available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainresrev

BRAIN RESEARCH REVIEWS

Review

Descending control of nociception: Specificity, recruitment and plasticity

M.M. Heinricher[a,b,*], I. Tavares[c,d], J.L. Leith[e], B.M. Lumb[e]

[a]Department of Neurological Surgery, Oregon Health & Science University, Portland, OR, USA
[b]Department of Behavioral Neuroscience, Oregon Health & Science University, Portland, OR, USA
[c]Institute of Histology and Embryology, Faculdade de Medicina, Universidade do Porto, Portugal
[d]IBMC—Instituto de Biologia Celular e Molecular, Porto, Portugal
[e]Department of Physiology and Pharmacology, School of Medical Sciences, University of Bristol, Bristol, UK

ARTICLE INFO

Article history:
Accepted 29 December 2008
Available online 25 December 2008

Keywords:
Pain modulation
Pronociception
Antinociception
Brainstem
Periaqueductal gray
Raphe
Caudal ventrolateral medulla

ABSTRACT

The dorsal horn of the spinal cord is the location of the first synapse in pain pathways, and as such, offers a very powerful target for regulation of nociceptive transmission by both local segmental and supraspinal mechanisms. Descending control of spinal nociception originates from many brain regions and plays a critical role in determining the experience of both acute and chronic pain. The earlier concept of descending control as an "analgesia system" is now being replaced with a more nuanced model in which pain input is prioritized relative to other competing behavioral needs and homeostatic demands. Descending control arises from a number of supraspinal sites, including the midline periaqueductal gray-rostral ventromedial medulla (PAG-RVM) system, and the more lateral and caudal dorsal reticular nucleus (DRt) and ventrolateral medulla (VLM). Inhibitory control from the PAG-RVM system preferentially suppresses nociceptive inputs mediated by C-fibers, preserving sensory-discriminative information conveyed by more rapidly conducting A-fibers. Analysis of the circuitry within the RVM reveals that the neural basis for bidirectional control from the midline system is two populations of neurons, ON-cells and OFF-cells, that are differentially recruited by higher structures important in fear, illness and psychological stress to enhance or inhibit pain. Dynamic shifts in the balance between pain inhibiting and facilitating outflows from the brainstem play a role in setting the gain of nociceptive processing as dictated by behavioral priorities, but are also likely to contribute to pathological pain states.

* *Corresponding author*. Department of Neurological Surgery, CR137, Oregon Health & Science University, Portland, OR 97239, USA. Fax: +1 503 494 2664.
E-mail address: heinricm@ohsu.edu (M.M. Heinricher).

Abbreviations: COX, cyclo-oxygenase; C+ve, C-fiber input positive; C–ve, C-fiber input negative; DOR, δ opioid receptor; DRt, dorsal reticular nucleus of the caudal medulla; MOR, μ opioid receptor; PAG, periaqueductal gray; PGE_2, prostaglandin E_2; RVM, rostral ventromedial medulla; VLM, ventrolateral quadrant of the caudal medulla

0165-0173/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainresrev.2008.12.009

Contents

1. Introduction

The dorsal horn of the spinal cord is the location of the first synapse in pain pathways, and as such, offers a very powerful target for the regulation of nociceptive transmission by both local segmental and supraspinal mechanisms. Supraspinal (or descending) control of spinal nociception originates from many brain regions and plays a critical role in determining the experience of both acute and chronic pain. Initial reports in the 1970's and 1980's were of inhibitory influences from sites in the midbrain periaqueductal gray (PAG) and from the midline nucleus raphe magnus and adjacent reticular regions in the pons and medulla, the rostral ventromedial medulla (RVM, see Fields et al., 2006 and Heinricher and Ingram, 2008 for recent reviews). For many decades attention focused on these areas as sources of descending *inhibitory* control, with a role in endogenous analgesia (antinociception) in states of extreme stress(Bolles and Fanselow, 1980; Terman et al., 1984) or in creating contrast in sensory signals that sharpened the signalling of pain by ascending pathways (Le Bars, 2002).

It is now evident that descending control can be *facilitatory* as well as inhibitory. Indeed, facilitatory and inhibitory influences on spinal events are often reported to emanate from a single brain region (e.g., Zhuo and Gebhart, 1997)]. Some descending influences are tonically active, but the balance between inhibition and facilitation is dynamic, and can be altered in different behavioral, emotional and pathological states. As already noted, it has long been recognized that intense stress and fear are associated with hypoalgesia (a decreased responsiveness to noxious stimuli) that reflects a shift towards descending inhibition. By contrast, inflammation and nerve injury, sickness, and chronic opioid administration are associated with hyperalgesia (an increased responsiveness to noxious stimuli) that in part reflects a shift towards descending facilitation. Of clinical importance, there is much evidence to suggest that descending facilitation of spinal nociception is a major contributor to central sensitization and the development of secondary hyperalgesia, indicating that the balance shifts in favor of facilitation in the transition from acute to chronic pain.

Descending control arises from a number of supraspinal sites, but the best studied is the PAG-RVM system mentioned above (Fig. 1). The PAG is heavily interconnected with the hypothalamus and limbic forebrain structures including the amygdala, and also receives direct spinomesencephalic input. The PAG projects to the RVM, which in turn sends its output to dorsal horn laminae important in nociceptive function. This system has a pivotal role in organizing strategies for coping with intrinsic and extrinsic stressors, and is also recognized as the central site of action of analgesic agents including opioids, cyclooxygenase inhibitors, and cannabinoids (Hohmann et al, 2005; Leith et al, 2007; Yaksh et al, 1976). Understanding the PAG-RVM system is thus of considerable importance from both a behavioral and therapeutic point of view. Spinal mechanisms that mediate descending control from the PAG are discussed in Section 2, and intrinsic organization of the RVM and recruitment of PAG-RVM system are considered in Section 3. Additional sources of descending modulation include pontine noradrenergic cell groups (Pertovaara, 2006) and two areas of the caudal medulla discussed in Section 4, the dorsal reticular nucleus (DRt) and ventrolateral medulla (VLM) (Tavares and Lima, 2007).

2. Descending control from the PAG distinguishes between the spinal processing of different sensory qualities, including different components of the pain signal

In the 40 years since Reynolds first described the phenomenon of stimulation-produced analgesia (Reynolds, 1969), the therapeutic potential of descending control has fuelled intense