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Review

Intercellular communication in sensory ganglia by purinergic receptors and gap junctions: Implications for chronic pain

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ABSTRACT

Peripheral injury can cause abnormal activity in sensory neurons, which is a major factor in chronic pain. Recent work has shown that injury induces major changes not only in sensory neurons but also in the main type of glial cells in sensory ganglia—satellite glial cells (SGCs), and that interactions between sensory neurons and SGCs contribute to neuronal activity in pain models. The main functional changes observed in SGCs after injury are an increased gap junction-mediated coupling among these cells, and augmented sensitivity to ATP. There is evidence that the augmented gap junctions contribute to neuronal hyperexcitability in pain models, but the mechanism underlying this effect is not known. The changes in SGCs described above have been found following a wide range of injuries (both axotomy and inflammation) in somatic, orofacial and visceral regions, and therefore appear to be a general feature in chronic pain. We have found that in cultures of sensory ganglia calcium signals can spread from an SGC to neighboring cells by calcium waves, which are mediated by gap junctions and ATP acting on purinergic P2 receptors. A model is proposed to explain how augmented gap junctions and greater sensitivity to ATP can combine to produce enhanced calcium waves, which can lead to neuronal excitation. Thus this simple scheme can account for several major changes in sensory ganglia that are common to a great variety of pain models.

Contents

Abbreviations: CX, connexins; GFAP, glial fibrillary acidic protein; ICWs, intercellular calcium waves; DRG, dorsal root ganglion; P2R, type 2 purinergic receptors; SGC, satellite glial cell; TG, trigeminal ganglion

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1. Introduction, a brief survey of sensory ganglia

Sensory ganglia contain the cell bodies of sensory neurons, which have a bifurcating axon, with one branch going to the periphery, and the other projects into the dorsal horn of the spinal cord. The two main types of sensory ganglia are the dorsal root ganglia (DRG), which innervate most of the body, including internal organs, and the trigeminal ganglia (TG), which innervate the head, face and teeth. The traditional view has been that the main role of the neuronal somata in these ganglia is metabolic, that is, to support the axon, which is usually very long. However, research in the last two decades revealed that sensory ganglia are also the site of neural information processing. First, although devoid of synapses, sensory neurons display a variety of receptors for neurotransmitters and hormones (Devor, 1999; Julius and McCleskey, 2006) and also release several neurotransmitters, such as glutamate, ATP, substance P, and CGRP (Huang and Neher, 1996; Holz et al., 1988; Matsuka et al., 2001; Gu et al., 2010). Second, there is evidence that sensory neurons can communicate with each other by a process called 'cross-talk', which appears to be mediated by chemical messengers (Amir and Devor, 1996). Moreover, recent work showed that there are bidirectional interactions between neurons and glial cells in these ganglia (Gu et al., 2010; Suadicani et al., 2010). Thus, it can be stated that sensory neurons are able to communicate chemically among themselves and with other cell types, but the significance of such communications is still largely obscure. It is well established that under pathological conditions sensory neurons can generate spontaneous electrical activity, and thus play an active role in chronic pain (Devor, 2006; Dib-Hajj et al., 2010). It was reported that the sensitivity of sensory neurons to ATP, acting on purinergic P2 × 3 receptors (P2 × 3Rs, Zhou et al., 2001; Chen et al., 2008), and to substance P (Xu and Zhao, 2001) is increased in pain models, which may contribute to neuronal sensitization. Therefore, interactions within the ganglia are potentially very relevant for the understanding and treatment of chronic pain.

In addition to communicating chemically, sensory neurons can, in principle, interact electrically via gap junctions, but very little is known on this topic. We have shown that in control mice there is virtually no dye coupling between neurons in DRG and TG and there is no evidence from electron-microscopy (EM) for gap junctions in these cells (Hanani et al. 2002; Cherkas et al., 2004), which argues against this mode of communication, but does not entirely rule it out. However, after peripheral injury, a small proportion (6–12%) of sensory neurons in DRG display dye coupling (Dublin and Hanani, 2007; Ledda et al., 2009; Huang et al., 2010). The failure so far to detect gap junctions in sensory neurons by EM might be due to the scarcity of these structures.

2. Satellite glial cells in sensory ganglia

Sensory neurons are surrounded by specialized glial cells known as 'satellite glial cells' (SGCs), and recent work indicates that these cells must be taken into consideration when discussing cellular interactions in sensory ganglia. Satellite glial cells are unique in that they usually form a sheath around individual neurons, which is tight, but still permeable to large molecules (for a review see Hanani, 2005). Fig. 1 shows a low power electron micrograph of a sensory neuron and its SGC sheath. The gap between the neuron and SGCs, which is about 20 nm wide and cannot be seen at this magnification, constitutes the extracellular space of the neurons, and its small volume allows SGCs to control the neuronal environment. The close proximity of neurons and SGCs facilitates non-synaptic chemical communication between these two cell types (Li et al., 2008; Takeda et al., 2009; Gu et al., 2010; Suadicani et al., 2010). Satellite glial cells share several properties with astrocytes, including the expression of glutamine synthetase and various neurotransmitter transporters (Hanani, 2005; Takeda et al., 2009; Jasmin et al., 2010). These cells were found to release ATP (Zhang et al., 2007; Gu et al., 2010;

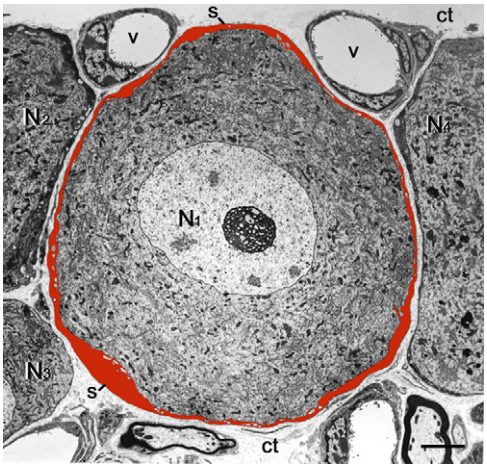

Fig. 1 – Low magnification electron micrograph of mouse DRG showing the nerve-cell body of a sensory neuron (N1) enveloped by a SGC sheath, which was painted red. Note that the entire outer contour of the sheath is smooth and is completely separated from the sheaths encircling the adjacent nerve cell bodies (N2–N4) by the connective tissue space (ct). The small empty regions within the SGCs envelope are fine neuronal protrusions (see Pannese, 2002) that increase the contact between the two cell types. v, blood vessel. Scale bar, 4 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)