and Kozlova, 1998; Bignami and Dahl, 1995; Raivich et al., 1999; Sofroniew, 2009; Verkhratsky and Butt, 2007). The expression of intermediate filaments is greatly increased in reactive astrocytes, in particular glial fibrillary acidic protein (GFAP) and vimentin. In fact, the increase in GFAP level has become the main hallmark of glial activation (Pekny and Nilsson, 2005). Whether astrocytes undergo proliferation during activation has been debated, and probably this phenomenon is not universal. When proliferation does occur, it appears to be confined to the site of injury (Bignami and Dahl, 1995). Reactive gliosis in CNS is characterized by hypertrophy of cellular processes of astrocytes (Sofroniew, 2009). At the ultrastructural level, reactive astrocytes display increased glycogen granules, fat inclusions, filaments (e.g., GFAP), myelin fragments and dense bodies (Pannese, 1994). The presence of cell fragments indicated that reactive astrocytes participate in the phagocytosis of degenerated structures. In a late stage of the reactive process the astrocytes fill the empty space occupied previously by degenerated neurons, which leads to the formation of glial scar. Astrocyte activation by cortical lesion is not associated with a change of domain organization (Wilhelmsson et al., 2006). In contrast, reactive gliosis in epileptic mice was accompanied by a marked loss of astrocytic domain organization, and processes from neighboring reactive cortical astrocytes exhibited an 8- to 15-fold increase in overlap in these mice (Oberheim et al., 2008). It thus appears that not all glial activations are the same.

There are several types of immune cells in the CNS: lymphocytes, microglia, mast cells in the menninges, and others. Although astrocytes are not considered to be the basic cells of the CNS immune system, they are considered to be immunocompetent because they can be induced to express class II major histocompatibility complex (MHC) antigens by various cytokines, which enables them to activate T lymphocytes (Dong and Benveniste, 2001; Milligan and Watkins, 2009; Wesemann and Benveniste, 2005). Astrocytes can produce immunologically relevant molecules such as cytokines, for example interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1) (Aloisi, 2005). Thus, astrocytes can influence a variety of immune and inflammatory activities. Astrocytes can respond to substances released by immune cells (microglia, macrophages) by releasing cytokines (e.g., IL-6), chemokines and growth factors. These, in turn can influence neurons and immune cells (Aloisi, 2005).

### 1.2. *Satellite glial cells in sensory ganglia*

The main type of glial cell in sensory ganglia is the SGC. These cells share many properties with astrocytes, including expression of glutamine synthetase and various neurotransmitter transporters (for reviews see Hanani, 2005; Ohara et al., 2009; Takeda et al., 2008). A unique feature of SGCs, which distinguished them from astrocytes, is that they usually completely surround individual sensory neurons. SGCs are coupled by gap junctions (Cherkas et al., 2004; Hanani et al., 2002) and express purinergic receptors (Weick et al., 2003; Ceruti et al., 2008). These two features are noteworthy as they have been shown to mediate intercellular calcium waves spread in these cells (Suadicani et al., 2010). SGCs possess mechanisms for the release of cytokines (Takeda et al., 2008; Zhang et al., 2007), ATP (Suadicani et al., 2010), and possibly other chemical messengers. SGCs undergo major changes as a result of injury to peripheral nerves, and appear to contribute to chronic pain in a number of animal pain models (Dublin and Hanani, 2007; Huang et al., 2010; Ohara et al., 2009). SGCs in autonomic ganglia, which are the topic of this review, have received much less attention than their counterparts in sensory ganglia. For a comparison of SGCs in autonomic ganglia and other peripheral glial cells, see Section 5.

## 2. Autonomic ganglia

The peripheral autonomic nervous system is divided into three divisions, parasympathetic, sympathetic and enteric. The

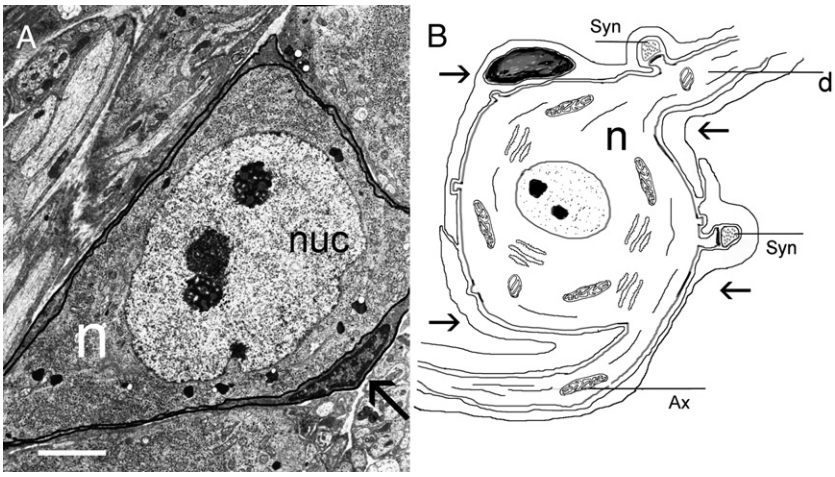


**Fig. 1 – The morphology of the neuron–glial unit in a sympathetic ganglion. (A) A low power electron micrograph showing a sympathetic neuron (n) surrounded by an envelope consisting of satellite glial cells. The borders of the SGCs are traced by a thick black line. Note that the contour of the SGC is very thin at certain points. The nucleus of a SGC is indicated with an arrow. Nuc, nucleus of the neuron. Mouse superior cervical ganglion. Calibration bar, 2 μm. Courtesy of Drs. M. Egle De Stefano and Paola Paggi, "La Sapienza" University, Rome, Italy. (B) Schematic diagram, of a sympathetic neuron (n) surrounded by SGCs (arrows). Note that the synapses (Syn) are covered by SGC processes and that these processes extend beyond the neuronal soma and ensheathe an axon (Ax) and a dendrite (d).**

definition of these divisions is based on anatomical considerations: sympathetic ganglia receive preganglionic inputs from nerve fibers emerging from the thoraco-lumbar regions of the spinal cord, and parasympathetic ganglia receive preganglionic inputs from the vagus nerves and also from the sacral region of the spinal cord. Sympathetic ganglia consist of two major groups: paravertebral ganglia (e.g., superior cervical ganglion), which are arranged as a chain along the spinal column, and prevertebral ganglia, located near large blood vessels in the abdomen (e.g., celiac ganglion). In contrast to sympathetic ganglia, which are in most cases located far from their target organs, parasympathetic ones are located near their targets, and in many cases they are found within the target organs; for example, cardiac, tracheal, and urinary bladder ganglia are embedded within the muscles of these organs. As a result, access to most parasympathetic ganglia is difficult, and some of them have not yet been studied functionally, e.g., those within the kidneys (Liu et al., 1996) and blood vessels (Baluk and Gabella, 1987). The enteric nervous system consists of ganglia located within the walls of the digestive system and includes two networks, the myenteric and submucosal plexuses (Kunze and Furness, 1999; Wood, 2008).

The various types of neurons in sympathetic ganglia have been characterized thoroughly (McLachlan, 1995; Skok, 1973; Szurszewski and Miller, 2006). In particular much is known about the physiology and pharmacology of neurons in the superior cervical and stellate ganglia (paravertebral) and celiac and inferior mesenteric ganglia (prevertebral). Among parasympathetic ganglia the most studied ones are the ciliary and cardiac ganglia (Akasu and Nishimura, 1995; Armour, 2008; McLachlan, 1995).

Autonomic ganglia innervate virtually all body organs and regulate all the involuntary functions: heart beat, blood pressure, glandular secretions, movements of smooth muscles, digestion, etc. The sympathetic and parasympathetic divisions are largely under central control, whereas the enteric nervous system is considerably more autonomous.

## 3. Glial cells[1] in sympathetic ganglia

The main types of cells in sympathetic ganglia are the ganglionic neurons, small intensely fluorescent (SIF) cells, and SGCs. SIF cells are characterized by being smaller than the neurons, and by numerous granules that contain noradrenaline, dopamine and serotonin (Matthews, 1989). SIF cells in both parasympathetic (Knight, 1980) and sympathetic ganglia (Elfvin, 1968) are almost completely invested by a sheath of SGCs. In sympathetic ganglia usually a group of SIF cells is covered by a common satellite sheath (Elfvin, 1968). SIF cells receive and send synapses, but their physiological role is obscure. The discussion below will focus on SGCs around neurons.

### 3.1. *Structure*

SGCs in sympathetic ganglia are derived from the neural crest. During embryonic development these cells proliferate mainly after most of the neurons are already present (Hall and Landis, 1992). SGCs, at least in dorsal root, are distinct from Schwann cells already at early developmental stage (see Section 5). It appears that neurons supply the signals for SGC division and maturation. Neurons in sympathetic ganglia normally have dendrites, and when grown in culture, the neurons extend dendrites only when glial cells (presumably SGCs) are present (Tropea et al., 1988), and it can be concluded that SGCs have a role in the maintenance of the characteristic phenotype of ganglionic neurons. In sensory ganglia, neurons are devoid of

[1] *In the early literature glial cells surrounding autonomic neurons were given various names, including 'capsule cells' and 'satellite cells', which can cause confusion. In the context of peripheral ganglia, a capsule is the connective tissue layer surrounding the entire ganglion, and satellite cells are the progenitor cells of skeletal muscle. Therefore the term 'satellite glial cells' (SGCs) is recommended, and will be used in this review.*

dendrites, and in contrast to the situation in sympathetic ganglia, it was found that NGF induces neonatal rat sensory neurons to extend dendrites in culture only after removal of satellite cells (De Koninck et al., 1993). There is a correlation between neuronal size and number of SGCs (Gabella, et al., 1988) in these ganglia, as found for sensory ganglia.

Fig. 1 shows the basic organization of a neuron in sympathetic ganglia and its attending SGCs. Each neuron is surrounded by its own glial cover, and together they form a distinct unit, largely isolated from other similar units in the ganglion. Fig. 1A is a low power electron micrograph of a mouse superior cervical ganglion, and Fig. 1B is a schematic diagram of a sympathetic neuron with its glial envelope. A striking feature is the small volume of the SGC relative to the neuronal volume. Also note the thickening of the SGCs sheath in the nuclear region, and the relative large size of the glial nucleus. Much of the SGC sheath is very thin, and therefore these cells contain a small amount of cytoplasm. More cytoplasm is present in the nuclear region, which can be defined as the cell body, which sends flattened processes surrounding the neuron. The basic organization of SGCs around neurons in sympathetic ganglia is similar to that found in sensory ganglia (Matthews, 1983; Pannese, 1981, 1994), however, unlike sensory neurons, sympathetic neurons receive synapses, and therefore some differences between these two systems do exist. For example, in sympathetic ganglia SGCs cover axon terminals that make synaptic contacts on, or near the neuronal somata (Elfvin, 1971; Matthews, 1983). This enables SGC to control the synaptic environment, and thus to influence synaptic transmission. An example of synaptic boutons making contact with a postganglionic sympathetic neuron is shown in Fig. 2. It is known that

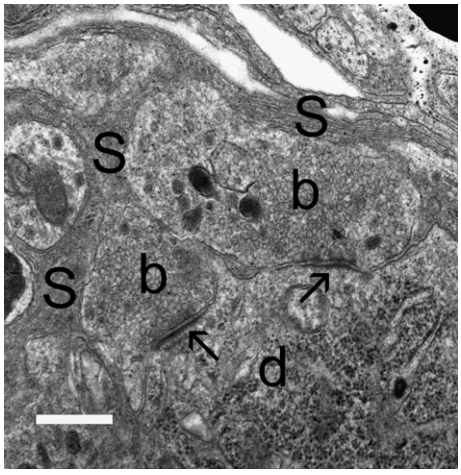


**Fig. 2 – Electron micrograph showing the relation between SGC processes and the postsynaptic sympathetic neuron. Mouse superior cervical ganglion. A dendrite of a sympathetic neuron (d) is contacted by two cholinergic boutons (b), filled with synaptic vesicles. A spinous appendage of the neuron is visible between the two boutons. The SGC processes (S) surround both boutons and neuron and do not insert between them. Arrows indicate the postsynaptic densities. Calibration bar, 0.5 μm. Courtesy of Drs. M. Egle De Stefano and Paola Paggi, "La Sapienza" University, Rome, Italy.**

astrocytes in the CNS can control the chemical content of the synaptic environment, but specific details on these putative functions in sympathetic ganglia are largely missing. The ultrastructure of sympathetic ganglia has been examined by numerous investigators (e.g. Dixon, 1968; Elfvin, 1963; Gabella et al., 1988; and see Matthews, 1983; Baluk, 1995 for reviews).

Dixon (1968) described the ultrastructure of SGCs in the rabbit superior cervical ganglion under normal and pathological conditions. The main normal features of these cells are:

1. The space between SGCs and neurons is 20 nm, which is noteworthy, as it means that the extracellular space of the neurons is extremely small, and even minute amounts of substances released into this space would lead to large changes in their concentrations. Conversely, the small volume allows an effective control of the extracellular environment by both neurons and SGCs. The presence of neurotransmitter transporters in the SGCs is consistent with this idea (see below).
2. The SGC envelope around a neuron is not continuous, and shows occasional gaps. This allows limited direct exchange between the neuronal extracellular space and the connective tissue space surrounding the SGCs. The thickness of the glial envelope is highly variable; it can consist of a single layer of SGC process or up to ten overlapping layers. These layers are 0.1 μm thick, and contain very little cytoplasm. In some cases the SGC envelope contains an axo-dendritic synapse close to the nerve cell body. Axo-somatic synapses are very rare. The SGC cytoplasm contains mitochondria measuring up to 1 μm in length. The cytoplasm contains microtubules and solid filaments and also a limited number of vesicles.

The observations above were largely verified by other ultrastructural investigations (Elfvin, 1963; Gabella et al., 1988; Matthews, 1983), but not all of them are general; for example, in prevertebral ganglia, most synapses are axo-somatic, and in certain ganglia the SGC envelope is continuous (Elfvin, 1963; Matthews, 1974). Later studies provided important information on the relations between neurons and their attending SGCs. As mentioned above, the SGC layers around the neurons are usually very thin, but they are much thicker at the vicinity of the SGC nuclei, where the amount of cytoplasm is relatively large. The sheath is also thicker near synapses, but the significance of these observations is not known.

Usually most of the synapses in sympathetic ganglia (at least in the paravertebral ones) are between preganglionic axons and dendrites or small protrusions from the neuronal somata, and only a minority are axo-somatic. Thus it would seem that SGCs have little contact with synapses. However, ultrastructural studies have shown that the synapses are close enough to the soma, and that in fact they are enclosed by SGC processes (Elfvin, 1963, 1971; Matthews, 1983). Elfvin (1963) has shown that SGC processes wrap around dendrites that emerge from neuronal somata. He noted that all ganglion cells and their processes in the superior cervical ganglion are covered by an SGC sheath, but it is not clear how far along the length of the processes this sheath extends These glial processes are continuous with the sheath SGCs make around the neuronal somata. Our preliminary observations using dye injections are in excellent correlation with this observation. We found that SGCs send tube-like

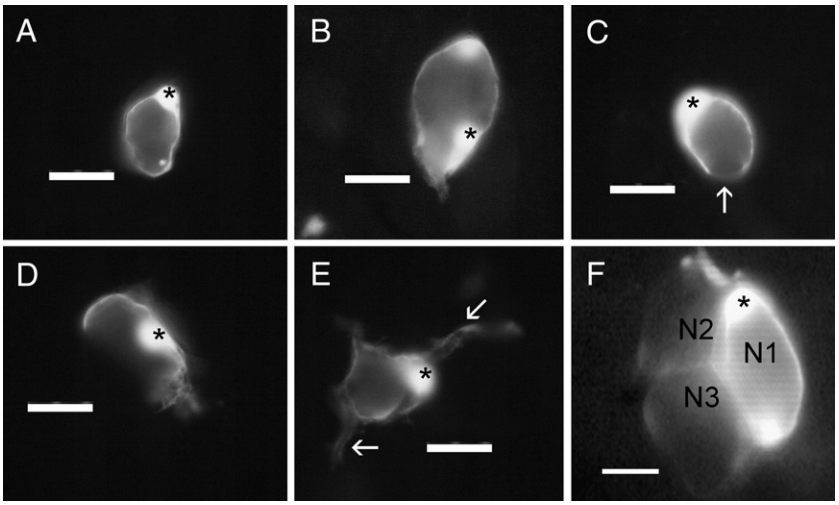


**Fig. 3 – Characterization of the SGC envelope in the mouse superior cervical ganglion with intracellular injection of the fluorescent dye Lucifer yellow. All images were obtained on live tissue during the injection experiments, which enabled a positive identification of the injected cell (marked with an asterisk). (A) A single SGC makes a complete envelope around the neuron. Here, and in the rest of the images, neurons were not stained. (B) The dye has passed from the injected SGC into another SGC around the same neuron. (C) An example of an SGC that makes a nearly complete sheath around a neuron, but a small neuronal region appears not to be covered by the injected SGC (arrow). This may be due to a great attenuation of the glial envelope in this region, or to an incomplete investment of the neuron by this cell. It is quite possible that another SGC (which was not coupled to the injected cell) covers this region. (D) An example of an SGC making a partial envelope around a neuron. In this case it is very likely that another SGC covers the left part of the neuron, and again is not coupled to the injected cell. (E) The injected SGC fully surrounds the neuron and also wraps around two neuronal processes. Note the tube-like glial cover of these processes (arrows). (F) An example of inter-envelope dye coupling. An SGC around neuron N1 was injected with dye, which spread to another SGC around this neuron, and also to SGCs around two adjacent neurons (N2 and N3). This type of coupling is rare (in about 3% of the cells) under normal conditions, but its incidence increases 8-fold following peripheral injury. Calibration bars, 20 μm. M. Hanani et al., unpublished results.**

structures having length of at least 30–40 μm, which enwrap neuronal processes in mouse superior cervical ganglion (Fig. 3E). It can therefore be concluded that SGCs cover the majority of synapses in sympathetic ganglia. Therefore, any discussion of synaptic transmission in these ganglia must take into account a possible contribution of SGCs, just as astrocytes are partners in most aspects of synaptic function in the CNS (Haydon and Carmignoto, 2006; Perea et al., 2009).

It is instructive to compare the organization of glial cells in sympathetic ganglia and the CNS. The astrocytic domains, in which each astrocyte contacts numerous neurons are absent in the sympathetic ganglia. Just the opposite, in sympathetic ganglia each neuron is surrounded by several SGCs that are in close contact with each other, and are separated from SGCs surrounding other neurons. Thus one can define the neurons and their attending SGC as one functional unit, as found in sensory ganglia (Hanani, 2005). A possible parallel between SGCs and astrocytes concerns the astrocytic microdomains, which are functionally independent. Matthews (1983) commented that there is "strong impression of independence of dendritic territories in sympathetic ganglia". These territories are determined to a large degree by the SGCs sheaths wrapping the dendrites. The possible functional significance of this organization remains to be explored.

Using the freeze etching technique, Elfvin and Forsman (1978) identified gap junctions in SGCs in para- and prevertebral ganglia of rabbits and guinea-pigs. Gap junctions are likely to have important implications for the function of glial cells as they allow the passage of ions (electrical currents) and also metabolites of up to molecular weight of 1000. Extensive coupling of glial cells by gap junctions enables astrocytes to control the extracellular concentration of potassium ions ('$K^+$ buffering'). This is done by uptake of $K^+$ ions into glial cells, and their distribution over the glial network, which is formed by the gap junctions (Reichenbach, 1991). It should be noted that the presence of gap junctions is not sufficient evidence that the cells are connected by gap junctions because the observed gap junctions could be by one cell on itself (reflexive gap junctions, Kamasawa et al., 2005). Using intracellular dye injections (Fig. 3), we showed that SGCs in mouse superior cervical are coupled both around a given neuron, and very rarely is there coupling between SGCs surrounding different neurons. Fig. 3 also illustrates several features of the SGC envelope.

### 3.2. *Satellite glial cells in the adrenal medulla?*

Chromaffin cells in the adrenal medulla are analogous to neurons in sympathetic ganglia, and several investigators asked whether these cells are ensheathed with SGCs. The cells that surround (partly) the chromaffin cells are termed "sustentacular cells". Cocchia and Michetti (1981) detected the glial marker S100 in sustentacular cells of rats and raised the possibility that these cells are homologous to SGCs in sympathetic ganglia. They commented on the functional implication

of this idea: if sustentacular cells display glia-like properties they can interact with chromaffin cells like glia and neurons do via the release various bioactive substances. In a light- and electron-microscopic (EM) study, Kameda (1996) showed that sustentacular cells of guinea-pigs contain the glial markers S100 and vimentin, confirming the earlier report. Further work is needed to determine whether sustentacular cells are genuine SGCs, and how they interact with chromaffin cells.

### 3.3. *Functional studies on SGCs*

Only few studies have been carried out on the functions of SGCs in sympathetic ganglia. Still, the published investigations on this topic provide some useful insights into this important topic.

#### 3.3.1. *Do SGCs control neuronal microenvironment?*

The observation that SGCs form complete, or nearly complete, envelopes around the neurons raises the question of whether the SGC sheath can block the diffusion of molecules into the neuronal extracellular space. This question is particularly relevant if the walls of ganglionic blood vessels are permeable to these molecules. Most regions of the CNS are protected against the penetration from the circulation of proteins and many other types of molecules by the blood brain barrier (BBB). The BBB is formed by tight junctions between endothelial cells in the CNS blood vessels. In specific brain regions the BBB does not exist because capillaries display fenestrations, which provide channels across capillary walls. Whether capillaries in sympathetic ganglia form a barrier has been a controversial issue (Kiernan, 1996). This question has been addressed by using various tracers that can be visualized at the light or electron microscopic levels. Such tracers include lanthanum DePace (1984), proteins like horseradish peroxidase (HRP) (Jacobs, 1977; Ten Tusscher et al., 1989), or fluorescently labeled albumin (Allen and Kiernan, 1994). Ten Tusscher et al. (1989) injected HRP directly into the rat superior cervical ganglia (thus bypassing the circulation), and found no tracer near the neuronal surface, indicating that the SGC sheath around the neurons is impermeable to proteins. Other authors (Allen and Kiernan, 1994; Jacobs, 1977) injected tracers into the circulation and did observe them near the neuronal surface, which led to the conclusion that both capillary walls and SGC sheaths are permeable to proteins. These findings were supported by the observation of fenestrated capillaries in sympathetic ganglia (Arvidson, 1979; Jacobs, 1977). In contrast, DePace (1984) reported that lanthanum did not cross capillary walls in rat sympathetic ganglia, and also that there was no evidence for capillary fenestrations. He concluded that there is blood–nerve barrier in these ganglia. It is difficult to reconcile this disagreement, especially as Ten Tusscher et al. (1989) used the same animals for studying tracer penetration in sensory ganglia, where they found no barriers, in full agreement with other studies on sensory ganglia (Hanani, 2005; Kiernan, 1996).

To add to the confusion around this issue, Chau and Lu (1996) reported that systemically applied lanthanum and HRP were excluded near the neurons in rodent sympathetic ganglia, but were present near small granule containing cells (SIF cells). Thus the presence of a barrier depended on the specific location in the ganglion. These observations are in accord with those of Matthews and Raisman (1969), who noted capillary fenestrations near SIF cells in rat superior cervical ganglion. Interestingly, these fenestrations were adjacent to gaps in the SGCs sheath around the SIF cells, an arrangement that allows direct exchange of substances between SIF cells and the blood. This feature was hardly ever seen in relation to the neurons in the ganglion.

Whether ganglionic capillaries are permeable or not is highly pertinent to the function of SGCs and neurons, because if there is no blood–nerve barrier in the ganglia, SGCs will be exposed to various signaling molecules and to harmful substances that might affect SGCs directly. For example, certain signaling molecules (such as ATP) can raise intracellular $Ca^{2+}$ in these cells, which in turn can lead to the release of chemical mediators onto the neurons. If the capillaries are leaky, but SGCs can form a barrier, these cells can provide protection to the neurons. Of course, if the SGC sheath is leaky as well, then the neurons will be exposed directly to a variety of chemical influences. This topic is also relevant to the actions of drugs on sympathetic neurons because if capillaries and/or SGCs form a barrier to the access of molecules to the neurons, such drugs will not have the desired therapeutic activity. Conversely, if the barriers fail, the cells may be exposed to harmful influences. Unfortunately, in view of the controversies mentioned above, these questions cannot be settled at present, and more definitive studies are needed. For example, the health status of the animals should be monitored carefully, as inflammation or disease may alter blood wall permeability (Vestweber, 2000).

Glial cells in the CNS have an important role in the regulation of pH (Coles and Deitmer, 2005). This function depends on $HCO_3^-$ and $H^+$ transport and on the activity of the enzyme carbonic anhydrase (CA). There is no report on such transporters in SGCs, but Korhonen and Hyyppä (1967) showed the presence of CA in SGCs in the rat celiac ganglia, using enzyme histochemistry. However, in a later immunohistochemical study (Kumpulainen and Korhonen, 1982), the enzyme was not found in the same ganglion. Modern methods, such as $H^+$ imaging should resolve this disagreement.

#### 3.3.2. *Neurotransmitter transporters in SGCs*

The discussion above deals with passive transport across capillary walls and glial envelopes, but there is another important means for controlling cellular environment, which is by membrane transport. In the CNS, neurotransmitter transporters are crucial for maintaining low extracellular levels of amino acid transmitters, like glutamate and gamma aminobutyric acid (GABA) (Anderson and Swanson, 2000). In the CNS, astrocytes carry out most of the control of extracellular levels of glutamate, and to a lesser degree of GABA (Verkhratsky and Butt, 2007). For sympathetic ganglia only GABA uptake by SGCs has been reported. However, the available information is consistent with the idea that SGCs are actively engaged in the control of the composition of the extracellular space of the ganglia.

Young et al. (1973) measured the uptake of radioactive GABA as an assay for the transporter activity in rat superior cervical ganglion. Autoradiography demonstrated the accumulation of GABA around neurons, suggesting that GABA was present in SGCs. The GABA uptake was depressed by reducing external $Na^+$ concentration and by ouabain, indicating that the GABA uptake depended on $Na^+$ influx (Bowery et al., 1979b).

These results showed the presence of GABA uptake into SGCs by a $Na^+$-dependent transporter, as was found for astrocytes. Brown and Galvan (1977) recorded membrane potentials in neurons in the same ganglion and found that when glial uptake of GABA was inhibited, the electrophysiological actions of GABA on neurons were enhanced, apparently due to GABA accumulation in the extracellular space. This study also confirmed that GABA transport was $Na^+$ dependent. The dependence on $Na^+$ was reported also for bullfrog sympathetic ganglia (Sakai et al., 1990).

Roberts (1976) obtained similar results for GABA, but added that the significance of the GABA transporters is not easy to explain, because the level of this amino acid in the ganglia is extremely low. However, later work showed that GABA is released from nerves in inferior mesenteric ganglion and facilitates acetylcholine release from colonic afferents (Stapelfeldt et al., 1993), indicating that the presence GABA transporters is relevant physiologically. [The source of the endogenous GABA appears to be preganglionic nerves (Dobó et al., 1989; Ito et al., 2007).] Moreover, there is physiological evidence that neurons in the rat superior cervical ganglion are depolarized by exogenously applied GABA, (Adams and Brown, 1975), indicating the presence of functional GABA receptors in the neurons. [(Although GABA is usually considered as an inhibitory transmitter, activation of its receptors can cause depolarization when the intracellular concentration of $Cl^-$ is high (Gallagher et al., 1978).] These findings highlight again the functional similarities between SGCs and other types of glial cells. GABA uptake is electrogenic (2 $Na^+$ ions per one GABA molecule) and therefore during its activity, the transporter can depolarize the cell membrane potential. The functional implications of this effect are currently not clear.

Bowery et al. (1979a) studied both GABA uptake and release by SGCs in the rat superior cervical ganglion. They observed GABA release in response to high (>50 mM) $K^+$-induced depolarization. Thus SGCs in sympathetic ganglia can take up and also release GABA in response to physiological stimulations. The mechanisms of GABA release (vesicular, transporter-mediated, or other) are not yet known.

Astrocytes and retinal Müller cells are known to control extracellular $K^+$ concentration ($K^+$ buffering, Reichenbach, 1991). It can be hypothesized that SGCs are also endowed with this ability, but surprisingly this question has not been addressed in any study so far.

### 3.3.3. *Physiological studies on SGCs in sympathetic ganglia*

Electrical recordings from cells presumed to be SGCs in sympathetic ganglia were obtained as a by-product in electrophysiological studies on neurons. The neurons were identified as those cells that fire action potentials, whereas SGCs were characterized by that lack of action potentials in response to depolarizing currents, very negative resting potentials, and low input resistance. Blackman and Purves (1969) described inexcitable cells in sympathetic ganglia of the thoracic chain of guinea-pigs, which were characterized by high resting potential and low input membrane resistance. These cells responded to repetitive stimulation of the preganglionic fibers with a slow depolarization, which decayed with a time constant of 5–7 s. The cells were not directly identified, but they are likely to be SGCs. The large resting potential and low input resistance are probably due to both high $K^+$ conductance and electrical coupling among these cells, consistent with the presence of gap junctions, and with the results of dye coupling experiments mentioned above (Fig. 3).

Bowery et al. (1979a,b) focused their investigation on SGCs in rat superior cervical ganglion, and provided a more detailed account of the electrical properties of inexcitable cells that were very likely to be SGCs. These cells were characterized by:

1. Resting potential of about −90 mV, compared with −70 mV for the neurons.
2. Low input resistance (<10 MΩ).
3. Short time constant <5 ms.
4. No action potentials in response to depolarizing current pulses.
5. No synaptic potentials in response to preganglionic nerve stimulation. Instead, there were slow potentials in response to presynaptic nerves, as described above.

These properties are similar to those of astrocytes, and are also consistent with later patch clamp studies on SGCs.

Purves (1975) recorded from SGCs in the guinea-pig superior cervical ganglion. These cells had resting potentials of −80 to −60 mV, and responded to preganglionic nerve simulation with a slow depolarization, lasting many seconds.

The mechanism underlying the slow responses induced by nerve stimulation was not investigated in detail, but they could be due to $K^+$ accumulation and/or responses to neurotransmitters. The mode of neuron–SGC communication is of great interest. In sensory ganglia there is evidence for the release of ATP (Zhang et al., 2007), and cytokines (Takeda et al., 2008) from neurons, which in turn act on neighboring SGCs and neurons.

Patch clamp recordings from SGCs in sympathetic ganglia have been made by Gola et al. (1993) in a prevertebral ganglion, and by Konishi (1996) in a paravertebral ganglion. Gola et al. (1993) found that SGC had resting membranes potentials of −79.1 mV, which was very close to $K^+$ reversal potential, and about 20 mV more negative than in the neurons. The membrane properties were nearly ohmic, with $K^+$ channels showing slight inwardly rectifying (Kir) properties. These channels were open at resting potentials, and apparently are the main $K^+$ channels open under resting conditions, as found for astrocytes (Verkhratsky and Steinhäuser, 2000). In addition to determining the resting potentials, these channels might be able to perform the role of $K^+$ buffering, as observed in other types of glial cells (Reichenbach, 1991). Konishi (1996) compared the presence of Kir channels in the superior cervical ganglion in adult and young mice. In young animals the density of the Kir channels was lower than in adults, and increased with age, but did not depend on nerve activity, as it was not altered by decentralization of the ganglion. In contrast, blocking presynaptic activity in the adult with tetrodotoxin reduced the density of Kir channels, and enhancing it by reserpine had the opposite effect. It was concluded that nerve activity is important for maintaining the density of Kir channels in adults. Konishi (1996) noted that SGCs are similar in some, but not all, aspects to non-myelinating Schwann cells and drew some parallels between SGCs and the endfeet of retinal Müller cells, which are known to possess a high density of Kir channels, and to be important for $K^+$ buffering. The author emphasized the role of Kir channels for regulating $K^+$ levels near the neurons and also at the synapses.

### 3.3.4. SGCs and ATP-mediated signaling

Receptors for ATP (purinergic) are arguably the most abundant receptors in glial cells (Abbracchio et al., 2009). There is evidence for ATP release from neurons in sympathetic ganglia (e.g., McCaman and McAfee, 1986; Vizi et al., 1997), apparently from preganglionic nerve terminals, and SGCs can be an obvious target for this neurotransmitter. Activation of P2 purinergic receptors leads to the elevation of intracellular $Ca^{2+}$ concentration, and therefore $Ca^{2+}$ imaging is a convenient method to characterize the function of these receptors. Purinergic P2 receptors are divided into ionotropic (P2X) and metabotropic (P2Y) subtypes, and the $Ca^{2+}$ imaging method can distinguish between them. Calvert et al. (2004) used $Ca^{2+}$ imaging in cultures of mouse superior cervical ganglia, which contained both neurons and glial cells. In both cell types, P2 agonists raised the intracellular $Ca^{2+}$ concentration. The authors concluded that the neurons responded via the activation of P2Y receptors. Using selective P2Y agonists such as UTP and UDP, they identified P2Y1 and P2Y6 receptors in neurons and glia, and also P2Y2 receptors in glia. P2X receptors were identified in the neurons, and they may present in the glia as well. Calvert et al. (2004) suggested that nucleotides can mediate communication between neurons and glial cells in sympathetic ganglia. It should be noted that glial cells were identified visually, and because these cells may change their phenotype in culture, the exact type of cell (SGCs or Schwann cell) is not known.

Kumagai and Saino (2001) used $Ca^{2+}$ imaging in rat superior cervical ganglion, and obtained somewhat different results. They identified P2Y receptors in neurons and P2X receptors in SGCs. These authors describe their tissue as intact ganglion, although they incubated the ganglia in collagenase for 12 h (at 4 °C), but clearly this preparation is closer to the physiological situation than culture, where cell phenotype can be altered, as mentioned above. The different results may be explained by the species difference or the different preparation type. As purinergic signaling is a major mode of neuron–glia communication, this topic deserves a closer look.

An important feature of purinergic signaling is the presence of enzymes that break down extracellular ATP (ectonucleotidases), thus terminating its action. Such an enzyme has been found in SGCs in sympathetic ganglia (Connolly and Duley, 2000; Forsman and Elfvin, 1984; Vizi et al., 1997). Nacimiento et al. (1991) identified the enzyme 5′-nucleotidase, which breaks down AMP (a breakdown product of ATP) into adenosine, in the superior cervical ganglion of cats and guinea-pigs. The enzyme is located in SGCs and Schwann cells. It is noteworthy that the enzyme is confined to the SGC side facing the neurons, implying that the enzyme is optimally located to control the AMP level in the narrow space between SGCs and neurons. Species differences were observed; in rat superior cervical ganglia 5′-nucleotidase was not observed under normal conditions, but was present after axotomy of the pre- or postganglionic fibers (Nacimiento and Kreutzberg, 1990). These observations are significant physiologically because sympathetic neurons are endowed with adenosine receptors and it was found that the activation of these receptors on the neurons inhibits voltage-dependent $Ca^{2+}$ current in neurons in the rat superior cervical ganglion (Henon and McAfee, 1983). It remains to be explored whether SGCs in sympathetic ganglia are sensitive to adenosine and other products of ATP breakdown. In the studies above, the enzymes were studied using enzyme histochemical methods. Currently, a more sensitive immunolocalization method for ectonucleotidases is available (e.g., Braun et al., 2004), and reexamination of the presence of these enzymes in sympathetic ganglia is clearly warranted.

Together, these histological and functional observations indicate that ATP is an obvious candidate to mediate neuron–glia signaling in sympathetic ganglia. In sensory ganglia neurons release ATP and glutamate (Zhang et al., 2007), and SGCs release ATP (Suadicani et al., 2010), and it will be interesting to find out whether this is also the case for SGCs in sympathetic ganglia. Another open question is whether purinergic signaling in SGCs is altered under pathological conditions, as found for sensory ganglia (Ceruti et al., 2008).

### 3.3.5. Other receptors in SGCs

Knowledge of the pharmacology of SGCs is very rudimentary, and except for the work on ATP mentioned above there is no functional evidence for other receptors in these cells. There is immuno-EM evidence for nicotinic acetylcholine receptors (specifically the α7 subunit), in SGCs from rat superior cervical ganglion (Del Signore et al., 2004). An autoradiographic study on the rat superior cervical ganglion showed an uptake of [$^3$H] dexamethasone, but not [$^3$H]corticosterone in SGCs and Schwann cells, indicating the presence of dexamethasone receptors in these cells (Warembourg et al., 1981). This interesting observation has not been followed up and therefore its functional significance is still obscure.

### 3.3.6. SGC–neuron interactions

A most interesting aspect of SGCs' function is their interactions with the neurons they ensheathe. Direct information on this topic is not available, but through indirect experiments some relevant insights have been obtained. Ariano et al. (1982) used immunohistochemistry to learn about signaling between neurons and SGCs in the rat superior cervical ganglion. They found that the β-adrenergic agonist isoproterenol induced cAMP synthesis in SGCs and that preganglionic electrical stimulation had the same effect. Interestingly, in the neurons cGMP rather than cAMP was elevated by these stimuli. The elevation of cAMP in SGCs is probably due to the release of chemical mediators from the neurons and subsequent activation of SGC receptors, which leads to cAMP synthesis in these cells. Although the precise receptor mechanism underlying these observations is not known, these results clearly indicate the presence of communications between neurons and SGCs. One possible mediator might be noradrenaline, acting via β receptors on SGCs, although the presence of such receptors in SGCs has not been demonstrated. Moreover, preganglionic stimulation should release acetylcholine, rather than noradrenaline from nerve terminals, and more work is needed to clarify this point. It has been suggested that the ability of SGCs to respond to synaptic activity should be considered in the context of long term potentiation (LTP) in sympathetic ganglia (Briggs, 1995), but this idea has not been pursued further. Ariano and Kenny (1987) further asked whether cAMP accumulation in SGCs depended on rat strain. Using immunofluorescent staining for cAMP, they compared

Sprague–Dawley and WKY (both normal) with SHR (stroke-prone) rats. SGCs in SHR rats displayed much more intense glial immunofluorescence for cAMP than either of the other two rat strains. The significance of the intriguing finding is still unknown, but it would be very interesting to find out whether SGCs contribute to stroke occurrence.

Another possible role of SGCs in hypertension emerges from work on the actions of the hormone endothelin-1 (ET-1) in producing the superoxide anion ($O_2^{\bullet-}$). It is known that $O_2^{\bullet-}$ is elevated in the vasculature in several hypertension models. Dai et al. (2004) found that in prevertebral ganglia of a rat hypertension model, $O_2^{\bullet-}$ was 4-fold greater than in controls in both neurons and glial cells. Although the glia were not identified positively, they are very likely to be SGCs, judging by their size and location. Treating ganglia from normotensive rats with ET-1 had the same effect as found in the hypertension mode. The authors concluded that ET-1 acted by activating $ET_B$ receptors, and proposed that $O_2^{\bullet-}$ production evoked by ET-1 may play a role in the increased sympathetic excitability and pathogenesis in hypertension. The same group further studied the action of an ET-agonist in vivo and observed that activation of $ET_B$ receptors increased $O_2^{\bullet-}$ levels in both neurons and glia in sympathetic ganglia (Lau et al., 2006). How these changes contribute to hypertension is still not known, but these results suggest that both neurons and SGCs in sympathetic ganglia may participate in the pathogenesis of ET-dependent hypertension, and could be a target for antioxidant-based therapy of hypertension and other cardiovascular diseases.

Astrocytes can modulate synaptic transmission in several regions of the CNS (Barres, 2008; Haydon and Carmignoto, 2006). Likewise, perisynaptic Schwann cells in the neuromuscular junction, respond to nerve activity, and in turn can influence synaptic transmission (Rousse and Robitaille, 2006). The presence of close contacts between SGCs and synapses in sympathetic ganglia suggests that such interactions might take place in these ganglia as well. This appears to be a promising avenue for future research.

In an early study on sympathetic ganglia of cats and dogs, Kuntz and Sulkin (1947) looked for morphological changes in SGCs after prolonged electrical stimulation of the preganglionic fibers (the duration and other parameters of the stimulation were not specified). The authors found that in stimulated ganglia some neurons degenerated, whereas SGCs showed both hyperplasia and hypertrophy. There was also direct evidence for amitotic division of SGCs. [Amitosis is a direct cell division, by simple cleavage of the nucleus (Nagata, 2003). It is quite rare, and there is no further confirmation of this observation for SGCs.] These results could indicate that intense electrical activity of neurons was associated with high metabolic demand on SGCs, leading to these morphological changes in them.

Schwyn (1967) took a similar approach and investigated the effect of electrical stimulation of preganglionic nerve on SGCs in the cat superior cervical ganglia. A sine wave of 0.01 V at ten pulses per second and duration of 10 ms was administered continuously for a period not exceeding three hours. This voltage appears rather low, but adequate stimulation was indicated by complete retraction of the nictitating membrane and dilation of the pupil on the stimulated side of the animal. The main observation was the incorporation of thymidine-$H^3$ into the nuclei of SGCs, which is an index for cell proliferation. Schwyn found that the electrical simulation greatly increased the incorporation of thymidine-$H^3$ into SGCs, but not neurons. When acetylcholine esterase activity was inhibited with neostigmine, the number of labeled SGCs increased 2–4-fold, consistent with the involvement of acetylcholine in this effect. Injecting the animals with atropine sulfate (1 ml of 0.1% solution) prevented the thymidine-$H^3$ incorporation, indicating that muscarinic acetylcholine receptors play an important role in the observed effects. These results have been explained as follows: preganglionic stimulation evokes acetylcholine release, which acts on postganglionic neurons via muscarinic receptors, evoking action potentials in them. This excessive neuronal electrical activity induced metabolic stress in the neurons, requiring a greater metabolic support from SGCs, forcing them to proliferate. This argument is clearly teleological, and lacks experimental support. A major flaw in this explanation is that acetylcholine acts mainly on nicotinic receptors in the neurons (Skok, 1973), and an alternative explanation is that acetylcholine acted on muscarinic receptors in SGCs, affecting them directly, but there is no information on the presence of these receptors in SGCs. It is disappointing that this line of investigation has not been pursued. Modern tools can reveal how SGCs sense neuronal distress.

#### 3.3.7. *Response to injury: morphological changes*

A large number of studies focused on changes in sympathetic ganglia in response to nerve injury. The impetus for these studies was both the clinical implications of such injury, and the suitability of sympathetic ganglia as a convenient model for investigating nerve injury and regeneration. A widely used method for studying the effects of injury on the nervous system is sectioning nerve tracts (axotomy), usually of postganglionic nerves, which causes a variety of pathological changes in the neuronal somata. This reaction, termed “axon reaction” has been intensively investigated in sympathetic ganglia (for reviews see Kreutzberg, 1995; Lieberman, 1974; Taxi and Eugène, 1995). Although the involvement of SGCs in this reaction received relatively little attention, there is sufficient evidence indicating a major role for SGCs in the response to nerve damage.

Dixon (1968) reported that postganglionic axotomy had a marked effect on the ultrastructure of SGCs surrounding the affected neurons. The main changes were:

1. At days 3–5 after the axotomy there were numerous endocytotic vesicles within the SGC cytoplasm, which may be due to phagocytotic activity.
2. At weeks 1–3, mitochondria were greatly enlarged and could reach a length of 5 μm. This change is consistent with greatly enhanced metabolic activity of SGCs following injury.
3. Also at weeks 1–3 the number of SGC layers around the neurons decreased sharply, and there were only 1–2 of them instead of up to ten in control ganglia. However, the sheath appeared much thicker than normal, measuring over 2 μm. The reduction in the number of layers was explained by the sliding of SGCs to accommodate the doubling of the neuronal volume after axotomy. At this

stage the number of cytoplasmic filaments in SGCs greatly increased, and it was suggested that the filaments had a role in reinforcing the cytoskeleton.

4. At a later stage the number of filaments decreased. Some filament aggregation was evident as long as six months after axotomy.

A coherent picture of the functional significance of these changes was not presented, and is still missing currently.

A major change in sympathetic ganglia following axotomy is the detachment of the presynaptic terminals from the postsynaptic membrane ("synaptic stripping", see Kreutzberg, 1995). In a seminal work, Matthews and Nelson (1975) examined physiological and ultrastructural changes in rats. Using extracellular electrical recordings, they found that after axotomy, synaptic transmission in the ganglion was greatly depressed. Similarly, Purves (1975), who made intracellular recordings from guinea-pig superior cervical ganglion after axotomy, observed a 70% reduction in synaptic potential amplitude. Matthews and Nelson (1975) also noted that after axotomy, sympathetic neurons lost most or all of their synaptic inputs and became physically separated from them. Importantly, presynaptic terminals appeared normal, consistent with a study showing normal release of acetylcholine from them after axotomy (Brown and Pascoe, 1954). These findings indicate that the reduction in synaptic transmission was not due to changes in the presynaptic compartment. Matthews and Nelson (1975) noted that glial processes become interposed between the retracting terminals and the postsynaptic cells (see Fig. 4) and therefore apparently played a role in synaptic stripping. They aptly called SGCs "agents of separation". Detached presynaptic profiles were often wrapped by one or more narrow lamellae of SGC cytoplasm, which enveloped the specialized presynaptic region. Thus it appears that after injury SGCs formed new extensions. The presence of glial processes between pre- and postsynaptic elements after injury was confirmed by more recent ultrastructural studies (Del Signore et al., 2004; De Stefano et al., 2007), and although the mechanism of this reaction is still not entirely clear, some progress on this topic has been made in recent years; see the next section.

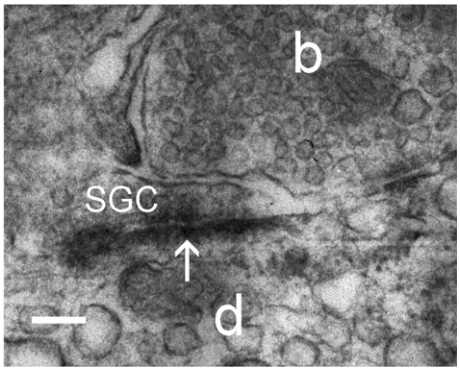


**Fig. 4 – The effect of postganglionic nerve damage on synaptic contacts in rat superior cervical ganglion. Seven days after crush of the postganglionic nerves, a process of a perineuronal SGC intrudes between a bouton (b) and the dendrite (d) of a neuron, participating in the process of "synaptic stripping". The postsynaptic specialization in the dendrite is still visible (arrow). Calibration bar, 0.2 μm. Courtesy of Drs. M. Egle De Stefano and Paola Paggi, "La Sapienza" University, Rome, Italy.**

Morphological studies showed that microglia can move along nerve fibers, and it was hypothesized that these cells might contribute to synaptic stripping in the CNS (Schiefer et al. (1999). The peripheral counterparts of microglia are macrophages, and it was found that after sciatic nerve transection there was an influx of macrophages (and also T-cells) into sympathetic ganglia (Hu and McLachlan, 2004; Schreiber et al., 1995). Thus a role for macrophages in peripheral synaptic stripping may be hypothesized. Another explanation for the decline in synaptic transmission is the marked reduction in the expression of nicotinic receptors following axotomy (Zhou et al., 1998). A role for the depletion of growth factors in the ganglia in this process has also been proposed because the reduction in synaptic transmission was prevented by applying nerve growth factor (Purves and Njå, 1976; Zhou et al., 1998).

A conclusion from these studies is that SGC processes can be highly mobile. A direct demonstration of this ability is difficult to obtain in vivo or in intact ganglia, but is feasible in culture. Chamley et al. (1972) studied sympathetic neurons and SGCs in culture over extended periods, and found some SGCs in close proximity to neurons, whereas others were at some distance from them. Unlike neurons, SGC were highly motile; their cell bodies showed grouping and regrouping over time, and their processes moved rapidly. These observations may not reflect the in vivo situation, but suggest that SGCs can change their position and morphology, consistent with the ultrastructural observations after peripheral damage, as described above.

One point agreed upon by all authors is that SGCs display some phagocytic activity. This is based on the presence of neuronal debris within the SGC cytoplasm.

These results suggest a close interaction between neurons and SGCs, which probably involves chemical signaling, the nature of which is still not known. Recovery from these changes was very slow and was not complete even after several months (which are equivalent to many years in humans). If SGCs participate in the synaptic detachment, it can be proposed that they contribute to the reinnervation process as well, but this question still needs to be studied. Some insight into this question has been gained by De Stefano et al. (2007), who suggested that SGCs also participate in the recovery phase. Their observations on changes in expression of plasminogen by these cells after damage, suggested that this enzyme is involved in both stages of synaptic remodeling (stripping followed by recovery), by acting on the extracellular matrix (ECM).

Purves (1975) used intracellular electrical recordings from neurons in the guinea-pig superior cervical ganglion to study functional changes in synaptic activity after interrupting postganglionic axons. He recorded a 70% decrease in the excitatory postsynaptic potentials (EPSP) amplitude 4–7 days after the injury. There was a large decrease in the number of synapses and a 30% increase in the number of SGCs. There is yet no information on physiological changes in SGCs after injury.

As mentioned above, glial proliferation may be part of glial responses to injury. Whether this holds for SGCs in sympathetic ganglia is not clear. Hendry and Campbell (1976) reported that axotomy of neurons in superior cervical ganglia in 6-day old rats

led to the loss (with no recovery) of 90% of the neurons. The number of non-neuronal cells (presumably SGCs) initially declined (by about 30%), but then slowly increased to a level that was much below normal even after 90 days. This is in apparent contrast to the hyperplasia of SGCs in sensory ganglia after axotomy (Pannese, 1981). As the size of the surviving neurons deceased after the axotomy, it is not clear how a large number of SGCs are accommodated around the reduced number of smaller neurons, and it might be that many of the non-neuronal cells were not SGCs. It would be interesting to reinvestigate this topic with more advanced tools. Treating the axotomized animals with NGF resulted in a great increase in the number of the non-neuronal cells. This is explained by the marked increase in the size of the neuronal neuropil, induced by NGF.

Hou et al. (1998) studied the effect of axotomy on the superior cervical ganglia of near adult rats. They found that the number of both neurons and SGCs was reduced at one day after postganglionic neuron axotomy (by 27 and 35%, respectively), and presented evidence that this was largely due to apoptosis.

### 3.3.8. *Response to injury: molecular changes*

Identifying specific molecules associated with injury is not an easy task. By the use of DNA microarray technology, it was found that after axotomy there were changes in over 200 genes in the rat superior cervical ganglion (Boeshore et al., 2004). Still, educated guesses can help in making some progress on this topic. In a later study, Del Signore et al. (2006) identified changes in the expression of a number of molecules in the rat superior cervical ganglion after postganglionic axotomy. It is noteworthy that among the 27 genes that were altered, vimentin (a protein located in SGCs), was upregulated.

As noted above, the presence of GFAP is one of the typical features of astrocytes. This marker was also found in SGCs in sympathetic ganglia (Elfvin et al., 1987). Alvarez et al. (1989) made similar observations in sympathetic ganglia from cats, and suggested that the presence of GFAP in normal SGCs in sympathetic ganglia is an indication that these cells are similar to astrocytes. Although SGCs were not identified in these studies with a specific antibody, it is quite certain that the GFAP staining was located in these cells. This is in contrast to SGCs in sensory ganglia, which display little or no GFAP under normal conditions. The intensity of the SGC staining increased 7–11 days after the pre- or postganglionic fibers were sectioned (Elfvin et al., 1987). Interestingly, Hu and McLachlan (2004) observed that after sciatic nerve resection GFAP was upregulated in SGCs in rat thoracic sympathetic ganglia localized around both axotomized and uninjured SG neurons starting from 1 day after the lesion. This indicates that a signal (probably a chemical released from the injured neurons), spreads in the ganglion and affects SGCs. A similar observation was made in sensory ganglia (Stephenson and Byers, 1995). In analogy with observations on astrocytes, it can be proposed that the SGCs were activated after axotomy, but confirmation using additional criteria is needed; such criteria include hypertrophy, proliferation, and augmented cytokine synthesis. Another indication for the involvement of SGCs in pathological changes following peripheral injury is the observation that after neuronal injury, they express immediate early genes c-jun, jun B and jun D (Koistinaho et al., 1993).

In addition to reducing synaptic transmission, axotomy alters peptide expression in sympathetic neurons. Sun et al. (1994) noted a large increase in the synthesis of vasoactive intestinal peptide (VIP) in neurons of rat superior cervical ganglia after axotomy in vivo, or after isolating the ganglia. This change was induced by the release of the cytokine leukemia inhibitory factor (LIF) from non-neuronal cells (SGCs and/or Schwann cells). Sun et al. (1994) proposed that similar mechanism is likely to underlie the production of other peptides (e.g., substance P) in sympathetic neurons following axotomy. Another cytokine, the bone morphogenic protein (BMP), is also a candidate for glia-to-neuron signaling (Lein et al., 2002), but again no distinction was made between SGCs and Schwann cells. These observations suggest that cytokines are important signaling molecules between SGCs and sympathetic neurons, but further work is required to confirm this idea.

The enzyme 5′-nucleotidase in SGCs was mentioned above in the context of purinergic transmission. It has been found that damage to the pre- or postganglionic fibers of sympathetic ganglia increased the expression of this enzyme in SGCs (Nacimiento and Kreutzberg, 1990). The authors speculated that this process is related to their role in synapse disruption and recovery, but evidence in support of this idea is still lacking.

Zigmond and Vaccariello (2007) looked for the presence in sympathetic ganglia of activating transcription factor 3 (ATF3), which has been proposed as a marker for injured neurons. It was found that following preganglionic neuron axotomy, ATF3-like immunoreactivity was present in both the deafferented neurons affected, and in a large population of SGCs throughout the ganglion. This indicates that SGCs are influenced by neuronal injury, but the significance of this finding is not known.

Schreiber et al. (1995) induced damage to postganglionic sympathetic nerves by two different methods, axotomy and systemic injection of the neurotoxin 6-hydroxydopamine (6-OHDA), which selectively destroys sympathetic nerve terminals. Both treatments induced an apparent macrophage accumulation in the superior cervical ganglion. The authors suggested that these two treatments led to the loss of a retrograde signal normally coming from the target organ to the ganglionic neurons, and that SGC activation is involved in the events taking place in the ganglion. This interesting proposal, which places SGCs as a major component in the reaction to injury, has not been followed up.

Mundinger et al. (2008) also used systemic administration of 6-OHDA in rats and examined changes in the celiac ganglia. This treatment decreased neurotransmission in the ganglia, apparently by reducing the expression $\alpha 3$ unit of nicotinic acetylcholine receptors in the postsynaptic neurons. In spite of this, during 1–5 days after 6-OHDA injection there was a 9.5-fold increase in *fos* mRNA level in the ganglia, which reflects augmented metabolic activity in cells. Interestingly, Fos protein elevation was not found in the neurons, but in non-neuronal cells, which are very likely to be SGCs. The authors correlated the large increase in Fos protein in SGCs with the morphological changes taking place in them after axotomy, namely the growth of SGC processes, which may underlie synaptic stripping, as discussed above. Mundinger et al. (2008) did not focus their attention on SGCs, and the role of SGCs in the effects of 6-OHDA on the celiac neurons deserves further study.

Heat-shock proteins (HSPs) are a large family of proteins that are induced under various stressful stimuli and protect against them (for review see Lanneau et al., 2008). In rat superior mesenteric and celiac ganglia HSP27 was found not only in neurons, but also in SGCs (Yamamoto et al., 2001). As the rats were not stressed, the authors concluded that this protein was expressed constitutively; however, it is quite possible that the level of HSP27 can increase above the basal one. Hou et al. (1998) examined SGCs and neurons in the rat superior cervical ganglion after sectioning of the carotid nerves, and described the changes in HSP72 level as "dramatic". Whereas HSP72 was not detectable in control ganglia, it was expressed in both neurons and SGCs after axotomy of ganglionic neurons.

The actions of nerve growth factor (NGF) and other neurotrophins on sympathetic neurons have been known for several decades, but the role of SGCs in growth factor signaling received very little attention. Wetmore and Olson (1995) used immunohistochemistry and in situ hybridization to localize neurotrophins and their receptors on neurons and SGCs in rat superior cervical ganglia. They found that SGCs contained mRNA for the truncated form of brain derived neurotrophic factor (BDNF) receptor. As neurons in this ganglion contain receptors for BDNF (trkB), the results indicate that SGCs can have trophic actions on the neurons. In the pelvic ganglion, which is mixed sympathetic/parasympathetic, the low affinity neurotrophin receptor p75 was found in SGCs (Lin et al., 2006), again suggesting a role for these cells in survival and regeneration.

Fibroblast growth factor 2 (FGF-2) is a member of the FGF family, which consists of 22 cytokines, having a variety of actions (Eswarakumar et al., 2005). FGF-2 was detected in SGCs in the rat superior cervical ganglion (Klimaschewski et al., 1999). Western blot analysis showed that after axotomy of the neurons projecting into the carotid nerve, the amount of FGF-2 in the ganglion greatly increased, and immunostaining revealed that a greater number of SGCs was positive for FGF-2 (possibly due to their proliferation), and staining intensity was slightly increased. FGF-2 was found to promote the survival of cultured ciliary ganglion neurons (Unsicker et al., 1992). The importance of these findings is in demonstrating that SGCs may exert trophic actions in sympathetic ganglia. Axotomy prevents the supply of growth factors from the periphery, and augmented production of these factors by SGCs can protect neurons from injury and death. Similar observations were reported for sensory ganglia (for review see Hanani, 2005). Klimaschewski et al. (1999) also suggested that FGF-2 released from SGCs might promote the proliferation of these cells by autocrine mechanisms.

Work from Paggi's group has added important information on the molecular changes occurring in the superior cervical ganglia from rats and mice following postganglionic axotomy or nerve crush. The following account is a brief summary of this work. The cytoskeletal proteins dystrophin and utrophin are very important for the function of muscles, but play also key roles in the CNS, being expressed in specific neuronal populations and glial cells (Waite et al., 2009). Full length dystrophin and some of its shorter isoforms have been detected by immuno-light- and electron-microscopy in neurons, SGCs, and Schwann cells in the mouse superior cervical ganglia (De Stefano et al., 1997). In ganglionic neurons, dystrophin is localized at several subcellular domains, but it is mainly associated with specialized membrane regions involved in intercellular interactions, such as postsynaptic apparatus and adherens junctions, and it was proposed that it has a role in the organization of the postsynaptic apparatus. Dystrophin, along with the glycoproteic complex with which it is associated, is involved in the stabilization of both synapses and postsynaptic clusters of neurotransmitter receptors, as demonstrated in studies utilizing postganglionic nerve crush to induce synaptic remodeling (Zaccaria et al., 1998, 2000). In these studies, synaptic detachment from cell somata and dendrites was preceded by a decrease in dystrophin immunolabeling in neurons, but not in SGCs (Zaccaria et al., 1998).

Paggi and her co-workers conducted several studies on the molecular modifications underlying the synaptic remodeling caused by postganglionic neuron axotomy. They emphasized the role that extracellular proteases may have in injury-induced changes in the linkage between neurons and SGCs and the ECM, possibly mediated by the dystrophin glycoprotein complex. Changes in cell–cell and cell–ECM contacts may be determined by the action of several extracellular proteolytic enzymes, such as matrix metalloproteinases (MMPs) and the plasmin activator/plasmin system. Therefore it has been proposed that synaptic stripping may also be the result of the extracellular enzymatic cleavage of the proteic link between pre- and postsynaptic elements and the ECM. Indeed, it has been found that after crushing the postganglionic nerves of the rat superior cervical ganglion, both levels and activity of MMP-2 (Leone et al., 2005; Paggi et al., 2006), as well as that of components of the plasmin activator/plasmin system (De Stefano et al., 2007), were significantly increased. One of the proteins cleaved by MMP-2 is β-dystroglycan subunit, which bridges the ECM and the cytoskeleton via dystrophin. Thus, MMP-2 may play an important direct role in the injury-induced synaptic detachment by modulating dendritic retraction, synaptic detachment and SGC activation (Leone et al., 2005). In fact, immuno-EM showed that MMP2 was localized in both neurons (including postsynaptic sites) and SGCs, which again indicates that SGCs actively participate in synaptic remodeling following injury. The same hypothesis holds for the plasmin(ogen) system, which increases in terms of mRNA, protein levels, and activity after injury in both neurons and SGCs, and may contribute to both synaptic detachment and subsequent regeneration.

Apolipoprotein D (apoD) is strongly upregulated in the regenerating sciatic nerve and in dorsal root ganglia after nerve injury, where it is thought to be involved in the redistribution of lipids (Kim et al., 2001). Del Signore et al. (2006) observed that apoD mRNA and protein levels increased in SCG after axotomy. At three and six days after axotomy the increase in the protein level was mainly localized around the neurons, presumably in SGCs. At these post-injury times SGCs extend their processes between the pre- and postsynaptic elements that mediate the detachment of preganglionic terminals from the injured ganglionic neurons. Thus, apoD upregulation possibly supports the increased extension of SGC processes. This upregulation also correlates well with the removal of membranes and therefore of lipids, consistent with the function of apoD.

Together, these observations indicate that synaptic remodeling in sympathetic ganglia is mediated by complex molecular interactions. It is likely that not all the details are currently known, but it is clear that components of the ECM are crucial for this process. Moreover, it appears that SGCs are an essential element in both synaptic stripping and recovery.

## 4. Satellite glial cells in parasympathetic ganglia

Much less research has been conducted on SGCs in parasympathetic ganglia than in sympathetic ganglia. It can be claimed that sympathetic ganglia received more attention because they are more important functionally as they innervate blood vessels, heart and other key organs. However, parasympathetic ganglia innervate blood vessels too, for example in hindlimb skeletal muscles, brain, salivary glands, bronchi, and genital organs (Branston, 1995; Buckley and Caulfield, 1992; Sato et al., 2004). Vagal innervation of the heart, which is cholinergic, is mediated by the cardiac ganglia and is extremely important. Moreover, sympathetic–parasympathetic interactions within the cardiac ganglia have functional relevance (Randall et al., 2003). Parasympathetic ganglia are present within internal organs (respiratory system, genito-urinary system, kidney, and others), and also in the head and neck (the submandibular, ciliary, otic, and pterygopalatine ganglia). Most parasympathetic ganglia are relatively inaccessible, which makes them rather difficult to investigate. Also, in contrast to sympathetic ganglia, which are compact and well defined structures that are located at a large distance from their targets, parasympathetic ones are more diffuse, and therefore more difficult to isolate. All these factors contributed to the current paucity of information on these ganglia.

### 4.1. *Structure*

The general organization of nerve and glial cells in parasympathetic ganglia is very similar to that seen in sympathetic ganglia. The glial cells wrap around the neurons, and thus are classified as SGCs (Fig. 5). Glial cells in most parasympathetic ganglia have not been investigated to any degree. The intrinsic ganglia of the urinary bladder are typical for this system (Gabella, 1990), and SGCs in them make a thin sheath around individual neurons, which is attenuated in some regions, but is still continuous. In the guinea-pig tracheal ganglia, neurons and their processes are almost always covered by a sheath consisting of several SGCs, which can be extremely thin (about 0.2 μm) (Baluk et al., 1985). This sheath is interrupted in only very small areas, where a thin neuronal process protrudes between two SGCs, making contact with the basal lamina. It will be interesting to find out whether these protrusions have any functional role, like sensing the ganglionic environment. The neuronal plasma membrane and SGC membranes displayed complex interdigitations, which greatly increase the surface area of both cells, and can promote intercellular interactions. In the guinea-pig pancreas (Liu et al., 1997) and in mouse pulmonary vein ganglia (Baluk and Gabella, 1987), neurons are fully covered by the SGC sheath. Similar organization has been described for most other parasympathetic ganglia, but there are few exceptions, such as ganglia located in the choroid in the eye, where neurons are incompletely covered by glial cells (May et al., 2004). This difference might be related to the specific functions of choroid ganglia, which are currently obscure. The space between neurons and their attending SGCs is about 20 nm, as found for SGCs in sympathetic ganglia. This morphology allows SGCs to exert tight control of the neuronal extracellular space, as mentioned above for sympathetic ganglia, but direct evidence for such function for parasympathetic ganglia is not yet available. Several studies have been carried out on pancreatic ganglia, but the focus has been on the neurons (see for example, Sha et al., 1996; Love et al., 2007).

Pomeroy et al. (1996) followed structural changes in mouse salivary duct ganglia in vivo over several weeks and found that the number of SGCs per neuron depends on the neuronal volume, and with the postnatal growth of the neurons, the ratio SGC:neuron increased up to about 3:1 at 8 weeks of age. They also observed that regions of the neuronal surface that had gained glial nuclei over time displayed increased synaptic bouton staining, suggesting that synapses and SGCs proliferate in parallel. This observation complements a previous study showing that boutons concentrate near the region of SGC nuclei (Pomeroy and Purves, 1988). Together, these findings suggest that SGCs are involved in synaptic maintenance and remodeling. It was proposed that SGCs secrete growth factors that could influence synaptic plasticity (Pomeroy and Purves, 1988), but specific information on this topic is not available.

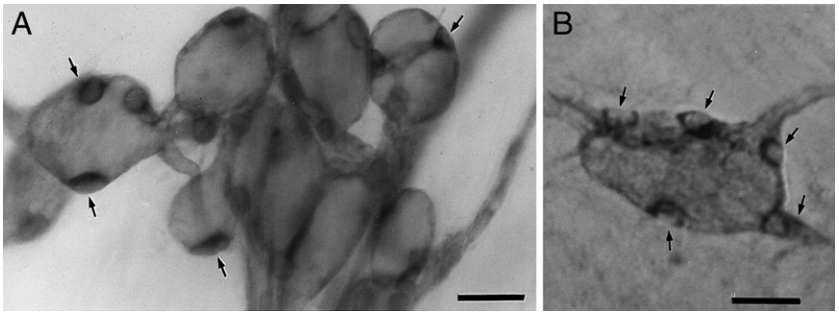


**Fig. 5 – Observations on SGCs in the intrinsic ganglia of the guinea-pig urinary bladder. (A) Immunostaining for the glial marker S100β. Some of the SGCs are marked with arrows. (B) A small ganglion immunostained for the glial marker glutamine synthetase. SGCs are marked with arrows. In both (A) and (B) the ganglia are shown in whole mounts (of intact ganglia, not sections), demonstrating the loose organization of the neurons in the ganglia and the organization of SGCs around the neurons. Calibration bars, 20 μm.**

Hanani et al. (1999) studied dye coupling among SGC in the intramural ganglia of the guinea-pig urinary bladder. They found only a small degree of dye coupling among SGC forming the envelope of given neurons. The SGCs were positive for S100 and glutamine synthetase (Fig. 5), but surprisingly not for GFAP, which is unlike SGCs in sympathetic ganglia, but similar to SGCs in sensory ganglia. Confirmation of these results in other parasympathetic ganglia is still awaiting.

No information is available on whether there is blood–nerve barrier in parasympathetic ganglia. Also, there is no systematic study on the capillary structure in these ganglia, or on tracer permeability, and therefore it is not known whether SGCs in these ganglia can perform a barrier role.

Some parasympathetic ganglia are accessible in living animals, which makes them a suitable model to study plasticity of neurons and SGC. Pomeroy et al. (1996) observed SGC in salivary duct ganglia of living mice, and re-examined them after several months. They found that in parallel with the growth of neuronal somata there was an increase in the average number of SGC around the neurons. This was accompanied by rearrangement of synaptic boutons, and it appeared that the boutons were concentrated near SGC nuclei. The significance of these observations is not clear, but the authors suggested a possible role for SGC in neuronal plasticity and growth.

### 4.2. *Cardiac ganglia*

Cardiac ganglia are located within the heart walls (usually in the atria and the interatrial septum), and mediate vagal effects on the heart. Because of their important function, there has been considerable interest in neurons in these ganglia, and the neuronal physiology has been investigated in numerous studies (see Whyte et al., 2009 and references therein), however, still little is known about their SGCs. Wong et al. (1987) conducted an ultrastructural study on cardiac ganglia from monkeys and noticed that the entire surface of the neurons is covered with SGCs sheath.

Ellison and Hibbs (1976) studied the ultrastructure of cardiac ganglia in rats, guinea-pigs, kittens and monkeys. They found that in all species, neurons and their processes were ensheathed by SGCs, which means that the synapses were enclosed in SGC processes. At least in the kitten, the SGC sheath covered the entire neuronal surface. In kittens and monkeys, SGC processes formed a single, easily identified layer on the surface of the neurons. In contrast, in the rat and the guinea-pig, SGC processes, dendritic knobs and presynaptic terminals intermingled, forming a complex multilayered surface zone around the neuronal somata. SGCs and presynaptic endings formed intimate contacts, favoring intercellular interactions, the nature of which is still unknown.

In an extensive ultrastructural investigation on human cardiac ganglia (Pauziene and Pauza, 2003), it was found that in all the examined subjects, the SGCs surrounded neuronal somata in a single layer. However, in the same ganglia there were neurons, around which the SGC sheath was multilayered, showing many foldings and interdigitations, which resemble the description for rat and guinea-pigs (Ellison and Hibbs, 1976). Some parts of the neuronal plasma membrane were not covered by a SGC sheath and were in contact with the interstitial space. This is in contrast with another report on human cardiac ganglia, where neurons were found to be completely invested by SGCs (Armour et al., 1997). Pauziene and Pauza (2003) also found that the dendrites as a whole were surrounded by SGC processes, but part of the dendritic surface was not covered, and had direct contact with the basal lamina. The gaps in the glial covers in soma and dendrites probably enable the neuron to sense the interstitial environment directly. Still, as most of the surface is covered by SGC processes, SGCs are likely to have a dominant role in controlling the neuronal microenvironment.

### 4.3. *Ciliary ganglia*

A widely studied parasympathetic ganglion is the ciliary ganglion, which innervates the smooth muscles in the eye (controlling the lens, iris, and choroidal blood vessels). An unusual arrangement of the preganglionic terminals was found in avian and reptilian ciliary ganglia. In newly hatched chicks a single preganglionic fiber reaches a postganglionic neuron, forming a large ending or 'calyx' (cup-like structure), which covers most of the neuronal surface. The calyx is in contact with the neuronal surface and is covered with an SGC sheath (De Lorenzo, 1960). Thus, SGCs are in contact with only a small portion of the soma (Fig. 6). With age, the calyx is broken up into numerous endings, forming a complex brush-like structure that involves SGCs processes (Gabella, 1976; Ehinger et al., 1983). Two additional unique characteristics of these ganglia are that preganglionic fiber makes both electrical and chemical synapses with the postganglionic neurons, and that SGCs produce myelin. It appears that the myelin sheath facilitates the flow of electrical current through the gap junctions (Hess et al., 1969). SGCs in the ciliary ganglion were found to be connected by gap junctions (Forsman et al., 1989).

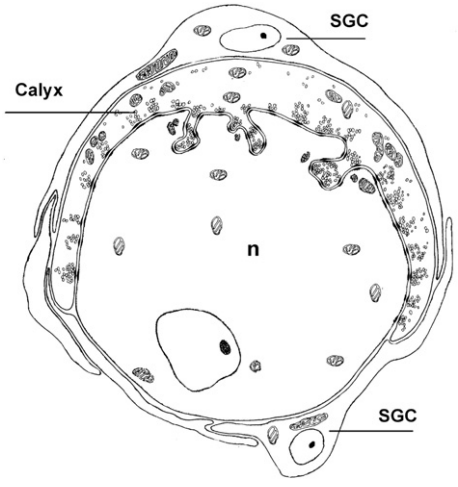


**Fig. 6 – A highly schematic drawing of the caliciform endings in the chick ciliary ganglion at late embryonic and newly hatched stages. The calyx is in contact with neuronal surface and makes synaptic with it. Some of the synapses are made between interdigitations of the presynaptic and postsynaptic cells. SGC processes invest the entire calyx, and the part of neuron that is not covered by the calyx.**

The potentially important role of cytoskeletal proteins dystrophin and utrophin in injury-induced changes in sympathetic ganglia has been mentioned above. Using immunohistochemistry, Blitzblau et al. (2008) found that these proteins are present in small cells that surround neuronal somata and axonal processes in the avian ciliary ganglion; neurons were not labeled. The authors suggested that the immunopositive cells are Schwann cells, but judging by their location and structure, these cells are likely to be SGCs. Considering the unusual nature of the ciliary ganglia, these cells are probably not typical SGCs, but for convenience, they can still be termed SGCs; indeed earlier workers described them as "satellite cells" (Landmesser and Pilar, 1972). Blitzblau et al. (2008) suggested that dystrophin and utrophin play a role in glia–neuron interactions and myelination. It will be interesting to further explore the roles of these proteins in ciliary and other autonomic ganglia.

Mammalian ciliary ganglia display the regular features of parasympathetic ganglia (Ehinger et al., 1983). In the rat ciliary ganglion synapses occurred four times more frequently on the portion of neuronal cell body membrane adjacent to the glial cell perinuclear area (Robertson and Jackson, 1996), as in other parasympathetic ganglia (see above).

### 4.4. *Functional studies*

There are very few reports on the functional or pharmacological properties of SGCs in parasympathetic ganglia. Ruan et al. (2006) examined P2 receptors in the intrinsic ganglia of the cat urinary bladder. Using immunohistochemistry they showed that whereas the neurons displayed all P2X subtypes (1–7) and four subtypes of P2Y receptors (2, 4, 6 and 12), SGCs were immunopositive only to P2Y1 receptors. Ruan et al. (2006) stressed the potential role of P2Y receptors in neuron–glia interactions, but direct evidence for such interactions in parasympathetic ganglia awaits further investigation. These authors also carried out $Ca^{2+}$ imaging study using various P2 agonists, but focused on the neurons only. This study was done on cultured ganglia, where SGCs can be easily missed because after several days in culture they migrate away from the neurons and change their morphology, making them difficult to distinguish from other non-neuronal cells (personal observations).

In the course of electrophysiological investigations of parasympathetic neurons, recordings were obtained from cells that did not fire action potentials, and were presumed to be SGCs. In a study of pancreatic ganglia in cats (Sha et al., 1996), SGCs had a higher resting membrane potential compared with that of neurons, (−74 mV, vs. −46 to −50 mV for neurons), a lower membrane input resistance (−13.6 MΩ, compared with neuronal value of over 60 MΩ), and a shorter time constant (1.4 vs. 3 ms for neurons). Similar values were obtained in an earlier study by King et al. (1989). The higher resting potential is typical for other types of glial cells, as discussed above. The identity of the cells was verified by intracellular injection of a fluorescent dye, which yielded a typical SGC morphology (Sha et al, 1996). When nerve trunks were electrically stimulated repetitively, a frequency-dependent membrane depolarization was observed in the glial cells (King et al., 1989), and the authors suggested that these responses were due to $K^+$ accumulation.

### 4.5. *Response to injury*

Because parasympathetic ganglia are usually embedded in their target tissues, axotomy of their postganglionic fibers is not feasible in most cases. This can explain why much less research on axonal injury has been carried out in these ganglia compared with sympathetic ganglia. One of the few exceptions is the ciliary ganglion, which is located at some distance from its targets, and has been the subject of several axotomy studies. The effects of vagotomy have been also investigated.

In an EM study on monkey cardiac ganglia, Tay et al. (1984) noted the following morphological changes SGCs following vagotomy: cell hypertrophy, prominent Golgi complexes and an increase in the number of lysosomes. The plasma membrane in contact with the neuronal soma showed numerous ruffles, probably indicating increased cellular interactions. On the basis of these changes the authors proposed that SGCs were activated. SGCs contained phagocytosed degenerating dendrites from the transneuronally affected neurons, suggesting that SGCs behave like Schwann cells, whose phagocytic activity is well documented and was also observed by Tay et al. (1984). Another prominent finding was the massive infiltration of macrophages into the neuronal space. These cells were seen to cross the glial sheath surrounding the neurons and to settle in the space between SGCs and neurons. The nature of the interactions between SGCs and macrophages is likely to be a promising topic for future research. The authors concluded that Schwann cells, macrophages, and SGCs are all involved in phagocytic activity after axotomy. In a follow-up study, Wong et al. (1987) reported that several days after bilateral vagotomy, SGCs in monkey cardiac ganglia were hypertrophied and appeared activated, and that this activation persisted for the entire period of observation (1–288 days). The presence of neuronal fragments within the SGC cytoplasm indicated that SGCs engage in phagocytosis of degenerating neurons following the vagotomy. Similar observations of neuronal phagocytosis by SGCs have been described in the rat superior cervical ganglion undergoing retrograde degeneration (Matthews and Raisman, 1972), in the chicken ciliary ganglion the during embryonic development (Pilar and Landmesser, 1976), and in the embryonic chicken spinal ganglia (Pannese, 1981).

Phagocytosis by SGCs was observed in an EM study on ciliary ganglia in cats and monkeys after preganglionic axotomy (Zhang et al., 1996). Here too, it appears that three types of non-neuronal cells – Schwann cells, macrophages and SGCs – engage in phagocytosis after nerve damage. In addition, Liu et al. (1997) investigated the ultrastructure of pancreatic ganglia in guinea-pigs and found that seven days after left cervical vagotomy, SGCs appeared activated and contained engulfed axon terminals, indicating phagocytic activity. Thus, work in several laboratories on a variety of species and parasympathetic ganglia showed that SGCs possess a phagocytic capacity.

As discussed above, one of the major effects of retrograde effect of sympathetic postganglionic nerve injury is synaptic stripping, but less is known on this aspect in parasympathetic ganglia. Important insights into this topic have been provided by De Stefano et al. (1994) and Squitti et al. (1999), who studied the adult quail ciliary ganglion. Here, postganglionic nerve

crush induced chromatolysis in the ganglion neurons and also massive synaptic detachment (De Stefano et al., 1994). However, unlike in sympathetic ganglia, SGCs did not seem to participate in the synaptic stripping, and remained apparently unperturbed, outside the layer of detached synaptic boutons. Therefore the observations made on sympathetic ganglia do not apply in all cases. In a further study (De Stefano et al., 2001) it was found that the expression of the cell adhesion molecules N-cadherin and neural cell adhesion molecule (N-CAM) decreased soon after nerve crush. The two proteins were present in the interface between pre- and postsynaptic elements, and between these and the SGCs. The observed changes were reversible, and paralleled the recovery of the intraganglionic synaptic contacts and the reinnervation of the peripheral targets (20 days). These results indicated a role for adhesion molecules such as N-cadherin and N-CAM in the stabilization of synaptic contacts and, as these molecules are abundant in SGCs, these cells are very likely to have roles in both synaptic maintenance and plasticity.

In a recent interesting study, Nangle and Keast (2009) examined c-jun expression in pelvic ganglia, following section of the penile nerve (which is postganglionic). The protein c-Jun, a product of the immediate early gene *c-jun*, is linked with the regenerative activity of neurons following injury. Penile nerve axotomy caused an expression of C-jun in both neurons (largely parasympathetic) and SGCs, located near the injured neurons. A similar effect was also observed after preganglionic axotomy. The significance of the C-jun upregulation in the SGCs is not clear, but it is conceivable that these cells have a role in neuronal regeneration, and that glial C-jun participates in this process. Nangle and Keast (2009) commented that "it will be of interest to determine how axotomy altered neuron–glial communication and whether this communication drives any of the regenerative processes. The mechanisms may be different following deafferentation where c-Jun is upregulated in some glia but there is no direct injury stimulus to the ganglion neurons". This is of course correct, but no less important is it to learn about glia–neuron interactions in autonomic ganglia under normal conditions.

Obviously, knowledge on SGCs in parasympathetic ganglia is still very limited. The functional importance of parasympathetic ganglia in the heart and trachea is well recognized and therefore it can be hoped that SGCs in these ganglia will attract more attention in the future.

## 5. Comparison between autonomic SGCs and other types of peripheral glia

To put SGCs in autonomic ganglia in better perspective it may help to compare them briefly with other types of peripheral glial cells, which include Schwann cells (with emphasis on non-myelinating Schwann cells — NMSC), enteric glia, and SGCs in sensory ganglia. All these cell types derive from the neural crest (White and Anderson, 1999) and share several characteristics. Because much more is known about SGCs in sympathetic than in parasympathetic ganglia, mainly SGCs in sympathetic ganglia will be discussed here. For a comparison of the structure and possible functions of peripheral glia see Pannese (1981,1994).

### 5.1. *Non-myelinating Schwann cells*

The most familiar type of peripheral glia cells are Schwann cells. Peripheral ganglia and nerve tracts contain NMSCs, which accompany virtually all non-myelinated axons (Griffin and Thompson, 2008). In dorsal root ganglia, Schwann cells are distinct from SGCs already at early developmental stage; embryonic SCGs express the transcription factor Erm, which is not detectable at any developmental stage in Schwann cells (Hagedorn et al., 2000). NMSCs are distinct from SGCs also because they require neuregulin, a member of the epidermal growth factor superfamily, for normal development, whereas SGCs in sympathetic and sensory ganglia can develop without neuregulin (Jessen and Mirsky, 2005). Like SGCs, NMSCs are laminar structures, but morphologically they are very distinct from SGCs; they are usually elongated, with length of 20–400 μm (Pannese, 1994) and are associated with axons, whereas SGCs are wrapped around the neuronal cell bodies. Moreover, SGCs are usually associated with a single neuron, and together with the neuron constitute a structural and functional unit. In contrast, each NMSC is usually associated with several axons, forming a Remak bundle, where axons are located within troughs formed by NMSCs (Campana, 2007; Pannese, 1994). Like SGCs, NMSCs are likely to be involved in the regulation of the neuronal microenvironment, as both cells types are endowed with transporters for GABA, and possibly for other neurotransmitters (Brown et al., 1979). Perisynaptic Schwann cells in the neuromuscular junction are a specialized type of NMSCs, and their interactions with nerves are well known (Rousse and Robitaille, 2006).

The widely used glial markers GFAP, S100 and vimentin label both NMSCs and autonomic SGCs (Jessen and Mirsky, 1983), and therefore cannot be used to distinguish these cell types. A more specific marker for NMSCs is Schwann cell myelin protein (Dulac et al., 1988). NMSCs are endowed with a variety of receptors; for example for ATP (Ansselin et al., 1997) and cytokines (Lara-Ramírez et al., 2008), which enable them to communicate with adjacent axons (Fields and Stevens-Graham, 2002).

Table 1 summarizes several important features of peripheral glia.

### 5.2. *Satellite glial cells in sensory ganglia*

SGCs in sensory ganglia have attracted recently considerable attention because they appear to contribute to chronic pain (for reviews see Hanani, 2005; Ohara et al., 2009; Takeda et al., 2008). Structurally, they are very similar to SGCs in autonomic ganglia, as both types wrap around the neuron, forming a neuron-glia unit. Unlike SGCs in sympathetic ganglia, sensory SGCs are only weakly GFAP positive, but peripheral damage increases GFAP expression in SGCs in both types of ganglia (Elfvin et al., 1987; Hanani, 2005). In contrast to autonomic ganglia, sensory ones contain no synapses (but they do have receptors to various transmitters). Some pharmacological similarities between the two cells types are detailed in Table 1.

### 5.3. *Enteric glial cells*

Enteric glia are a special type of cells located within the intrinsic ganglia of the gastrointestinal tract — the enteric nervous system. Enteric ganglia are unique in comparison with other

**Table 1 – Comparison between the main types of peripheral glial cells.**

| Cell type/property | Autonomic SGCs | Sensory SGCs | Non-myelinating Schwann cells | Enteric glia | References |
|---|---|---|---|---|---|
| Neurotransmitter transporters | + | + | + | + | 1–3 |
| Vimentin, S100 | + | + | + | + | 4 |
| GFAP | + | ± | + | + | 4–6 |
| Glutamine synthetase | ?[a,b] | + | + | +[c] | 4,7 |
| Schwann cell myelin protein | – | – | + | – | 8 |
| Coupling by gap junctions | + | + | + | +++ | 9–12 |
| P2 receptors | P2Y1,2,6 | P2X7, P2Y1,2,4,6,12,13 | P2X7, P2Y1,2 | P2X7, P2Y2,4 | 13–19 |
| Ecto-ATPase | + | + | + | + | 20 |
| Calcium waves | ? | + | ? | + | 21,22 |
| Cytokine expression | LIF | IL-1β, TNFα | IL-1β, IL-10, TNFα | IL-1β, IL-6, TNFα | 23–26 |
| Cell processes | – | – | – | +++ | 27,28 |
| Inward rectifying $K^+$ channels | + | + | + | + | 29–33 |
| Contacts with blood vessels | – | – | – | + | 28 |
| Relation with neuronal somata | Form a complete cover | Form a complete cover | Do not contact somata | Form a partial cover | 27,34 |
| Engagement in phagocytosis | + | + | + | ?[d] | 27,35,36 |

Abbreviations: Vim, Vimentin; BMP, bone morphogenetic proteins; LIF, leukemia inhibitory factor.
References: 1, Brown et al. (1979); 2, Fletcher et al. (2002); 3, Keast and Anderson (2000); 4, Jessen and Mirsky (1983); 5, Stephenson and Byers (1995); 6, Elfvin et al. (1987); 7, Kato et al. (1990); 8, Dulac et al. (1988); 9, Konishi (1990); 10, Hanani et al. (1999); 11, Hanani et al. (2002); 12, Hanani et al. (2010); 13, Vanderwinden et al. (2003); 14, Kimball and Mulholland (1996); 15, Calvert et al. (2004); 16, Gulbransen and Sharkey (2009); 17, Ceruti et al. (2008); 18, Weick et al. (2003); 19, Chessell et al., 2005; 20, Braun et al. (2004); 21, Zhang et al., 2003; 22, Suadicani et al. (in press); 23, Takeda et al. (2008); 24, Campana (2007); 25, Rühl (2005); 26, Sun et al. (1994); 27, Pannese (1994); 28, Hanani and Reichenbach (1994); 29; Gola et al. (1993); 30, Konishi (1996); 31, Hanani et al. (2000); 32, Cherkas et al. (2004); 33, Vit et al. (2008); 34, Gabella (1981); 35, Dixon (1968); 36, Matthews and Raisman (1972).
[a] The question mark indicates a lack of information in the literature.
[b] Glutamine synthetase was found in parasympathetic SGCs (Hanani et al., 1999), but there is no similar information in sympathetic SGCs.
[c] Several authors identified glutamine synthetase in enteric glia, but Rühl (2005) reported a failure to reproduce this result.
[d] The only report on phagocytosis by enteric glia is an abstract (Hollenbach, E. et al., Gastroenterology 2000; 118: A184).
The following symbols denote the degree to which a protein or a function is presence in the cells: – absent; ± scarce; + present; +++ abundant.

peripheral ganglia, and are structurally and functionally similar in many ways to the CNS, and accordingly, enteric glia are similar to astrocytes (Rühl, 2005). The most prominent structural feature of these cells is the numerous processes that extend from the cell body. Such processes are absent in other types of peripheral glia. Markers for enteric glia are GFAP and S100 (Jessen and Mirsky, 1983; Rühl, 2005). There is evidence for the presence of glutamine synthetase in enteric glia (Jessen and Mirsky, 1983; Kato et al., 1990), but see Rühl (2005).

Enteric glia are extensively coupled by gap junctions and thus, like astrocytes, can form a functional syncytium (Hanani et al., 1999). In contrast, under resting conditions, SGCs are only coupled to other SGCs around the same neuron (Hanani et al., 2002). As mentioned in Section 1, calcium waves are an important mode of glial intercellular signaling. This phenomenon has been described for cultured enteric glia (Zhang et al., 2003) and cultured sensory SGCs (Suadicani et al., 2010), but not for other types of peripheral glia.

Like astrocytes, enteric glia extend processes, termed 'endfeet' that contact blood vessels (Hanani and Reichenbach, 1994). These structures are believed to have a role in the exchange of substances between astrocytes and the circulation, but such function has not been verified for enteric glia. Endfeet, or any other distinct structure contacting blood vessels have not been identified in SGCs. Interestingly, the water channel aquaporin-4, which is important for the transport processes in astrocytic endfeet, is missing in enteric glia (Thi et al., 2008).

The importance of enteric glia to the integrity of intestinal capillaries was revealed in studies where these cells were ablated in transgenic mouse models. This manipulation led to vascular and mucosal lesions and severe intestinal inflammation. It was proposed that dysfunction of enteric glia may lead to a variety of intestinal diseases (for review see Savidge et al., 2007).

Enteric glia respond to numerous bioactive molecules such as ATP, serotonin, histamine, glutamate acetylcholine, and lipid mediators (Kimball and Mulholland, 1996; Nasser et al., 2007; Segura et al., 2004; for review see Rühl, 2005). For SGCs, so far only the actions of ATP have been explored, and clearly much further work needs to be done in this area.

In summary, although the three main types of peripheral glia – SGCs, Schwann cells, and enteric glia – share several chemical markers, they are very distinct from each other by their morphology and their association with the neurons. It can be generalized that SGCs of sensory and autonomic ganglia and NMSCs share many similarities, and are quite different from enteric glia, which resemble astrocytes. The unique feature of autonomic SGCs is that they cover synapses of postganglionic neurons, but the functional implications of this arrangement still need to be explored. It can be concluded, as stated by Gershon and Rothman (1991), that morphological and functional differences are more reliable than chemical markers for distinguishing between peripheral glia.

## 6. Directions for future research

It is clear from this review that most research topics on glial cells in sympathetic and parasympathetic ganglia have been hardly

touched. In particular little is known on the nature of SGC–neuron communication. The following three topics offer promising opportunities for future work: 1. Characterization of neurotransmitter and hormone receptors on SGCs. Specifically, receptors for glucosteroids and ATP should be identified and studied in functional assays. 2. What active molecules are released from SGCs? These two points are essential for understanding SGC–neuron interactions, which on the basis of knowledge on other types of glial cells, are very likely to be chemical. 3. Synaptic boutons are covered by SGCs, and an obvious question is whether SGCs can influence synaptic transmission. For example, it will be important to find out whether the documented uptake of neurotransmitters by SGCs actually influences transmission, and if it does, how glial activity affects autonomic functions, such as blood pressure and cardiac activity. Knowledge on the pharmacological properties of SGCs will help in addressing this highly interesting question. Much progress has been made in recent years on SGCs in sensory ganglia (Hanani, 2005; Ohara et al., 2009; Takeda et al., 2008), and although SGCs in autonomic ganglia are not identical to those in sensory ganglia, adopting research strategies used in sensory ganglia is likely to facilitate progress on SGCs in autonomic ganglia.

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