Progress in Neurobiology 91 (2010) 38–54

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

The synaptic connectivity that underlies the noxious transmission and modulation within the superficial dorsal horn of the spinal cord

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ARTICLE INFO

Article history:
Received 4 March 2009
Received in revised form 10 December 2009
Accepted 14 January 2010

Keywords:
Spinal dorsal horn
Nociception
Antinociception
Synaptic connectivity

ABSTRACT

Noxious stimuli can usually cause the aversive sensations, pain and itch. The initial integration of such noxious information occurs in the superficial dorsal horn of the spinal cord (SDH), which is very important for understanding pain sensation and developing effective analgesic strategies. The circuits formed by pools of neurons and terminals within SDH are accepted as the platform for such complicated integrations and are highly plastic under conditions of inflammatory or neuropathic pain. Recent literature offers a complicated, yet versatile view of SDH intrinsic circuits with both inhibitory and excitatory components. However, our knowledge about the adaptative regulation of SDH local circuits is still far from sufficient due to the incomplete understanding of their organization as they are intermingled with primary afferent fibers (PAFs), poorly understood or identified SDH neurons, somehow contradictory data for descending control systems. A more positive view emphasizes abundant modern data on SDH neuron morphology and physiology riding on the back of significant technological advancements used in neuroscience. Reviewing the current literature on this topic thus produced an integrated understanding of SDH neurons and the SDH local circuits involved in noxious transmission and modulation.

Contents

Abbreviations: AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic; CB, calbindin-D28K; CGRP, calcitonin gene-related peptide; CTb, cholera toxin subunit b; CVLM, caudal ventrolateral medulla; DLF, dorsolateral fasciculus; DOR, δ-opioid receptor; DR, dorsal root; DRG, dorsal root ganglion; DRt, dorsal reticular nucleus; DYN, dynorphin; ENK, enkephalin; EPSC, excitatory postsynaptic current; EPSP, excitatory postsynaptic potential; GABA, γ-amino butyric acid; GFP, green fluorescent protein; Glu, glutamate; GluR2/3, glutamate receptor 2/3; Gly, glycine; 5-HT, 5-hydroxytryptamine (serotonin); INs, interneurons; INDAs, intrinsic neurons with dense axonal arborization; INSAs, intrinsic neurons with sparse axonal arborization; IPSC, inhibitory postsynaptic current; KA, kainite; KOR, κ-opioid receptor; KCC2, K^+-Cl^- cotransporter isoform 2; MDH, medullary dorsal horn; MOR, μ-opioid receptor; NE, norepinephrine; NKCC1, Na^+-K^+-Cl^--cotransporter isoform 1; NK-1R, neurokinin 1 receptor; NMDA, N-methyl-D-aspartate; NOS, nitric oxide synthase; NPY, neuropeptide Y; NT, neurotensin; PAFs, primary afferent fibers; PAG, the periaqueductal gray matter; PBN, the parabrachial nucleus; PKC, protein kinase C; PNs, projection neurons; PV, parvalbumin; SDH, superficial dorsal horn of the spinal cord; SG, substantia gelatinosa; EPSC, excitatory postsynaptic current; IPSC, inhibitory postsynaptic current; Sol, the nucleus of the solitary tract; SOM, somatostatin; SP, substance P; sst2AR, somatostatin 2A receptor; TK, tachykinins; TRH, thyrotropin-releasing hormone; TRPV1, transient receptor potential vanilloid type 1; VGLUT1,2, vesicular glutamate transporters 1 and 2; VIP, vasoactive intestinal peptide.

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0301-0082/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.pneurobio.2010.01.005

1. Introduction

Pain and itch, as the aversive sensations, are usually caused by peripheral noxious stimuli. It is commonly accepted that a serial chain of neuronal elements is involved in transmitting nociceptive information to the brain before the pain sensation is formed there. Peripheral nociceptors transmit noxious information by the thinly myelinated (Aδ) and unmyelinated (C) primary afferent fibers (PAFs) (Kumazawa and Perl, 1978; Sugiura et al., 1986; Yoshimura and Jessell, 1989b) first to neurons located in the superficial dorsal horn of the spinal cord (SDH, including laminae I and II). Some of these spinal neurons (projection neurons, PNs) further project axons through ascending tracts, and form synapses with neurons in supraspinal structures such as the thalamus (Al-Khater et al., 2008), lateral parabrachial nucleus (PBN)(Almarestani et al., 2007) and the periaqueductal gray matter (PAG) (Spike et al., 2003), etc., and finally onto the cerebral cortex. Other spinal neurons (interneurons, INs) send out axons mainly within SDH. Meanwhile, SDH neurons and PAFs receive dense descending inputs, including those containing serotonin (5-HT), gamma-amino butyric acid (GABA) or norepinephrine (NE) mainly originating from the raphe magnus and locus ceruleus in the brain stem (Kwiat and Basbaum, 1992). These descending systems act on both pre- and post-synaptic sites to control the gain of excitability during nociceptive transmission (Baba et al., 2000a; Hori et al., 1996; Ito et al., 2000; Kawasaki et al., 2003; North and Yoshimura, 1984; Yoshimura and Furue, 2006). In this way, the SDH noxious output conveyed by PNs to the higher brain structures are modulated by complicated interneuronal interactions within SDH. The platform for such complicated integrations is the circuits formed by pools of SDH neurons (INs and PNs) and fibers (PAFs and descending fibers) with different origins and it is highly plastic under conditions of inflammatory or neuropathic pain. Revealing such circuits is very important for understanding pain sensation and developing effective analgesic strategies.

Since the 1960s it has been understood that synaptic circuits mediating pain involve INs and PAFs. A basic concept of these theories is that nociceptive transmission can be modified by the concomitantly activated neuronal components within SDH. Influenced by Melzack and Wall's "gate control" theory, which emphasizes the role of inhibitory circuits in "maintaining the gate of nociceptive flow" in SDH (Melzack and Wall, 1965), much of the research in this field has predictably focused on inhibitory regulation of noxious transmission. Recent literature offers a more complicated, yet versatile view of SDH intrinsic circuits with both inhibitory and excitatory components. However, our understanding of their adaptative regulations is still far from complete.

One barrier is the incomplete understanding of the organization of local SDH circuits. These circuits involve a variety of PAFs, poorly characterized SDH neurons and descending fibers whose targets are not completely known. On the other hand, a more positive view emphasizes abundant modern data on SDH neuron morphology and physiology riding on the back of significant technological advancements used in neuroscience. Thanks to these new findings, we can present an integrated understanding of SDH circuits involved in noxious transmission and regulation in the current review.

We will introduce briefly the cytoarchitecture of SDH followed with the presentation of current knowledge on SDH neurons. Then, some possible local synaptic circuits underlying facilitatory or inhibitory effects within SDH will be introduced based on literature review. Electrophysiological data are also included when relevant. Readers who are interested in the neurochemical characteristics of SDH, or relevant behavioral studies are referred to other excellent reviews focusing on each topic (D'Mello and Dickenson, 2008; Jarvis and Boyce-Rustay, 2009). Another point that needs to be clarified beforehand is that although species differences exist for the SDH synaptic circuits, such content is not included in this review for the sake of clarity and to provide a more useful overview.

2. Brief introduction of SDH anatomy

2.1. Primary afferent fibers (PAFs)

2.1.1. PAFs anatomy

It is generally accepted that most of the PAFs projecting to SDH enter via the dorsal roots (DRs), while some ventral roots also contribute afferents. The PAFs demonstrate a size-dependent entry into the spinal cord: larger caliber myelinated fibers run medially into the dorsal funiculus (DF), whereas small caliber, often unmyelinated fibers, approach the dorsal horn via the dorsolateral fasciculus (Lissauer's tract, DLF) (Chung and Coggeshall, 1979). After entering the spinal cord, these PAFs terminate in the spinal gray matter following two principles. First, fine caliber fibers are distributed preferentially in SDH, whereas larger diameter axons project more ventrally. Second, somatic primary afferents terminate somatotopically along a mediolateral axis in SDH.