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REVIEW

NEURONAL NETWORKS AND NOCICEPTIVE PROCESSING IN THE DORSAL HORN OF THE SPINAL CORD

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Abstract—The dorsal horn (DH) of the spinal cord receives a variety of sensory information arising from the inner and outer environment, as well as modulatory inputs from supraspinal centers. This information is integrated by the DH before being forwarded to brain areas where it may lead to pain perception. Spinal integration of this information relies on the interplay between different DH neurons forming complex and plastic neuronal networks. Elements of these networks are therefore potential targets for new analgesics and pain-relieving strategies. The present review aims at providing an overview of the current knowledge on these networks, with a special emphasis on those involving interlaminar communication in both physiological and pathological conditions

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Key words: spinal cord, dorsal horn, nociception, pain, neuronal networks, sensory systems.

Contents

INTRODUCTION

The spinal cord is a caudal extension of the central nervous system localized within the vertebral foramina. The gray matter of the spinal cord contains neuronal cell bodies; it is surrounded by the white matter containing myelinated axons. In transverse sections, the gray and white matters of the spinal cord are symmetrical with respect to the sagittal plane, and possess two dorsal and two ventral extensions respectively termed dorsal and ventral horns. From the examination of cat spinal cord sections, Rexed (1952) has identified ten laminae according to histological criteria such as size and density of neuronal somata. This classification has been generalized to several species including humans and rodents. The first six laminae (lamina I–VI) form the dorsal horn (DH) of the spinal cord. Although

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Abbreviations: CVLM, caudal ventrolateral medulla; DAC, deep axon cells; DH, dorsal horn; GAD, glutamate decarboxylase; HTM, high-threshold mechanoreceptors; LAC, local axon cells; mEPSCs, miniature excitatory postsynaptic currents; NTS, nucleus tractus solitarius; PAD, Primary Afferent Depolarization; PAG, periaqueductal gray; PB, parabrachial nucleus; PKCγ, protein kinase Cγ; PSDC, postsynaptic dorsal column; sEPSC, spontaneously occurring excitatory postsynaptic currents; sIPSC, spontaneously occurring inhibitory postsynaptic currents; WDR, Wide Dynamic Range.

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Rexed's classification is widely accepted, another terminology based on older descriptions is also often found: marginal zone of Waldeyer (for lamina I), *substantia gelatinosa* of Rolando (for lamina II), *nucleus proprius* (for laminae III–IV). It is interesting to note that for functional studies, pairs of DH laminae are often considered together: laminae I–II (superficial DH), laminae III–IV (*nucleus proprius*), and laminae V–VI (deep DH), although in some studies laminae III–IV are considered as *deep* DH layers.

The sensory messages arising from the detection of peripheral sensory signals/stimuli are conveyed to the spinal cord by primary afferent fibers. Large-diameter primary afferent fibers (Aβ) directly project to the brainstem, but axon collaterals project to the DH. Hence, proprioception and fine touch involving information mediated by Aβ fibers do not need a spinal relay. By contrast, nociceptive and thermoceptive information, mainly conveyed by thin and medium-diameter afferent fibers (C and Aδ, respectively), involve at least one synaptic relay within the spinal cord. Primary afferent fibers of each type preferentially project into given laminae within the DH where they contact projection neurons, either directly or through polysynaptic relays via local interneurons. Importantly, even if fibers conveying nociceptive information mostly project to superficial laminae, every DH lamina processes nociceptive information. This implies also that none of the DH laminae is specialized in processing exclusively non-nociceptive information.

In *the gate control theory of pain mechanisms* (Melzack and Wall, 1965), DH networks involving inhibitory interneurons have been proposed to integrate the relative balance of inputs from primary afferents of different types, gating the response of projection neurons. Since that proposal, a diversity of DH neuronal types has been described, and the assessment of their organization in networks allowing such control of information is still ongoing. Although the six DH laminae differ in terms of morphology and of inputs they may receive, they are not disconnected entities and represent a strongly interacting functional ensemble that processes sensory information before forwarding it to brain areas. Several reviews have detailed the neuronal components of the DH (Ribeiro-da-Silva and De Koninck, 2008; Todd, 2010) and plasticity processes occurring in this structure (Sandkuhler and Gruber-Schoffnegger, 2012; Luo et al., 2014; Todd, 2015). This review summarizes the knowledge on neuronal, synaptic components, and inputs/outputs to the DH. It aims at examining what is known on the DH network organization, with a special emphasis on synaptic interactions between different DH laminae that have been little documented until recently.

SYNAPTIC AND NEURONAL COMPONENTS OF THE DH

The DH contains glutamatergic projection neurons and both excitatory and inhibitory interneurons: fast-acting excitatory neurotransmission is glutamatergic while fast-acting inhibitory neurotransmission is GABAergic and/or glycinergic. In addition other fast neurotransmissions have been demonstrated in some preparations (Jo and Schlichter, 1999; Hugel and Schlichter, 2003). As neuronal components and their morphology have been comprehensively reviewed recently (Todd, 2010), only relevant points for spinal neuronal networks involved in nociceptive processing are given here, focusing on fast acting neurotransmissions.

Cell bodies

The cell bodies of glutamatergic neurons cannot be easily identified with conventional immunohistochemical techniques because glutamate has a metabolic function and is therefore present in large amounts in all cells. The expression of the vesicular transporters for glutamate vGLUT1 or vGLUT2 is specific to glutamatergic neurons, but these proteins are preferentially located at neuron terminals, a situation that precludes their use as a somatic marker. Glutamatergic neurons are therefore empirically considered as being the non-GABA- and/or non-glycine-containing neurons (Todd, 2010), and represent more than half of DH neurons (Todd and Sullivan, 1990; Polgar et al., 2003). Transcription factors specifying the glutamatergic cell fate, such as *Tlx1* and *Tlx3* might be useful tools to identify excitatory neurons in the next future (Cheng et al., 2004; Guo et al., 2012).

From lamina I to lamina III, GABA is present in an increasing proportion of DH neurons, ranging from one quarter of lamina I neurons to about half of lamina III neurons (Todd and Sullivan, 1990; Polgar et al., 2003). No precise quantification is available for deeper laminae (Todd and McKenzie, 1989), but qualitative data suggest that a smaller subpopulation of neurons contain GABA, particularly in lamina IV (Hunt et al., 1981; Barber et al., 1982; Magoul et al., 1987; Nowak et al., 2011).

Glycine is present within a subset of neurons throughout the whole DH, in a low proportion of neurons in laminae I–II and a higher proportion in lamina III. No precise quantification is available for glycinergic neurons in deeper laminae where glycine immunoreactivity appears to be lower than in more superficial layers (Campistron et al., 1986) and displays some variability (Zeilhofer et al., 2005). In laminae I–III, where the colocalization of glycine and GABA has been addressed, both molecules were mostly colocalized within cell bodies. In addition to their content in transmitter, glycinergic and GABAergic neurons can be identified according to the expression of GlyT2, a neuronal transporter for glycine, or glutamate decarboxylase (GAD), an enzyme involved in the synthesis of GABA, respectively (Mackie et al., 2003; Zeilhofer et al., 2005). The two isoforms GAD_{67} and GAD_{65} are expressed in neurons, and are encoded by *GAD1* and *GAD2* genes, respectively. Transcription factors specifying the GABAergic cell fate, such as *Lbx1, Pax2* and *Lhx1/5* might prove useful tools to distinguish inhibitory neurons from excitatory neurons in the future (Gross et al., 2002; Muller et al., 2002; Cheng et al., 2004).

Synapses

Virtually every DH neuron receives fast glutamatergic excitatory synaptic inputs. Whereas in situ hybridization