Rev Bras Anestesiol. 2015;65(1):73–81

REVISTA BRASILEIRA DE ANESTESIOLOGIA

Official Publication of the Brazilian Society of Anesthesiology
www.sba.com.br

REVIEW ARTICLE

Satellite glial cells in sensory ganglia: its role in pain☆

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Received 30 October 2012; accepted 15 July 2013
Available online 6 November 2014

KEYWORDS
Satellite glial cells;
Sensory ganglia;
Pain;
Intraganglionar communication;
Purinergic receptors

Abstract
Background and objectives: Satellite glial cells in sensory ganglia are a recent subject of research in the field of pain and a possible therapeutic target in the future. Therefore, the aim of this study was to summarize some of the important physiological and morphological characteristics of these cells and gather the most relevant scientific evidence about its possible role in the development of chronic pain.
Content: In the sensory ganglia, each neuronal body is surrounded by satellite glial cells forming distinct functional units. This close relationship enables bidirectional communication via a paracrine signaling between those two cell types. There is a growing body of evidence that glial satellite cells undergo structural and biochemical changes after nerve injury, which influence neuronal excitability and consequently the development and/or maintenance of pain in different animal models of chronic pain.
Conclusions: Satellite glial cells are important in the establishment of physiological pain, in addition to being a potential target for the development of new pain treatments.

PALAVRAS-CHAVE
Células gliais satélite;
Gânglio sensitivo;
Dor;

Células gliais satélite de gânglios sensitivos: o seu papel na dor

Resumo
Justificativa e objetivos: As células gliais satélite de gânglios sensitivos são um objeto recente de pesquisa na área da dor e um possível alvo terapêutico no futuro. Assim, este trabalho tem

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http://dx.doi.org/10.1016/j.bjane.2013.07.013

Comunicação intraganglionar; Receptores purinérgicos

como objetivo resumir algumas das características morfológicas e fisiológicas mais importantes destas células e reunir as evidências científicas mais relevantes acerca do seu possível papel no desenvolvimento da dor crônica.
Conteúdo: Nos gânglios sensitivos cada corpo neuronial é envolvido por células gliais satélite, formando unidades funcionais distintas. Esta íntima relação possibilita a comunicação bidirecional, através de uma sinalização parácrina, entre estes dois tipos de células. Existe um número crescente de evidências de que as células gliais satélite sofrem alterações estruturais e bioquímicas, após lesão nervosa, que influenciam a excitabilidade neuronial e consequentemente o desenvolvimento e/ou manutenção da dor, em diferentes modelos animais de dor crônica.
Conclusões: As células gliais satélite são importantes no estabelecimento da dor não fisiológica e constituem um alvo potencial para o desenvolvimento de novos tratamentos da dor.

Introduction

Pain has a physiological protective role acting as a warning signal to any threat to the physical integrity of the body, but it can become a disease in itself when it persists and recurs for more than three months, becoming chronic and devoid of any biological function.[1] It is a perceptive, complex, subjective, and multidimensional phenomenon. Different forms of pain are produced by multiple molecular and cellular mechanisms acting alone or in combination with the central and peripheral nervous systems.[2] In search of new therapeutic targets it is essential to understand the mechanisms responsible for the generation and maintenance of pain and identify the cells and/or molecules involved.[3] In this context, the glial cells of the central nervous system (CNS), and more recently those of the sensory ganglia, have shown to be important in these mechanisms, as they have the ability to communicate with neurons and modulate its activity.[4,5] In sensory ganglia, particularly in dorsal spinal ganglia (DSG) and trigeminal ganglion (TG), satellite glial cells (SGC) establish a privileged relationship with the surrounding neuronal bodies.[6] Interactions between SGC and neurons and its consequences on neuronal excitability are one of the most recent research focuses on the field of pain, as in the last ten years the number of articles on the role these cells play in neuronal activity has increased significantly. Therefore, the aim of this study was to gather knowledge about the morphological and functional characteristics of SGC and its interaction with the primary afferent neurons. We also reviewed the available information on the changes seen in these cells in different models for the study of pain in animals and its impact on neuronal activity and consequently in chronic pain.

The SGC

The SGC, as well as the Schwann cells, are derived from the pluripotent neural crest cells.[7] Morphologically, these cells are characterized by a laminar, irregular shape, usually mononuclear, with lamellar expansions and microvilli that increase its surface area.[8–10] These cells surround each neuron and the proximal portion of its axon, forming a sheath around each cell body. Each cell body surrounded by a sheath of SGC forms a morphologically and functionally distinct unit.[6,11] The SGC from a sheath are connected together by adhesive and gap junctions, and are separated from the neighboring perineuronal sheath by connective tissue.[12–14] Physiologically, SGC are regarded as the equivalent cells in the peripheral nervous system to the CNS astrocytes, with the investigation of its features marked by this analogy. Properties such as regulation of ion concentration of extracellular space and the recycling of neurotransmitters are shared with them. They are molecular markers of glutamine synthase (GS), proteins of the S100 family involved in the regulation of intracellular calcium and expression of glial fibrillary acidic protein (GFAP).[6] Electrophysiologically, glial cells exhibit a highly negative membrane potential at rest and express voltage-dependent calcium and potassium channels Kir4.1.[15–17] They also express numerous receptors of bioactive molecules, potentially involved in interactions with other cells, with many of them recently implicated in the genesis and maintenance of chronic pain, namely, the P2Y[18,19] and $P2X_7$[20] purinergic, calcitonin gene-related peptide (CGRP),[21] substance P,[22] and cytokine and chemokine receptors—examples of which are tumor necrosis factor alpha (TNFα)[23] and interleukin-1 beta (IL-1β)[24] and endothelin-B[25] and N-methyl-D-aspartate (NMDAr) receptors.[26]

Intraganglionar communication

Initially, the main function assigned to the cell body of the afferent neurons was the metabolic support, ensuring the maintenance of optimal levels of ion channels, receptors, and proteins in the central and peripheral terminals. In recent decades, increasing evidence of morphological and physiological properties definitely put aside the passive role assigned to the cell body in the path of information from the periphery to the CNS. One of the morphological

peculiarities encountered is the presence of several neurotransmitter receptors in the cell body, although there is virtually no contact in synaptic ganglion.[27] Electrophysiological studies in vivo have found other indicators showing that the excitation of DSG neurons led to the development of action potential in neighboring neurons, a property called cross-excitation. This potential was confirmed in studies in vitro in which repeated stimulation of these neurons induced a transient depolarization of neighboring neurons in this ganglion, probably mediated by chemical messengers.[28,29] According to this assumption, it was found that in response to an electrical or chemical stimulation there is a calcium-dependent somatic release[30] of diffusible chemical mediators capable of altering the somatic excitability in sensory ganglia. Examples of such mediators are substance P, adenosine triphosphate (ATP), *gamma-amino-butyric acid* (GABA), CGRP, and glutamate.[20,21,30–34]

On the other hand, the cellular body is completely enveloped by the GSC sheath, suggesting that the effect of these mediators on surrounding neurons is indirect, involving the SGC.[34] The SGC peculiar arrangement in sensory ganglia guarantees an intimate association of the neuronal body with the SGC, allowing these glial cells to control the perineural environment and facilitate non-synaptic communication between these two cell types.[21,22,34,35] Indeed, the existence of two-way interactions between sensory neurons and SGC was recently demonstrated.[34,35] The way the CGS-neuron communication takes place, the actors in the process, and its impact on the modulation of afferent information are far from being understood. However, some potential candidate to mediate this paracrine signaling are substance P, CGRP, cytokines, endothelins, nitric oxide (NO), and ATP[22] (Fig. 1).

ATP seems to be the main mediator in the interaction between neurons and SGC[34,35] in sensory ganglia. P2 receptors are expressed in sensory neurons (all P2X, except $P2X_7R$ and P2YR 1, 2, 4, 6), Schwann cells, and SGC (for review see).[36] Through calcium imaging, the presence of functional P2Y receptors was detected in GSC of intact TG of rodents.[37] This expression was confirmed in studies with cultured TG cells, and the receptors were classified as P2Y 1, 2, 4 6, 12 and 13 subtypes.[18,19] In DSG, only the level of mRNA was assessed.[38] Among the ionotropic receptors, $P2X_4$ and $P2X_7$[39,40] subtypes are found in the SGC, but recent studies have reported the possibility that they also express $P2X_2$ and $P2X_5$ receptors.[41] The differential expression of $P2X_7$ and $P2X_3$ receptors in SGC and neurons, respectively, provided a way to distinguish the actions of ATP in neurons and SGC.[39,40] It was found that blocking the activation of the $P2X_7$ receptor with an antagonist or reducing its expression using RNA interference (RNAi) in normal rodents, there is an increased neuronal expression of $P2X_3$, suggesting that the tonic activation of the SGC $P2X_7$ receptors exerts an inhibiting control over the $P2X_3$. On the other hand, the ATP released by neurons can activate the $P2X_7$ receptor of the SGC leading to the release of cytokines, namely TNF-α, which enhances the neuron $P2X_3$ receptor mediated response. Thus, it was concluded that the $P2X_7$ exerts influence, either excitatory or inhibitory, on the sensory neuron soma.[20,40] It was also shown that the vesicular release of ATP by the cell body of neurons in the DSG acts on the P2X7 receptor by increasing the intracellular concentration of Ca^{2+} in the surrounding

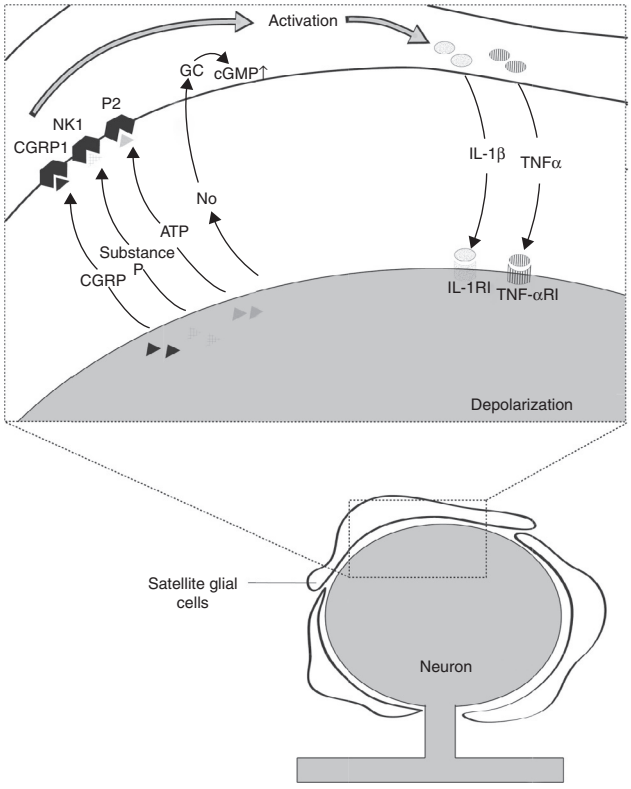

Figure 1 Intraganglionar communication. After peripheral nerve injury a somatic neurotransmitter release occurs, such as the calcitonin gene-related peptide (CGRP), substance P, adenosine triphosphate (ATP), and nitric oxide (NO) in perineuronal environment. These mediators activate satellite glial cells via their receptors located on the surface membrane of cells. This activation leads to release of cytokines such as tumor necrosis factor alpha (TNFα) and interleukin 1 beta (IL-1β), which in turn can influence neuronal excitability through specific receptors (TNFα-RI and IL-1RI). Adapted with permission Ref. [22].

SGC. This finding is relevant because the waves of Ca^{2+} are used as a mechanism of information transmission network among astrocytes, mediated by ATP and gap junctions.[42] Thus, given that SGC express P2 receptors and are connected by gap junctions, it was possible to conclude that these cells, similar to astrocytes, would also have the ability to sustain calcium waves. In this sense, a study was conducted in primary cultures of TG and it was found that the electrical or mechanical stimulation of a single cell body promoted an increase in intracellular calcium in neurons and surrounding SGC by a propagation similar to the Ca^{2+} waves. This propagation was essentially mediated by P2 receptors and, to a lesser extent, by the gap junctions, which demonstrated the existence of a bidirectional communication between neurons and SGC performed by Ca^{2+}.[35]

As for substance P, the finding of its increased somatic release after orofacial inflammation was the first indication that this substance plays an important role in paracrine signaling established in ganglia after inflammation.[31,43] This was later confirmed after finding that the increased release of substance P by Aδ and C nociceptors was accompanied by an increased expression of NK1 receptors in Aβ

non-nociceptive surrounding neurons.[44,45] Moreover, it has been suggested that this neuropeptide can activate the SGC through NK1 receptors, so that SGC respond with the synthesis and release of IL1-β.[22] The NK1 expression in SGC was not directly measured, but the NK1expression with high affinity for substance P has been shown in astrocytes and microglia.[46]

The finding that intraganglionar release of CGRP occurs after activation of trigeminal afferent neurons, along with the CGRP1 receptor expression in neurons and DSG,[21] made this neuropeptide a candidate for mediating the neuron–SGC interaction. This hypothesis was reinforced by TG studies, which have shown that CGRP can act in an autocrine manner, stimulating the promoter activity of CGRP and increasing mRNA levels.[47] Furthermore, it may also have a paracrine action on CGS, regulating the release of cytokines and chemokines[48] and increasing the expression of inducible nitric oxide synthase (iNOS), as well as the release of NO.[21] Nitric oxide is also a potential messenger between neurons and SGC, as NO released by neurons after nerve injury acts on SGC causing increased expression of guanylate cyclase α1, which catalyzes the formation of cyclic guanosine monophosphate.[49] Recently, the extreme sensitivity of the TG SGC to endothelin-1 by ET-B receptor activation was also demonstrated.[50] Because sensory neurons express endothelin-1 mRNA, this peptide may also be one of the actors in the communication between SGC and the neuron.[51]

The functional expression of NMDAr in SGC, whose activity may also modulate the SGC–neuron interaction in DSG,[26] was also verified recently. Several facts indicate the occurrence of glutamate release in ganglion, particularly the presence of glutamate receptors[52] and vesicular glutamate transporters in the neuronal body.[53] Besides this evidence, all proteins necessary for the uptake and recycling of glutamate were found in the SGC, including the glutamate aspartate transporter (GLAST) and glial glutamate recycling enzymes, such as GS.[6,54] In a study that sought to understand the role of glutamate in trigeminal ganglia, it was found that blocking the synthesis of SG in SGC leads to reduced activation threshold for mechanical stimulation of the face. Supposedly, this effect is associated with decreased release of glutamine by SGC and hence to a decrease in glutamine available for uptake by the neuron to produce glutamate.[55]

SGC response to nerve injury and effect on nociception

The studies evaluating the role of sensory ganglia in chronic pain were focused on changes in sensory neurons after nerve injury. Changes in intrinsic properties of the pericardium may lead to hyperexcitability, characterized by increased incidence of spontaneous activity and reduced activation threshold by peripheral stimuli, which result in hyperalgesia and allodynia phenomena seen after injury.[56,57] Research in an animal model of pain, mostly performed in rodents and based primarily on peripheral lesions due to axotomy, inflammation or constriction, indicates that nerve injury not only induces changes in neurons but also in sensory ganglia SGC. Similar to the CNS glial cells, the SGC are activated under these conditions. The concept of activation is based on the notion that, under normal conditions, glial cells are spectators of the nociceptive process, but after peripheral injury, they react exhibiting morphological changes and releasing glial mediators.[4] Because neurons are the lesion target, the changes seen in SGC are secondary to neuronal changes and involve activation of signaling mechanisms between neurons and these cells.

The event that triggers these changes seem to be related to increased neuronal firing induced by nerve injury.[58] This hypothesis is based on several assumptions. First, experiments with various pain models and methods of blocking neuronal activity demonstrated that the blockade of spontaneous activity prevents the development of pain associated with non-physiological behavior. One of the studies that establish this relationship used two different pain models in rodents: one induced by chronic constriction injury of the sciatic nerve and another induced by axotomy and ligation of tibial and common fibular nerves. The effect of two action potential blockers (tetrodotoxin and bupivacaine) was tested in these animals, administered alone, in normal and injured mice. Behavioral tests for thermal hyperalgesia and mechanical allodynia in these same animals showed a reduction in the behavioral signs of pain. In the same study, these blockers application prevented the spontaneous activity in the injured sciatic nerve, assessed by electrophysiology after the administration of blockers, before and after the animals were subjected to nerve injury.[59] The second assumption is based on the observation that the activation of SGC from DSG after sciatic nerve injury is prevented by the local nerve conduction blockade. In this study, performed in a model of L4 spinal nerve axotomy, with an implanted infusion pump of tetrodotoxin, there was a marked reduction in the SGC activation, when detected by the assessment of the GFAP levels of expression using immunohistochemistry. In that same study, this result was confirmed by local application of other sodium channel blockers (bupivacaine) in rats with peripheral injury induced by the binding of the fibular and tibial nerves.[60]

Despite this evidence, the abnormal spontaneous neuronal activity is only one candidate for a triggering event. In fact, this issue is a topic of recent research, and there are still no studies clarifying the mechanisms responsible for the SGC activation. However, several studies have shown that these cells undergo deep changes in response to nerve injury, mainly characterized by an increased expression of GFAP, decreased expression and sensitivity of potassium channels, increased SGC coupling by gap junctions, increased sensitivity to ATP, altered expression of purinergic receptors, and release of ATP and cytokines.[6,22,54,61] There is also evidence that these changes may contribute to chronic pain.[62,63]

Increased expression of GFAP

Under normal conditions the SGC exhibit low, almost undetectable, levels of GFAP by immunohistochemistry, by which the observation in several studies of its increased expression after injury made it the essential marker in the assessment of SGC activation.[16,60,62,64–68] The significance of this increased expression remains unclear. Regarding astrocytes, one of the explanations given relates this protein increase with the communication between astrocytes and neurons

via glutamate. According to this hypothesis, the extracellular increase of this neurotransmitter would trigger the GFAP increase required to support the increased expression of GLAST, since this filament is essential to anchor GLAST to the plasma membrane of astrocytes.[69,70] Based on these findings, it was hypothesized that, as in astrocytes, the glutamate released in sensory ganglia could trigger the increased expression of GFAP in SGC, but so far this has not been proven.[54] Even so, the expression of GFAP is considered the best known marker of SGC activation. Its usefulness could be proven in a study that used a model of neuropathic pain induced by ligation of the fifth lumbar spinal nerve, in which the GFAP reactivity to assess the SGC activation was analyzed. It was demonstrated that this activation contributes to the maintenance of the neuropathic pain symptoms in the early period of disease, more precisely the onset of mechanical allodynia.[58]

Increased expression and sensitivity of potassium channels

SGC are responsible for perineural K^+ homeostasis regulated through the input channels of rectified K^+ currents' glial cell-specific (Kir4.1)[15,16,71] and gap junctions.[52,72] The conventional model of neuronal ionic balance predicts that increased K^+ levels correspond to increased neuron excitability, which can lead to changes in sensory perception.[73] Thus, maintenance of low extracellular K^+ concentrations, mediated by SGC, may be crucial to control the resting membrane potential and neuronal excitability.[15] To help answer this question, several studies have evaluated if the SGC response to nerve injury would involve changes in Kir channels. Thus, the decreased expression of Kir4.1 was observed in SGC of TG, in a model of chronic constriction of the infraorbital nerve.[15,74] Also, in vitro electrophysiological studies of DRG from animals subjected to chronic compression of these ganglia, it was found that the SGC in injured ganglia exhibited a significant reduction of currents mediated by Kir.[16] Similar results were found when the effect of peripheral inflammation (facial skin) on currents mediated by Kir in rats in vivo was investigated by immunohistochemistry and patch clamp. In this study there was a significantly smaller increase of the currents mediated by Kir in rats with inflammation, compared to naive mice, followed by a decrease in the activation threshold to mechanical stimuli, suggestive of hyperalgesia.[75] The aforementioned studies showed that the SGC response to different types of injury includes the decreased expression of the Kir channels and decreased rectifying currents mediated by them. On the other hand, in the absence of injury, decreased expression of Kir channels has an impact on neuronal activity, as shown by the specific silencing of Kir4.1 expression using RNAi. This silencing was sufficient to produce behavioral signs of pain in mice, characterized by the development of spontaneous (measured by increased frequency of closing the eyes) and evoked pain (facial allodynia), which reinforced the importance of SGC in the clearance of K^+ and its ability to promote changes in neuronal activity.[74]

Increased coupling between SGC via gap junctions

The bridging connection between SGC distinct units and the increased number of gap junctions between them were the first evidence that SGC change in response to peripheral nerve injury.[12,13] Subsequently, studies of electrophysiology and dye injection confirmed this increased coupling after a nerve injury.[15,76] Indeed, the increased density (number) of gap junctions and coupling between sensory ganglia SGC after nerve injury are a consistent finding in several studies of pain. In SGC of DSG, this change was found in several models of pain, from colon[63,76] and thigh[71] inflammation to sciatic nerve neuritis[72] and DSG chronic compression.[17] TG studies also showed increased coupling between SGC in models of orofacial pain, particularly after infraorbital nerve axotomy[15] or chronic constriction.[16] In order to assess the significance of this increase in the coupling between the SGC, found in many models of chronic pain, a potent gap junction blocker (carbenoxolone) was used, which suppressed the increased coupling between the SGC caused by an inflammation previously induced by injection of complete Freund's adjuvant in the thigh, with an increase in the threshold of activation stimuli.[71] Similar analgesic effects were seen with other gap junction blockers, such as meclofenamic and palmitoleic acids, which favors the hypothesis that gap junctions between SGC play an important role in neuronal excitability.[63]

The identification of a constituent molecule of gap junctions, particularly connexin 43 (Cx43), allowed a different experimental approach to study the role of these junctions in SGC. Thus, it was found that after the infraorbital nerve injury, an increased expression of connexin also occurs.[16,55,62] Using RNAi for Cx43 to change the gap junction properties, it was observed that a disturbance in this protein expression is enough to cause changes in the activation threshold of afferent neurons.[16] Furthermore, the inhibition of Cx43 expression in TG of mice with orofacial neuropathic pain induced by chronic constriction of the infraorbital nerve was accompanied by a decreased behavior of spontaneous and evoked pain.[62] On the other hand, when the inhibition was carried out in the trigeminal ganglia of naive mice, a nociceptive response identical to that seen after nerve damage has occurred.[16,62] These studies suggest that inhibition of Cx43 can have pro-nociceptive or antinociceptive effect in normal animals after nerve injury. In trigeminal ganglia, some studies have found increased expression of other types of connexins, namely Cx36 and Cx40, after temporomandibular joint inflammation, suggesting that the type of connexin whose expression increases depends on the pain model in question.[73] Regardless of the approach, evidence indicates that the coupling between the SGC, which involves gap junctions and consequently Cx43, appears to be associated with the neuropathic pain development and maintenance. The underlying mechanisms are still unknown, but several hypotheses have been identified, namely the role of this coupling in maintaining the electrochemical gradient and buffering of K^+ to allow the rapid redistribution of K^+ after nerve injury.[15] Other hypotheses suggest that this coupling may contribute to the sensitization of nociceptors by increasing the diffusion of inflammatory mediators and/or

allogeneic substances (e.g., ATP, Ca^{2+}) from the site of injury to adjacent areas, leading to an amplification of the primary injury.[63] Finally, others suggest that it will have an action in the recycling of glutamate.[62]

Increased sensitivity to ATP and altered expression of purinergic receptors

Several studies reported the plasticity of P2 receptors on SGC in response to nerve damage or inflammation, which results in an increased sensitivity to ATP and altered expression of these receptors.[18,41,74] With the use of microfluorometry to determine the cytosolic concentration of Ca^{2+}, there was an increased sensitivity to ATP in cultured TG of SGC of mice with induced facial skin inflammation. Similar results were found in intact TG analysis in vitro, from rats subjected to axotomy of the infraorbital nerve, in which a 100-fold increase in sensitivity of SGC to ATP was recorded. Moreover, the occurrence of a reversal in purinergic receptor subtypes in cells of TG culture can be observed with the use of pharmacological tools. In fact, in normal mice, the response to ATP was mediated by P2Y receptors, while in mice with inflammation, it was predominantly mediated by P2X.[41] Recently, a preliminary model of the SGC role in chronic pain has been proposed in an attempt to explain how the increased gap junctions and high sensitivity to ATP can lead to abnormal neuronal activity both in injured and non-injured neurons. This model is based on the knowledge that when a peripheral nerve injury increases the excitability of sensory neurons, it also increases the excitatory signals from injured neurons to the SGC that surround them, and that these cells, communicating with SGC of adjacent units, will influence its neuron.[61] It also predicts that in response to peripheral injury a somatic ATP release occurs, which will activate the P2 receptors on the surrounding SGC and neuron itself. In turn, this activation should lead to an increase in intracellular Ca^{2+} in both cell types and consequently ATP release from both neurons and SGC (whose level of sensitivity to Ca^{2+} increases after injury). This ATP increase, along with the increased numbers of gap junctions between SGC of neighboring perineural sheaths, will allow the propagation of Ca^{2+} waves to these SGC and neighboring neurons, influencing the excitability of neurons not directly affected by the lesion (Figure 2). This intraganglionar communication model could be one explanation of how a peripheral injury can affect a large number of sensory neurons, contributing to signal propagation and chronic pain.[35,41]

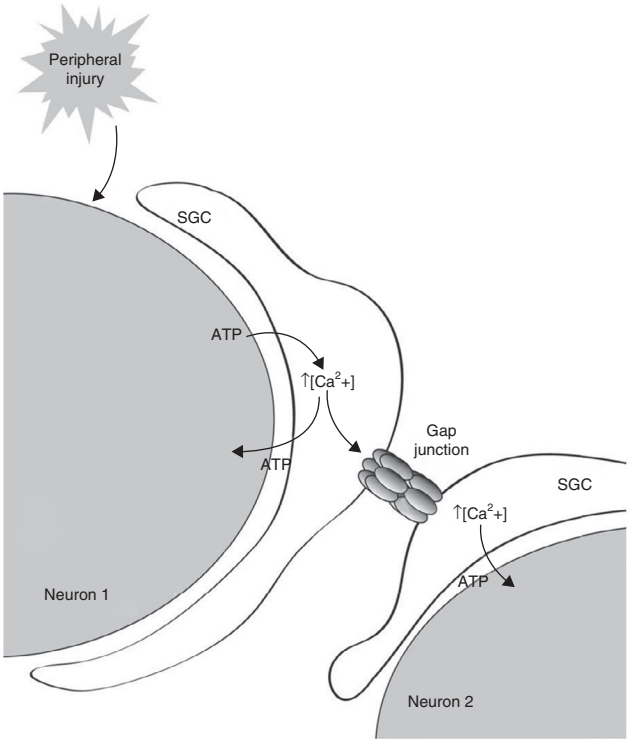

Figure 2 Model of interaction between neurons via satellite glial cells. Peripheral nerve injury leads to release of somatic ATP that acts via purinergic receptors on satellite glial cells (SGC), leading to a significant increase in intracellular calcium concentration ($[Ca^{2+}]$) in these cells. The communication with satellite glial cells of neighboring perineural sheath and the wave propagation of Ca^{2+} to these cells occurs through gap junctions, which leads to the release of ATP by these neighboring satellite glial cells. This ATP binds to the neuronal purinergic receptors, influencing the excitability of the neuron that was not directly affected by the injury.

Production of cytokines

SGC have similar characteristics to cells of the immune system, being activated by monocyte chemotactic protein-1 (MCP-1) through the receiver, and producing cytokines such as TNF-α,[23,67] IL-1β[77] and IL6.[78] The SGC ability to synthesize TNF-α in response to a peripheral injury was shown in one adapted model of lumbar spine facet joint injury in mice[67] and in three pain models in sciatic nerve (unilateral partial connection, spinal nerve connection, and transaction). In these models, immunocytochemistry showed increased expression of TNF-α and TNF-α-1 receptor on neurons and its SGC.[23] Moreover, it was found that the TNF-α activates the SGC causing increased phosphorylation of protein kinase regulated by extracellular signals (ERK[79]). Interestingly, the long-term increased activation of this protein in SGC after nerve injury has been associated with chronic pain.[80]

Another cytokine produced by activated SGC is IL-1β. The role of interleukin in the mechanism underlying the development of hyperalgesia and allodynia following peripheral inflammation has been extensively investigated in animal models of cutaneous inflammation. For example, it was shown that SGC respond to this inflammation with increased production of IL-1β and that an increased expression of IL-1RI in neurons occurs simultaneously. It was also shown that the application of IL-1β in neurons produces a greater increase of the action potential firing rate on inflamed mice compared to normal mice. Thus, it was postulated that SGC can modulate the excitability of TG nociceptive neurons via IL-1β, inducing membrane depolarization and increased expression of IL-1RI in neuronal body.[77] This conclusion was supported by a later study with the same model of orofacial pain, in which it was observed that local iontophoretic administration of IL-1RI antagonist caused a significant decrease in spontaneous activity in neurons of mice subjected to inflammation.[81] In another study of

orofacial inflammatory pain in vitro, it was found that IL-1-β suppresses the K^+ currents of voltage-dependent channels in small diameter neurons (i.e., mostly Aδ and C nociceptive neurons). These data suggest that IL-1-β released by SGC activated after inflammation potentiates the excitability of nociceptive neurons by suppression of K^+ currents.[82] Gathered evidence allowed the construction of a mechanism underlying the inflammatory hyperalgesia which predicts that, in inflammatory conditions, the activation of SGC can increase the excitability of Aδ nociceptive neurons via IL-1β. According to this hypothesis, the substance P released from the cell body of primary afferent nociceptive neurons, activated by peripheral injury/inflammation,[31] will act on NK1 receptors and will somehow potentiate the synthesis and/or release of IL-1β by SGC. This cytokine will, in turn, suppress the neuron voltage-dependent K^+ channels, thus contributing to the central sensitization responsible for the hyperalgesia and allodynia after inflammation.[22]

Finally, IL-6 also appears to be involved in the SGC response to neuroinflammation. In fact, a bilateral increased expression of IL-6 was observed in SGC of DSG as well as in its receptor in the ipsilateral ganglion, after sciatic nerve injury by chronic constriction.[78] In short, cytokines are involved in the interaction between a neuron and SGC, and there is growing evidence of a possible role for cytokines originating in sensory ganglia in the induction and maintenance of neuropathic pain.[83]

Final considerations

The progress in understanding the SGC biology, and the recognition of its interaction with sensory neurons, called the attention of the scientific community to the role of these cells in the nociceptive process. The perineuronal environment monitoring exerted by SGC as well as the cell communication occurring in sensory ganglia (neuron–neuron, neuron–SGC, SGC–SGC) can affect neuronal excitability.[22,35,61] In fact, the changes resulting from the activation of SGC, which have been observed in different pain models, enabled the observation that these cells may modulate chronic pain.[16,22,54,63,71] Therefore, contrary to what was initially postulated, sensory ganglion may become the first level of the pathophysiological changes of modulation of afferent signaling, as it allows the interaction between different types of information and seems to be a trigger of the central sensitization mechanism of the spinal cord dorsal horn neurons.[22] Thus, knowledge about the SGC and its mechanisms of interaction with the neuronal body assumes a growing importance in the search for new targets for chronic pain treatment.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

The authors acknowledge the help given by Prof. Daniel Humberto Pozza, Department of Experimental Biology, Faculdade de Medicine do Porto, in reviewing the text to Portuguese of Brazil.

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