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Chapter

Gap Junctions in the Dorsal Root Ganglia

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Abstract

Dorsal root ganglion (DRG) or spinal ganglia are present in relation to the dorsal ramus of the spinal nerves. The neurons in the dorsal root ganglion are pseudounipolar in type. The single process from the soma or body will divide into the central and peripheral processes. Dorsal root ganglion neurons constitute the first-order neurons for the pain pathways and can be categorized as small, medium and large varieties. Peripheral process collects the impulses from the peripheral receptors and the central process reaches out to the central nervous system. The neurons in the DRG were surrounded by the satellite glial cells (SGC). These cells ensheath the neurons from all the sides. Besides covering the neurons, they share features very much similar to the astrocytes such as expression of glutamine synthetase. Many quantitative studies have identified the different proportion of satellite glial cells for individual neurons. These cells have been identified to get activated when confronted by the noxious stimuli, injury or inflammation. Clinically, these cells were implied to be related to the many neurological disorders.

Keywords: neurons, satellite glial cells, communicating junctions, pain, connexin-43, glial fibrillary acidic protein, peripherin, Nissl stain, immunohistochemistry

1. Introduction

The human nervous system is an extremely efficient, compact, fast and reliable computing system, yet it weighs substantially less than most of the computers and performs at an incredibly greater capacity.

The nervous system is subdivided, morphologically into two components, the central nervous system (CNS) consisting of the brain and spinal cord and the peripheral nervous system (PNS) comprising of cranial and spinal nerves and ganglia.

Discrete collections of nerve cell bodies in the CNS are known as nuclei while in PNS, these are called ganglia. The nerve cell bodies are of varying sizes and shapes. Ganglia are present in the dorsal root of spinal nerves, the sensory root of the trigeminal nerve (Vth), Facial (VIIth), Glossopharyngeal (IXth), Vagus (Xth) nerves and in the autonomic nervous system [1]. Some of them have independent nomenclature like the "Gasserian ganglion" for the Vth nerve. Thus ganglia can be divided into two types somatic and autonomic (**Figure 1**). The nerve cell bodies in each of these differ in their size and shape. Somatic ganglia contain small to large pseudounipolar neurons while the autonomic ganglia contain small multipolar neurons.

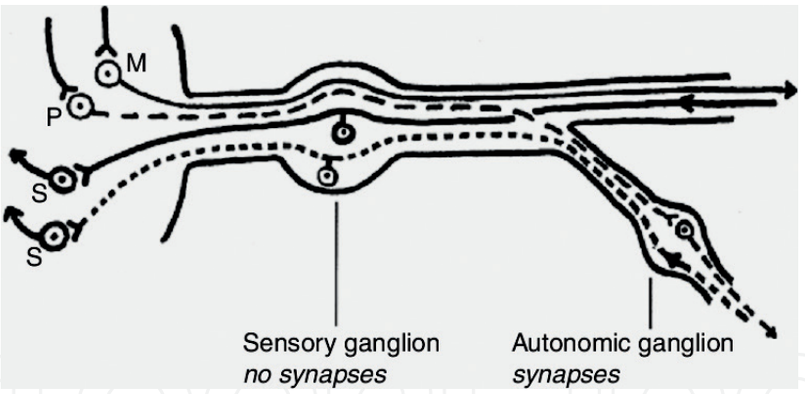

Figure 1.
Differences in sensory and autonomic ganglia (courtesy: Cranial Nerves and Functional Anatomy, 1st ed. p. 12).

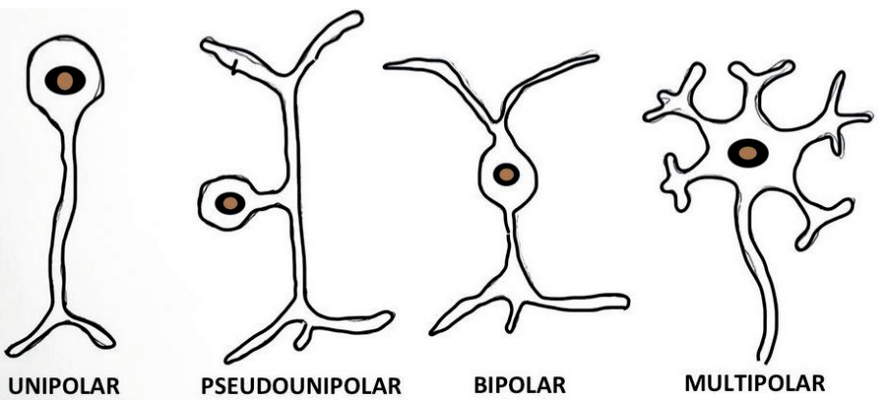

Figure 2.
Types of neurons in nervous system.

Depending on the number of processes, a neuron can be classified into various categories. Unipolar neurons (no dendrites only an axon) are rare in vertebrates, bipolar neurons (possesses an axon and a dendrite) present in olfactory mucosa and the retina and multipolar neurons (single axon and two or more dendrites) present in the central nervous system except the mesencephalic nucleus of the Vth cranial nerve. An additional type of neuron, the pseudounipolar neuron is present in sensory ganglia and the ganglia of Vth, VIIth, IXth and Xth cranial nerves. It divides into a central and peripheral process (**Figure 2**).

The neurons in sensory ganglia are at first bipolar, but the two neurites soon unite to form a single process during development. Structurally and electrophysiologically, both these processes show characteristic features of the axon [2]. Small satellite glial cells tightly wrap the cell bodies of the pseudounipolar neurons in the ganglion. The satellite cells that surround the pseudounipolar neuron are continuous with the Schwann cell sheath that surrounds the axon [3]. A distinctive feature of satellite glial cells by which they are distinguished from astrocytes is that they completely surround the individual sensory neuron. The neuron and its surrounding satellite glial cells form a distinct morphological and probably a functional unit [4]. The somatic ganglia of all the mammalian and avian species demonstrate this arrangement [5]. Satellite glial cells have been implicated in neuronal nutrition, homeostasis, and the process of apoptosis. It is known that astrocytes in the central nervous system perform 'spatial buffering' (regulation of K^+) and it is presumed

that SGCs also perform the same function [5]. Removing K^+ from the perineuronal environment would reduce neuronal excitation and therefore contribute to the lowering of pain.

2. Morphology of Dorsal root ganglia (DRG)

Dorsal root ganglia (sensory ganglia) contain the cell bodies of primary afferent neurons that transmit the sensory information from the periphery into the central nervous system (CNS) [6]. Sensory ganglia were located near the entrance of dorsal root into the spinal cord, and are not a part of CNS. Sensory (somatic) ganglia lie outside the blood-brain barrier and are densely vascularized by fenestrated capillaries, making the neurons and SGCs easily accessible to compounds in the circulation, including chemotherapeutic drugs [7]. Chemotherapeutic drugs show greater accumulation in sensory ganglia than in peripheral nerves [8]. Dorsal root ganglia are more sensitive to heat than other nervous tissues [9]. It is known that pulsed radiofrequency can selectively block sensory nerves while minimizing the destruction of motor nerves. Sluijter et al. reported that the placement of a cannula 1–2 cm peripheral to the dorsal root ganglia could result in maximum effect when pulsed radiofrequency was applied on dorsal root ganglia of the spinal cord [10]. Kikuchi et al. [9] classified anatomical positions and variations of dorsal root ganglia into intraspinal (IS), intraforaminal (IF), and extraforaminal (EF) (**Figure 3**).

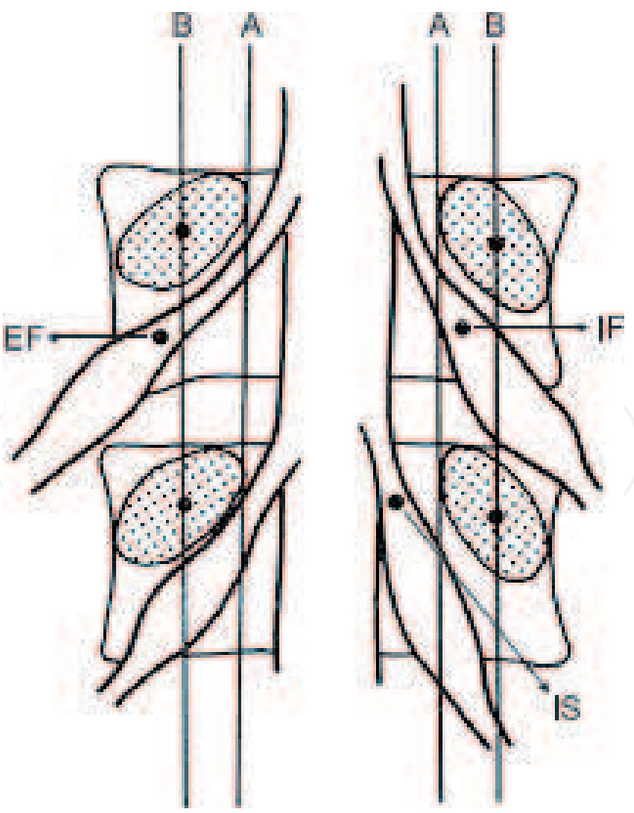

Figure 3.
Positions of dorsal root ganglia (DRG) were determined by two schematic lines and classified into three types. Line A: aligning the medial borders of L4 and L5 pedicles, Line B: aligning the centers of L4 and L5 pedicles, Intraspinal type (IS): DRG located proximal to line A, Intraforaminal type: DRG located between line A and B, Extraforaminal type: DRG located distal to line B [9].

3. Morphology and histology of sensory (somatic) ganglia

The segmental nature of the spinal cord is demonstrated by the presence of 31 pairs of spinal nerves, but there is little indication of segmentation in its internal structure. Each dorsal root is broken up into a series of rootlets that are attached to the spinal cord along the corresponding segment. The ventral root arises similarly as a series of rootlets. These rootlets join to form the ventral and dorsal roots. The dorsal and ventral roots traverse the subarachnoid space and pierce the arachnoid and dura mater. At this point, the dura mater becomes continuous with the epineurium. After passing through the epidural space, the roots reach the intervertebral foramina, where the dorsal root ganglia are located on the dorsal root.

Certain authors have put forward their views regarding the classification of the neurons in the dorsal root ganglia based upon their staining properties into two histological types called "large light" and "small dark", visible under the light microscope. This has been confirmed by recent electron microscopic analysis that indicates [11] the existence of two basic types of DRG neurons usually termed as type A and type B rather than large light and small dark [12]. The neurons in the dorsal root ganglion can also be divided into three types (small, medium and large neurons) based upon the size of their cell bodies. This classification seems to be more appropriate because the size of the neuronal cell bodies determine their function. The large neurons are mainly concerned with the transmission of proprioception and discriminative touch while the medium-sized neurons transmit nerve impulses associated with sensations like light touch, pressure, pain and temperature. However, the small-sized neurons exclusively transmit action potentials related to pain and temperature.

Glial cells are involved in various pathological processes affecting the central nervous system [13]. There is strong evidence that CNS glial cells are involved (microglia and astrocytes) in the induction and maintenance of neuropathic pain [14]. Following injury of a peripheral nerve, satellite glial cells (SGCs) in the dorsal root ganglia undergo changes in cell number, structure and function, similar to those in the CNS

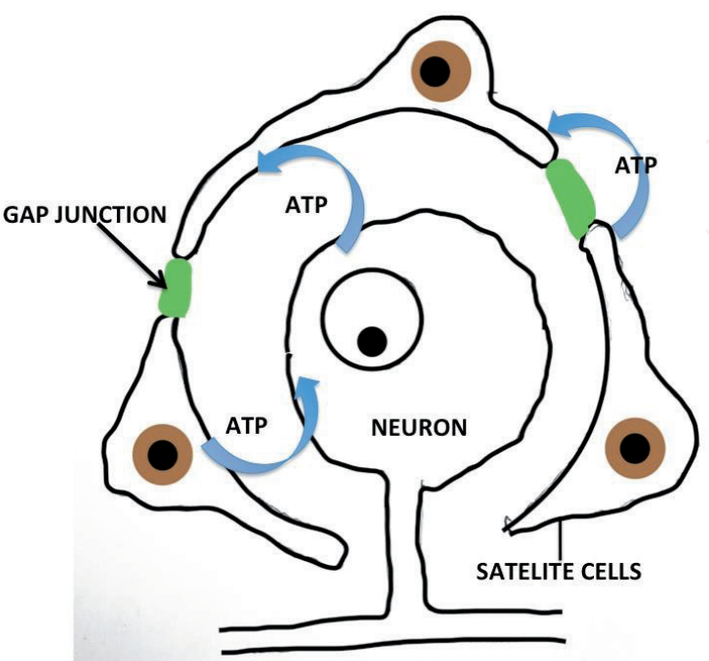

Figure 4.
Schematic diagram describing the structural and functional relations between SGCs and neurons in sensory ganglia, and the consequences of peripheral injury.

[15]. Peripheral nerve transection increases gap junctions and intercellular coupling of SGCs. SGCs also upregulated the production of proinflammatory cytokines such as tumor necrosis factor-α after lumbar facet joint injury [16].

Thus it is well established that glial cells play a critical role in the genesis and persistence of pain [17]. This is particularly true for the sensory ganglia. Though there are far fewer satellite glial cells than astrocytes or Schwann cells, yet because of their unique location in sensory ganglia, SGCs can strongly influence the afferent sensation. They also respond to the nerve injury by upregulating glial fibrillary acidic protein (GFAP) [18]. One of the ways glial cells in the sensory ganglia transmit signals is through intercellular calcium waves (ICWs) via gap junctions and adenosine-5′-triphosphate (ATP) acting on purinergic type 2 (P2) receptors [19]. This signaling has been shown to be bi-directional between SGCs and neurons (**Figure 4**).

4. Classification of pseudounipolar neurons of dorsal root ganglia into small, medium and large

Older literature suggests that neurons in dorsal root ganglia can be divided into two histological types called "large light (LL)" and "small dark (SD)" on the basis of staining properties under the light microscope [20]. This population overlaps, but still, they show the several physiological, biochemical and functional differences. Small dark neurons transmit the sensation particularly carried by C fibers (non-myelinated, slow conducting) [21]. Whereas Large light transmits the sensation carried via a fiber (myelinated and fast conducting). Many of the small dark neurons contain substance P or calcitonin gene-related peptide, and they are concerned with thermo- and mechanoreception, and many of them are nociceptive. The terminals of Large light neurons are low threshold mechanoreceptors [22]. Neurons in the sensory ganglia have no dendrites and also do not receive synapses but are still endowed with receptors for numerous neurotransmitters. More recently depending upon the electron microscopic appearance neurons in the dorsal root ganglia were divided into Type A and Type B for large light and small dark neurons respectively. Various other electrophysiological classification depending upon conduction velocity, modality and adaptation rate serves to distinguished large number of functional types of sensory neurons, but it is not clear how these are related to the two basic histological types.

There are contradictions among the researchers regarding the classification of dorsal root ganglia neurons into small, medium and large categories.

One of the studies involving chronic constriction injury model of Bennet and Xie [23] that retains the connection with the original receptive field so that hyperalgesia and allodynia can be demonstrated, classify the neurons in DRG into small (23–30 μm), medium (31–40 μm) and large (41–53 μm), based on the optical measurement of the average diameter [23]. These grouping roughly correspond to those giving rise to C, Aδ and Aβ fibers, respectively [21].

More recently sensory neurons in dorsal root ganglia were classified depending upon the immunohistochemical staining such as Nav1.8 expression in sensory neurons isolated from dorsal root ganglia into small (27–31 μm), medium (31–40 μm) and large (40–50 μm) [24]. There are two factors, namely DNA content and transcriptional activity, that are determinants of cell size [25]. Differences in neuronal body size seem to be primarily determined by the transcriptional activity. A positive correlation between the cell body and total RNA synthesis has been demonstrated in frog neurons, indicating that large neurons need higher transcriptional activities to maintain their large size [26]. The neurons transcription rate is, in turn, positively related to the magnitude of interactions between neurons and their targets, which contributes to the regulation of the soma size and metabolic activity [27].

Sensory neurons of the dorsal root ganglia express multiple voltage-gated sodium channels that substantially differ in gating kinetics and pharmacology. Small diameter (less than 25 μm) neurons isolated from the rat DRG express a combination of fast tetrodotoxin-sensitive (TTX-S) and slow TTX-resistant (TTX-R) sodium channels while large diameter neurons (more than 30 μm) predominantly expresses TTX-S Na current [28].

Viral study including adeno-associated viral vectors (AAV) are increasingly used to deliver therapeutic genes to the central nervous system where they promote transgene expression in postmitotic neurons for long periods with little or no toxicity. In adult rat dorsal root ganglia authors investigated the cellular tropism of AAV8 containing green fluorescent protein gene (GFP) after intra-lumbar DRG injection. And after injection, 2% of small DRG neurons (less than 30 μm) were GFP (+) as compared to 32% large (more than 60 μm) DRG neurons [29].

Electron microscopic features of dorsal root a ganglion divides the neurons depending upon their size and the distribution of their organelles (**Figure 5**). They were further subdivided into six subtypes according to the arrangement and three-dimensional organization of the Nissl bodies and Golgi apparatus in the perikarya. Type A1 cells were large, clear neurons in which Nissl bodies, separated from each other by pale narrow strands of cytoplasm containing small stacks of Golgi saccules and rod-like mitochondria, were evenly distributed throughout the perikaryon. In type A2, the Nissl bodies assumed a similar distribution but were separated by much wider strands of cytoplasm. Type A3, the smallest of the type A category, displayed densely packed Nissl bodies and long stacks of Golgi saccules which formed a perinuclear ring in the midportion of the perikaryon. Type B cells were smaller and showed a concentric zonation of their organelles. In type B1, large Nissl bodies located in an outer cytoplasmic zone were made of long piles of parallel cisternae interrupted by curved Golgi stacks. Type B2 was characterized by a ring-like Golgi apparatus separating the perikaryon in a cortical zone composed mainly of Nissl substance and a juxtanuclear zone containing mitochondria and smooth endoplasmic reticulum. Type C cells were the smallest of the ganglion cells

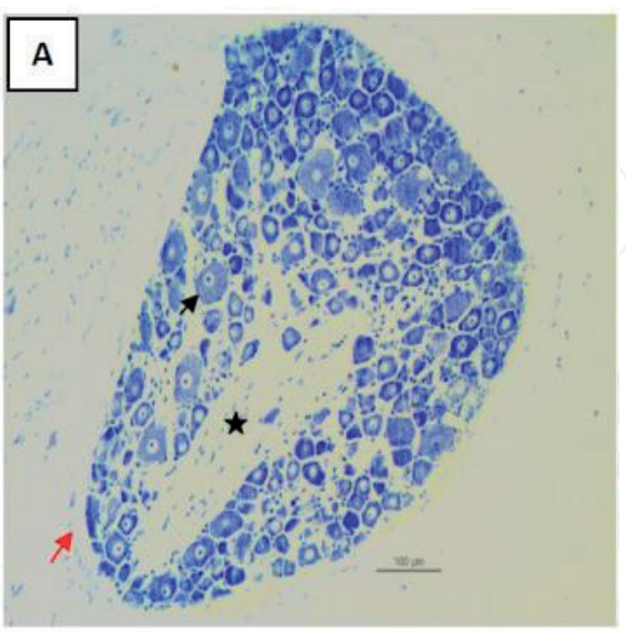

Figure 5.
Nissl's staining showing the variety of neurons in the dorsal root ganglion. Black arrow represents the large neurons, red arrow represents the surrounding capsule and the asterisk showed the location of centrally placed collection of nerve fibers [33].

and contained small, poorly demarcated Nissl bodies and a juxtanuclear Golgi apparatus [30].

Neurotransmitter study involving tachykinin like substance P (SP) and neurokinin A, which are released by the C-type primary afferent terminals of the small DRG neurons, plays important role in spinal nociception. By means of non-radioactive in situ hybridization and whole-cell recording, authors showed that the small rat DRG neurons also express the NK-1 tachykinin receptor. In situ hybridization demonstrated that the positive neurons in rat DRG sections were mainly small with a diameter of less than 25 μm. And the remaining positive neurons were cells with a medium diameter between 26 and 40 μm. No positive large neurons (more than 40 μm) were observed [31].

Depending upon the molecular weight of neurofilaments and their expression in various categories of neurons in dorsal root ganglia, three different neurofilament subunits have been identified, i.e. light (NF-L), middle (NF-M) and high (NF-H). Previous data showed that all the dorsal root ganglia neurons express NF-M and NF-H while only NF-L defines a distinct group of neurons and significantly large-light neurons [32].

5. Peripherin: marker to differentiate the neurons in the DRG

Peripherin, a protein formerly called Y, was first identified by two-dimensional gel electrophoresis in the insoluble fraction of cellular extracts from mouse neuroblastoma cell lines [34]. Its presence has been previously established in the rodent peripheral nervous system mostly by biochemical studies; moreover, biochemical characterization following nerve transection also supports its localization in neurons within the peripheral nervous system [35]. This observation leads to coining of the term "Peripherin" to designate this particular protein entity. Peripherin is a 57-kDa-type III neuronal intermediate filament protein, which is capable of either self-assembling or co-assembling with all of the individual neurofilament subunits [36]. In particular, the small cells of the dorsal root ganglia neurons selectively contain peripherin [35] and thus becoming a useful marker to define the small ganglion cell subpopulation. The exact function of the peripherin is still unknown though it has been suggested to be a determinant of the shape and architecture of the peripheral nerve axons and also provides structural integrity to the cells [37]. Peripherin immunolabeling has seen to be an important marker especially for the study of peripheral nerve development and regeneration since this intermediate filament protein is highly over-expressed during axon elongation [38]. Previously this neurofilament were thought to be inert but in fact these are highly dynamic structures with many diverse function such as relaying the signals from the plasma membrane to the nucleus [39], maintaining the position and function of cellular organelles, and also regulating the protein synthesis [40]. This neurofilament is clinically relevant because of their association with the pathogenesis of some major neuronal disorders. Mainly, accumulation of neurofilament protein and peripherin in proximal axons are associated with amyotrophic lateral sclerosis [41] and also seen in other diseases such as Alzheimer's disease [42]. Peripherin was used to identify the small to medium-sized neurons in the rat dorsal root ganglia in the present study as because these are associated with the transmission of pain from the periphery to the central nervous system. This would give an idea as to the actual number of neurons within the dorsal root ganglia involved in the transmission of pain (**Figure 6**).

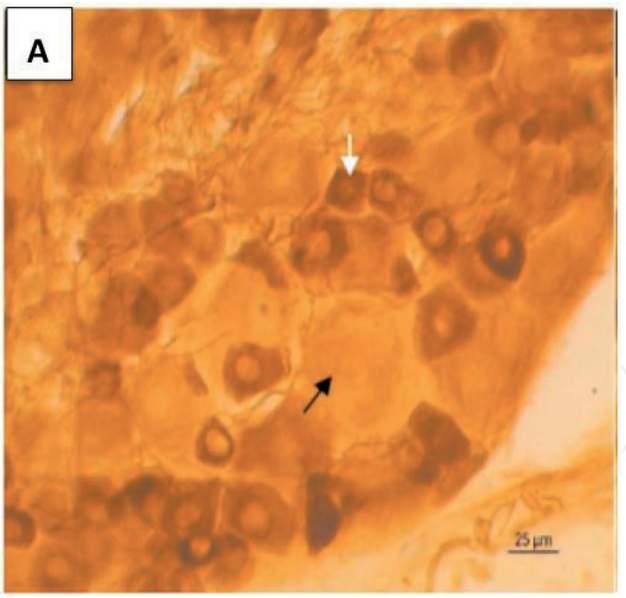

Figure 6.
Immunohistochemical stained section with peripherin antibody of dorsal root ganglion representing the specific staining in small to medium sized neurons (white arrows). Larger neurons (black arrows) [33].

6. Satellite glial cells

Sensory neurons in the dorsal root ganglia are ensheathed by specialized glial cells termed 'satellite glial cells' (SGCs). Recently, there has been considerable interest in these cells as they are profoundly altered by peripheral injuries used to study pain behavior and appear to contribute to chronic pain [43]. Satellite glial cells are the peripheral glial cells, but share many properties with astrocytes in the central nervous system (CNS), including the expression of glutamine synthetase and transporters of amino acids neurotransmitters. However, satellite glial cells differ in some respects from astrocytes, particularly by the tight sheath they make around the neuronal cell bodies [44]. In the dorsal root ganglion, Schwann cells and the satellite cells are activated in response to ischemia, traumatic injury and inflammation [45]. Application of various cytokines to the exposed Dorsal root ganglia resulted in an increase in the discharge rate as well as increased mechanosensitivity of DRG and peripheral receptive fields [46]. Satellite glial cells are the consistent component of the DRG in all the species, yet their contribution to the basic neuronal function remains unknown, although these satellite cells were implicated in neuronal nutrition, homeostasis and the process of apoptosis [5].

Recent studies have demonstrated that a specific glial cell population, the satellite glial cells, has the ability to regulate ion concentration [47] and possess mechanisms for the release of cytokines [48], ATP [19] and other chemical messengers like calcium. Satellite glial cells influence neuronal excitability via the gap junctions [49]. The satellite glial cells undergo major changes as a result of injury to peripheral nerves and appear to contribute to chronic pain [4]. Quantitative studies on several species showed that a number of satellite glial cells per neuron increases in proportion to the neuron's volume, consistent with the idea that these satellite glial cells support the neurons metabolically [50].

During pathological conditions, such as nerve injury or inflammation, SGCs demonstrate an altered phenotype similar to that seen in activated astrocytes, which includes increased expression of the glial fibrillary acidic protein (GFAP) and synthesis of cytokines [51]. SGCs are therefore said to undergo activation due

to injury. Increased coupling by gap junctions between SGCs has been observed in several inflammatory pain and axotomy models [52].

7. Satellite glial cells as a structural unit

Satellite glial cells (SGCs) in sensory ganglia wraps completely around the neuron. Several investigators claimed that SGCs bear processes and are therefore structurally similar to astrocytes but recent researches are that SGCs are laminar and have no true processes. In general, each sensory neuron has its own SGCs sheath, which usually consists of several SGCs, and thus the neuron and its surrounding satellite glial cells form a distinct morphological and probably functional unit. The region containing connective tissue separates these units. In some cases (5.6% in rat DRG) neurons from a small group containing two to three cells that are enclosed in common connective tissue space [44]. The neurons in the clusters are in most cases separated from each other by SGC sheath. The SGCs envelope usually consists of flat processes that lie close to the neuronal plasma membrane. The distance between the glial cell and neuronal plasma membrane is about 20 nm [44]. The neurons send numerous fine processes (microvilli), some of which fit into the invaginations of SGCs thus increasing the neuronal surface area and may allow an extensive exchange of chemicals between two cell types. A study on cultured SGCs of embryonic and neonatal rats showed that SGCs could transform into astrocytes, Schwann cells and oligodendrocytes [53].

Quantitative studies on several species showed that the number of SGCs per neuron increases in proportion to the neuron volume [50] consistent with the idea that SGCs support the neurons metabolically. It was also found that the mean volume of the nerve cell body corresponding to an SGC was lower for small neurons than for large neurons, which implies that the metabolic needs of small neurons are better satisfied than those of large ones. Therefore, smaller neurons have a higher resistance to insults, which seems to be the case for mercury poisoning. However, there is experimental evidence that smaller neurons are more likely to die following axonal damage [54]. As sensory ganglia are not protected from substances circulating in the blood, SGCs may be important in the context of exposure to toxic substances. In several studies, SGCs were examined after poisoning with heavy metals and it was found that these cells take up organic mercury compounds [55], and lead [56]. Mercury poisoning also caused SGCs proliferation [57]. Nineteen days after the administration of organic mercury to rats, SGCs in DRG were heavily labeled for mercury, and their ability to take up GABA was greatly diminished. Interestingly, small neurons were considerably less labeled for mercury than large neurons, which could be attributed to a more effective protection by SGCs. Prolonged (3–18 months) administration of lead acetate to rats resulted in prominent changes in SGCs in DRG, which included proliferation and hypertrophy of these cells. Although a certain degree of neuronal damage was observed, it can be proposed that the changes in SGCs provide a better protection to the neurons during lead poisoning.

8. Satellite glial cells maintain ionic concentration

The satellite glial cells neighboring the pseudounipolar neurons have a highly negative resting membrane potential and noticeable potassium permeability. The primary means of limiting extracellular levels of potassium in the sensory ganglia occurs through the process commonly called spatial buffering or syphoning which

is mediated by satellite glial cells. The maintenance of a low extracellular potassium concentration is crucial for controlling the neuronal resting membrane potential and neuronal excitability. In sensory ganglia increased neuronal excitability has been associated with the occurrence of altered sensation, including the development of the neuropathic pain [58]. In the CNS buffering of extracellular potassium ions is carried by astrocytes, which consist of uptake by inwardly rectifying potassium (Kir) channels and dissipation through other channels and gap junctions [59]. It is established that the Kir current and Kir4.1 expression occur in the satellite glial cells [60]. Voltage-gated potassium channels are one of the important physiological regulators of the membrane potentials in excitable cells including sensory ganglion neurons.

9. Neuron-glial interactions

Central nervous system glial cells are increasingly known to be important regulator of synaptic activity and the key functional unit of nervous system [61]. Even though many of the same voltage-sensitive ion channels and neurotransmitter receptors of neurons are found in glia; glial cells lack the membrane properties obligatory to fire action potentials. Nevertheless, these ion channels and electrogenic membrane transporters permit glia to sense indirectly the level of neuronal activity by monitoring activity-dependent changes in the chemical surroundings shared by these two cell types. Complex imaging methods, which allow observation of changes in intracellular and extracellular signaling molecules in real time, show that glia, communicate with one another and with neurons primarily through chemical signals rather than electrical signals. Many of these signaling systems overlap with the neurotransmitter signaling systems of neurons, but some are specialized for glial-glial and neuron-glial communication. Neuron-glia cell interaction through gap junctions and extracellular paracrine/autocrine processes are believed to be important in the development of peripheral sensitization within the trigeminal ganglia [62]. Peripheral sensitization, which is characterized by increased neuronal excitability and a lowered threshold for activation, may possibly trigger a migraine attack. Moreover, activation and sensitization of the trigeminovascular afferent fibers appear crucial for initiation of migraine pain and for subsequent central centralization, in which increased excitability of second-order neurons leads to pain and allodynia. Increased gap junction communication between neurons and satellite glial cells was observed in the trigeminal ganglion in response to chemical activation of sensory trigeminal nerves [62].

Increased neuronal-glial signaling by way of gap junctions is common in neuroinflammatory CNS disorders, such as cerebral ischemia and Alzheimer's disease and may have underlying pathological significance [63]. Tonabersat (SB-220453), a compound that binds selectively and with high affinity to a unique stereoselective site i.e. the gap junctions and inhibits it in rats and human brains [64]. After an injury, the numbers of gap junctions that connect satellite glial cells increases [43] in a probable adjust to the greater release of potassium ions with intense neuronal activity. Injury to a peripheral nerve does not directly impact satellite glial cells integrity. However, changes in injured neurons can influence the ability of the surrounding SGCs to regulate K^+ via neuromodulators such as adenosine triphosphate (ATP) and nitric oxide (NO) [65].

Satellite glial cells have unique proteins that include the inwardly rectifying K^+ channel Kir4.1 [43], the connexin-43 (Cx43) subunit of gap junctions the purinergic receptor P2Y4 [66] and soluble guanylate cyclase. There is also evidence of the presence of small-conductance Ca^{2+}–activated K^+ channel SK3 that is present only in satellite glial cells. All the above proteins are involved, either directly or indirectly,

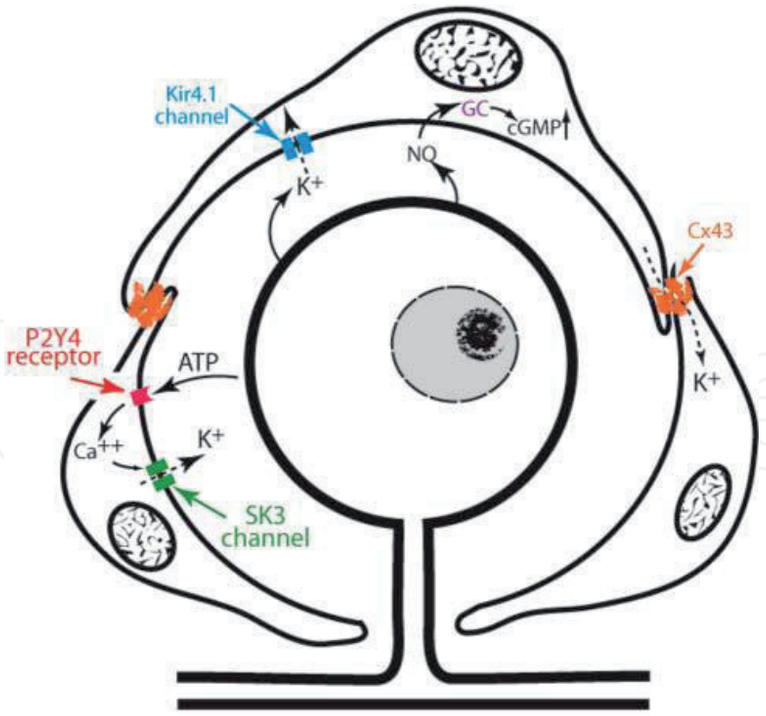

Figure 7.
Satellite glial cells involved in maintenance of potassium homeostasis [66].

in potassium ion (K^+) buffering and, thus, can influence the level of neuronal excitability, which, in turn, has been associated with neuropathic pain conditions (**Figure 7**). They also used in vivo RNA interference to reduce the expression of Cx43 (present only in SGCs) in the rat trigeminal ganglion and showed that this resulted in the development of spontaneous pain behavior. The pain behavior is present only when Cx43 is reduced and returns to normal when Cx43 concentrations are restored [66, 67].

10. Glial fibrillary acidic protein (GFAP): locator molecule for the satellite glial cells

Glial fibrillary acidic protein is principle intermediate filament in mature astrocytes of the central nervous system and satellite glial cells of sensory ganglia [4]. GFAP is strongly unregulated in response to CNS damage [68]. It is thought to be important in astrocyte neuronal interactions, astrocyte mobility and shape and for maintenance of homeostasis and vascular permeability at the blood-tissue interface [69]. GFAP is essential for normal white matter architecture and blood-brain barrier integrity and its absence leads to late-onset CNS dysmyelination [70]. Increased GFAP expression occurs in activated glial cells. Activated astrocytes are characterized by hypertrophy, the release of pro-inflammatory cytokines (IL-1, IL-6 and TNF-a), the release of nitric oxide and prostaglandins, and up-regulation of the intermediate filaments GFAP and vimentin [17]. Likewise, satellite glial cells (SGCs) display increased expression of GFAP after neuronal injury or inflammation and undergo a number of changes similar to those seen in astrocytes, such as synthesis of cytokines [71]. GFAP expression increases in the satellite glial cells of trigeminal ganglia after tooth pulp injury [72]. The present study also investigated the expression of GFAP in the satellite glial cells following acute pain (**Figure 8**).

GFAP is a marker of activated satellite glial cells and astrocytes [48]. These ropes like filaments are called intermediate filaments because their diameter of 8–10 nm is

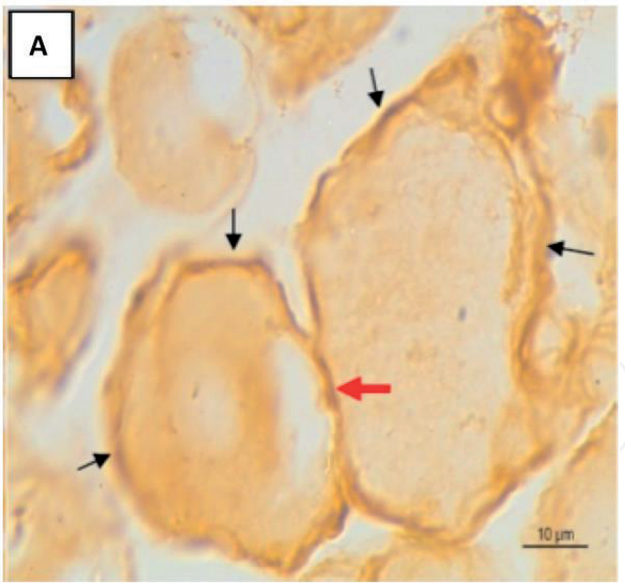

Figure 8.
Immunohistochemical staining for the section of DRG using GFAP antibody. Black arrows representing the location of satellite glial cells. Red arrow showing the communication between two neurons [33].

between those of actin filaments and microtubules. Nearly all-intermediate filaments consist of subunits with a molecular weight of about 50 kDa. Some evidence suggests that many of the stable structural proteins in intermediate filaments evolved from highly conserved enzymes, with only minor genetic modification. Intermediate filaments are formed from nonpolar and highly variable intermediate filament subunits. Unlike those of microfilaments and microtubules, the protein subunits of intermediate filaments show considerable diversity and tissue specificity. In addition, they do not possess enzymatic activity and form nonpolar filaments. Intermediate filaments also do not typically disappear and reform in the continuous manner characteristic of most microtubules and actin filaments. For these reasons, intermediate filaments are believed to play a primarily structural role within the cell and to compose the cytoplasmic link of a tissue-wide continuum of cytoplasmic, nuclear, and extracellular filaments. A highly variable central rod-shaped domain with strictly conserved globular domains at either end characterizes intermediate filament proteins. Although the various classes of intermediate filaments differ in the amino acid sequence of the rod-shaped domain and show some variation in molecular weight, they all share a homologous region that is important in filament self-assembly. Intermediate filaments are assembled from a pair of helical monomers that twist around each other to form coiled-coil dimers. Then, two coiled-coil dimers twist around each other in antiparallel fashion (parallel but pointing in opposite directions) to generate a staggered tetramer of two coiled-coil dimers, thus forming the nonpolarized unit of the intermediate filaments. Each tetramer, acting as an individual unit, is aligned along the axis of the filament. The ends of the tetramers are bound together to form the free ends of the filament. This assembly process provides a stable, staggered, helical array in which filaments are packed together and additionally stabilized by lateral binding interactions between adjacent tetramers [2].

Total six classes of intermediate filament are present in body, e.g., Class II and I include keratin and cytokeratin and class III include vimentin, glial acidic fibrillary protein (GFAP) and peripherin.

GFAP is the principal intermediate filament in mature astrocytes. GFAP is a soluble protein isolated from the multiple sclerosis plaques and presumably arising from the glial filaments [73]. The GFAP gene is located on the long (q) arm of chromosome 17 at position 21. Mutation in the GFAP results in Alexander disease

characterized by rare leukoencephalopathy affecting predominantly the brainstem and cervical cord with insidious onset of clinical features and unified by the presence in astrocytes of Rosenthal fibers (protein aggregates mainly contain glial fibrillary acidic protein (GFAP) and small stress proteins) in the astrocytes especially in the subpial and subependymal in location. It is strongly upregulated in response to the CNS damage [68]. It is thought to be important in astrocyte-neuronal communication and is believed to modulate astrocyte motility and shape. Satellite glial cells (SGCs) responsible for the maintenance of homeostasis and vascular permeability at the blood-tissue interface [69]. In the peripheral nervous system, neurons located in sensory ganglia are tightly surrounded by SGCs, following injury these cells undergo modification in structure and function [15]. According to Feng et al., after ligation of the L5 spinal nerve, mechanical allodynia developed in the ipsilateral hind paw and expression of GFAP in the ipsilateral DRG increased significantly as early as 4 hours after surgery, and gradually increases up to peak level at day 7 and then stayed at high level till day 56 [74]. Significant change seen among the sizes of neurons means small to medium size neurons shows maximum GFAP immunoreactivity at 12 hours and on day 7, a number of larger neurons was surrounded by GFAP stained satellite cells.

11. Gap junctions in the nervous system

Gap junctions, tight junctions, adherens junctions, desmosomes, hemidesmosomes, focal adhesions, chemical synapses, and immunological synapses are complex multiunit plasma membrane structures that assemble in a localized spatial and temporal organization to maintain structural tissue organization and to provide the cell signaling functions. At least nine connexins (Cx26, Cx32, Cx33, Cx36, Cx37, Cx40, Cx43, Cx45, Cx46) are expressed to various degrees in the nervous system. Functional studies in diverse cell types and in various exogenous expression systems have revealed that gap junction channels formed by different connexins are regulated differently, both at the single channel level (gating controls such as voltage sensitivity and variations in unitary conductance) and at the level of synthesis (expression, altered for example by hormones, extracellular matrix). Some gap junction channels are more sensitive to various gating stimuli than others, some display some degree of ionic selectivity, and some will pair promiscuously with other connexins (heterologous channels) while others are quite selective in their interaction (homologous channels). Such differences are important from the standpoint of the physiological roles of gap junctions in different cell types, as well as in the establishment of communication compartments within the nervous system [75]. Connexins are differentially expressed in the brain during ontogeny. Most recently, tissue culture preparations from embryonic neural tissue have allowed manipulation of individual cells and evaluation of changes in junctional distribution and expression during maturation. Such studies have clarified the relationships between sequential changes in phenotypes of neural cells, with the extent of coupling mediated by Cx43 (which is abundant in neural precursor populations) and the appearance of other gap junction proteins. Expression pattern of Cx32, Cx43 and Cx30 during the development in rat brain indicates the Connexin-43 appears first at embryonic days 12-18 [76] and that Cx32 protein and mRNA appear during first or second postnatal week and increases during development. Immunohistochemical analysis of postnatal rat brain has shown that Cx43 first appears along radial glial cells and is most intense along cerebellar Bergmann glial cells [77]. Glia represents the major cell population in the CNS coupled by gap junctions. Indeed, compared to neurons, the level of connexin expression is high in these cells and persists until the adult stage [75]. For the two main types

of macroglial cells, the astrocytes and the oligodendrocytes, several connexins have been detected [78]. Gap junctional communication is not limited to either astrocyte-to-astrocyte or oligodendrocyte-to-oligodendrocyte, but it also occurs in between both cell types. In the adult brains, the predominant connexin is Cx43, which is abundant in astrocytes and is also expressed in leptomeninges, endothelial cells and ependyma. The second type of microglia, the oligodendrocytes (and their peripheral counterparts, the Schwann cells), appear to express a different gap junction protein, Cx32, although to a lower extent in situ than the level of Cx43 expression exhibited by astrocytes. Astrocytes express Cx43 and are well coupled in vivo and under culture conditions. However, the strength of coupling and degree of Cx43 expression between astrocytes varies depending on brain regions being higher in the hypothalamus than in the striatum. Although glial gap junctions do not generate action potentials in normal conditions and are devoid of synaptic contacts, connexin channels provide a route that allows changes in membrane potential to be transmitted from one cell to its neighbors. Recently, the participation of astrocytic gap junction in neuroprotection has been investigated by comparing neuronal vulnerability in the presence of either communicating or non-communicating astrocytes [75].

12. Gap junctions and connexins

Gap junctions and their consistent connexin proteins have represented a new challenge in all tissues where they occur but no structure is more complex or more interconnected than the mammalian central and peripheral nervous systems (CNS and PNS). The term "Gap junctions" arose from the work of Revel and Karnovsky, who described the fine structure of the interconnections between mouse cardiomyocytes and between hepatocytes. Later development of specific antibodies to gap junction proteins and eventually the cloning of these connexin molecules have now led to the availability of a variety of techniques by which the distribution and expression patterns of specific types of gap junctions have been defined in a varied number of tissues, including the brain. Gap junctions are the clusters of intercellular channels that are composed of 12 subunits, 6 of which form a connexion or hemichannel contributed by each of the coupled cells [79]. Gap junctions are permeant to molecules up to 1 kDa and are found in virtually all cell types in mammals; few exceptions include circulating erythrocytes, spermatozoids and adult innervated skeletal muscle cells [80]. Gap junctional communication is essential for many physiological events, including cell synchronization, differentiation, cell growth, and metabolic coordination of avascular organ including epidermis and lens [81]. Connexin family members share a similar structural topology. Each connexin has four transmembrane domains that constitute the wall/pore of the channels. These domains are linked by two extracellular loops that play roles in the cell-cell recognition and docking processes. There are three unchanged cysteine residues in each loop, which solely form intraconnexin disulfide bonds [82]. The transmembrane domains and extracellular loops are highly conserved among the family members. Furthermore, connexin proteins have cytoplasmic N- and C-terminal and a cytoplasm loop linking the second and third transmembrane domains. Although the N-terminus is conserved, the cytoplasmic loop and C-terminus show great variation in terms of sequence and length. The cytoplasmic tail and loop are susceptible to various post-translational modifications (e.g., phosphorylation), which are believed to have regulatory roles [83]. Connexons (hemichannels) are then carried to the cell surface via vesicles transported through microtubules, which fuse to the plasma membrane. These hemichannels can either form nonjunctional channels in unopposed areas of the cell membrane or diffuse freely to regions of cell-to-cell contact to find a partner connexon from a neighboring cell to complete

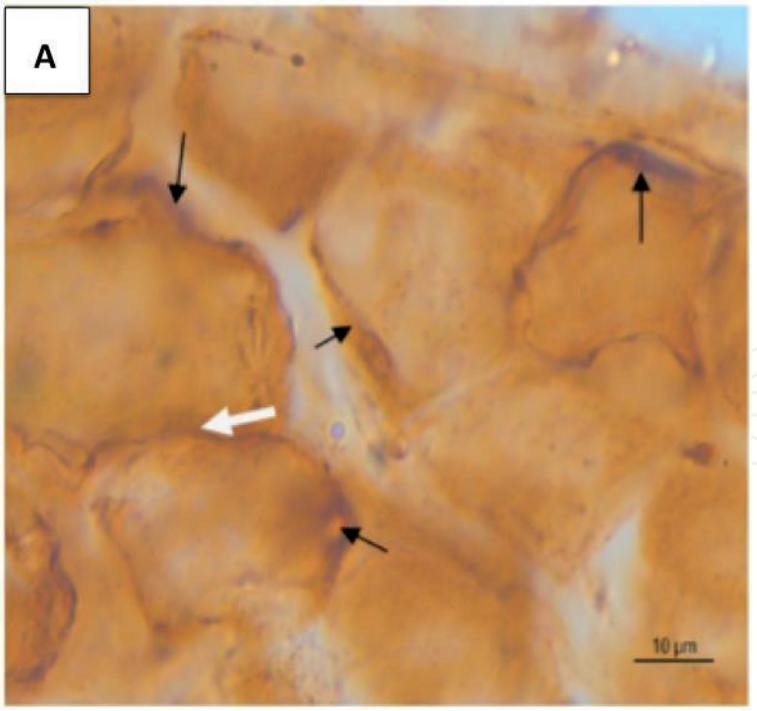

Figure 9.
Immunohistochemical staining using connexin-43 antibody. Black arrows represent the location of gap junctions between the satellite glial cells and the neuronal bodies [33].

the formation of intercellular channels. Intercellular channels then cluster into gap junction plaques, a highly dynamic event involving removal of old channels from the center of the plaque, while adding new gap junction subunits to the periphery [84]. The intercellular channels from the middle of the plaque are internalized into vesicular structures called "annular junctions" [85], which either fuse with the lysosome for degradation by lysosomal enzymes or are targeted to the proteasomal pathway [86]. The continuous synthesis and degradation of connexins through these mechanisms may provide for the quick adaptation of tissues to changing environmental conditions. Unopposed hemichannels can also be functional under certain conditions, including mechanical and ischemic stress. Under these circumstances, open hemichannels are thought to facilitate the release of a variety of factors such as ATP, glutamate, and NAD+ into the extracellular space, generating different physiological responses [87].

Up to date, there were 20 proposed members of the connexin family of proteins that form gap junctional intercellular communication channels in mammalian tissues, and over half are reported to be present in the nervous system. Identification of the several connexin proteins at gap junctions between each neuronal and glial cell type is necessary for the sensible design of investigations into the functions of gap junctions between glial cells and into the functional contributions of electrical and "mixed" (chemical plus electrical) synapses to communication between neurons in the mammalian nervous system (**Figure 9**).

13. Pathophysiology of connexins

Gap junction's role has been well evaluated concerning cell-to-cell interaction. There are two effects derived from gap junction's function that may determine life and death of the connected cells [89]. The bystander effect promotes the death of normal cells adjacent to an apoptotic cell by diffusing toxic metabolites through gap junctions. In the same way there is the Good Samaritan effect that allows

a condemned cell to live by draining the toxic metabolites to adjacent cells and maintaining cells integrity and thus tissue homeostasis. In this way gap junctions perform a dual function either saving or killing interconnected cells [88]. Some pathological conditions are directly related to gap junctions or to their altered function. Some human diseases are caused by mutated connexins [89]. Mutations on Cx32 induce a peripheral neuropathy named Charcot-Marie-Tooth disease. The many conductivity changes observed in this disease may be caused by altered protein traffic to the junctions, altered channel permeability and, sometimes, altered conformation of heterotypic channels [78]. Mutations of Cx36 may lead to the most common hereditary non-syndromic deafness. Cx43 structure may be altered in some forms of human epilepsy where Cx43 mRNA expression may or may not be altered. High Cx43 levels have been detected in β-4 positive amyloid plaques of Alzheimer's disease [77], indicating either astrocytes invasion of the plaques or increased Cx43 expression by astrocytes, as observed in PC12 cells (cells from a rat pheochromocytoma) with increased expression of carboxy-terminal portions of amyloid precursor protein [90]. However a higher Cx43 expression in that area may reflect the existence of many activated macrophages/microglia. The decrease of Cx43 within an inflammatory focus suggests that factors as IL-1 β are involved in astrocytic connectivity decrease as observed in autoimmune experimental encephalitis.

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