Medullary control of nociceptive transmission: Reciprocal dual communication with the spinal cord

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Control of pain perception, essential for organism surviving and recovery from disease, is exerted by higher brain centers integrating nociception with emotional and cognitive information and modulating the brainstem-spinal feedback loops that regulate spinal nociceptive transmission. Development of chronic pain deregulates the forebrain-brainstem-spinal pain control system, which leads to neuroplasticity and disruption of a balanced brain-spinal communication. Targets for impeding pain chronification are being developed using the manipulation of the cross talk between brain and dorsal horn, at both sites of the loop.

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Introduction
In 'normal' conditions, pain triggered by a small lesion is less intense and disappears in shorter time than after a large lesion, which represents the expression of a major biological protection mechanism to preserve organism integrity [1]. This proportionality between lesion and pain can be modified during intense emotional and cognitive situations [2]. Moreover, pain associated to diseases has the biological protective function of restricting body activities and concentrating organism efforts on body healing. These adaptative conditions result largely from brain modulation of spinal nociceptive transmission [3,4], an endogenous mechanism that can be modulated by reciprocal communications between the BRAINSTEM (see glossary) and spinal cord [4–8]. However, a prolonged pain condition can induce brain and spinal neuroplasticity associated to CENTRAL SENSITIZATION (see glossary) [9,10]. The resulting changes in neuronal properties can lead to a deregulation of the brain mechanisms modulating pain, which may account for the maintenance of CHRONIC PAIN (see glossary) long after lesion healing.

Endogenous pain control system
The PAG–RVM-dorsal horn circuitry
Although changes in pain behavior have been demonstrated by manipulation of several brain areas, the main pain control centers are located in the brainstem. The mesencephalic periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM) are known for long to be implicated in endogenous pain control through an antinociceptive PAG–RVM-dorsal horn descending circuitry [11] (Fig. 1a). However, increasing evidences also implicate the RVM in descending facilitation of spinal nociceptive transmission [9,11]. This dual effect is correlated with the co-existence at the RVM of neurons involved in descending antinociceptive actions (OFF-cells), along with cells responsible for descending pronociceptive effects (ON-cells) (Fig. 1a).

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Glossary

Allodynia: pain due to a stimulus that does not normally provoke pain.
Brainstem: the portion of the brain consisting of the medulla oblongata, pons and mesencephalon. It is the major route for communication between the forebrain and the spinal cord and controls various functions including respiration and regulation of heart rhythms. It includes the part of the reticular formation that plays a central role in bodily and behavioral alertness.
Central sensitization: increased excitability of central pain-transmitting neurons that may result from prolonged nociceptive barrage and involves descending nociceptive modulation from the brain.
Chronic pain: pain that persists beyond resolution of an underlying disorder or healing of an injury, and that is often more intense than the underlying process would predict.
Forebrain: the most anterior segment of the adult brain that develops from the embryonic telencephalon and diencephalon and includes the cerebrum (cortex, hippocampus, amygdala), thalamus and hypothalamus.
Hyperalgesia: an increased response to a stimulus that is normally painful.
Limbic system: a group of interconnected deep brain structures common to all mammals that includes the hypothalamus, amygdala, olfactory bubs and hippocampus. It plays an important role in the regulation of motivation, emotions and various autonomic functions.
Neuropathic pain: pain initiated or caused by a primary lesion or dysfunction in the nervous system.
NK1 receptors: receptors for ligation of substance P, one of the main neurotransmitters released by primary afferent nociceptive fibers in the spinal dorsal horn.
NMDA receptors: subtype of Glutamate receptors involved in synaptic potentiation at several neural pathways, including the pain system. Their activation at spinal synapses leads to facilitation of post-synaptic responses and enhanced neurotransmitter release and is implicated in central sensitization and chronic pain mechanisms.
Peripheral sensitization: increased excitability of peripheral nociceptors (primary afferents), often mediated by an inflammatory process.

Forebrain modulation of pain: role of the brainstem

Pain is a multidimensional experience where the sensory-discriminative information conveyed from the periphery by the nociceptive system is integrated with the emotional environment processed by the amygdala (AMY) and cognitive information concerning past experiences specific for each individual [12]. The motivational-affective component of the pain experience suggests that LIMBIC areas (see glossary) like the AMY, the insular cortex (INS) and the anterior cingulated cortex (ACC) should have the capacity to regulate the endogenous pain control system and the final pain perception. These FOREBRAIN areas (see glossary) are highly interconnected and output nuclei have neurons with long projecting axons terminating in areas like the PAG and RVM (Fig. 1). Several areas of the caudal medulla oblongata involved in pain modulation like the dorsal reticular nucleus (DRt), the caudal ventrolateral medulla (CVLM) and the nucleus tractus solitarius (NTS) are also targeted by the forebrain, which indicates that emotions and cognition can directly control brainstem areas implicated in nociceptive modulation (Fig. 1). Accordingly, depending on environmental and emotional conditions, the AMY, INS and ACC may exert a dual facilitating and inhibiting role in pain modulation [13,14] mediated by caudal brainstem areas, such as the RVM and DRt [13].

The caudal medulla oblongata

The caudalmost portion of the brainstem has several areas involved in pain modulation. Besides the DRt [3,15,16], CVLM [6] and NTS [17] referred above, it arbors other pain control centers like the ventral reticular [16] and paratrigeminal nuclei [18]. Like the RVM, the caudal medulla oblongata exerts a dual descending modulatory action by inhibiting or increasing nociception. Thus, the caudal medulla oblongata contributes to the fine balance between facilitation and inhibition of spinal nociceptive transmission and, ultimately, to pain perception. However, the descending modulatory actions exerted by the DRt and the CVLM exhibit special characteristics because they are conveyed by reciprocal monosynaptic spino–bulbo–spinal loops. Besides allowing rapid and dynamic pain modulation, these feedback loops may allow that sudden changes of the nociceptive home-ostasis triggers an adequate response of both medullary and spinal nociceptive neurons. On the basis of the extensive characterization of the brain connections of the DRt and CVLM, it is likely that the brainstem–spinal reciprocal loops also integrate nociception with other types of physiological information arriving from the periphery and important for body homeostasis.

The dorsal reticular nucleus

The brain–DRt–spinal circuitry is now well characterized [3,19] and several studies indicate that the DRt is implicated in nociceptive processing and modulation (Fig. 2a) [3,15]: DRt neurons are exclusively or mainly activated by cutaneous or visceral noxious stimulation; the DRt receives projections from spinal dorsal horn nociceptive neurons that establish asymmetrical, potentially excitatory, synaptic contacts with DRt neurons projecting back to the dorsal horn [3]; DRt neurons project to the dorsal horn and modulate spinal nociceptive activation [16] by establishing asymmetrical synapses with spinal neurons projecting back to the DRt. These data indicate that a reciprocal excitatory feedback loop occurs between the DRt and spinal dorsal horn, through which ascending nociception is increased by the descending branch of the circuit [3]. Moreover, DRt neurons project to [19] and receive projections from [3] brain areas implicated in the direct or indirect control of spinal nociceptive transmission, such as the CVLM, NTS, PAG, RVM, AMY, *locus coeruleus* (noradrenergic antinociceptive centre) and paraventricular hypothalamic nucleus (PVN – the main effector of the physiological response to stress). This suggests that reciprocal feedback loops occur not only between the DRt and the spinal cord but also between the DRt and brainstem and forebrain

areas modulating pain. Finally, DRt neurons project simultaneously to the spinal dorsal horn and the medial thalamus, an area that allows direct access to the neocortex [20]. This indicates that balanced nociception achieved by the DRt–spinal cord interaction can reach forebrain areas implicated in the affective dimension of pain.

The extensive ascending and descending connections with forebrain, brainstem and spinal areas implicated in pain processing and modulation supports the pain facilitating [3,16] and pain inhibiting [15] actions attributed to the DRt (Fig. 2a), as well as its role as a relay station mediating pain modulation triggered by the neocortex [13].

The caudal ventrolateral medulla

The characterization of reciprocal connections between the CVLM and the spinal cord suggested a special role of its lateralmost part- the VLMlat- in pain modulation [6]. The VLMlat targets exclusively spinal layers involved in nociceptive transmission, namely laminae I, IV–V and X, and receives nociceptive input from laminae I–III [6]. That the VLMlat is the CVLM region more relevant in pain modulation is in agreement with data showing that the hypoalgesia induced following VLMlat stimulation is more pronounced and long lasting than from other CVLM regions [6]. A closed reciprocal loop connects the VLMlat with lamina I (Fig. 2b) and the synaptic characterization of the loop suggests that the ascending nociceptive input triggers descending modulation mainly by inhibitory mechanisms and, in a lower extension, facilitatory (see glossary) actions [6]. These observations postulated that the CVLM could also be involved in pronociceptive effects, which was recently supported by the demonstration of coexistence of ON and OFF cells in the CVLM [21]. The functional relevance of the spino-VLMlat-spinal loop was demonstrated by the differential involvement of different types of lamina I neurons projecting to the VLMlat and by different nociceptive activation of these neuronal types after VLMlat lesions [6].

Descending modulation from the CVLM is dynamically conveyed by direct and indirect complex circuits. The α_2-adrenoreceptor mediated inhibition of spinal nociceptive transmission exerted by the CVLM is conveyed by the pontine A_5 noradrenergic cell group, whereas descending serotonergic modulation appears to involve the RVM [6]. Besides the A_5 noradrenergic cell group and the RVM, other brain regions are probably recruited in the descending modulation from the CVLM because this area targets pain control centers like the PAG, parabraquial area and *locus coeruleus* (Fig. 2b). The pattern of CVLM connections in the brain further suggests that it may play an important role in the integration of pain responses with other body functions. The CVLM participates in pain-cardiovascular integration and in the hypoalgesia detected during hypertensive conditions [22,23]. Finally, the arrival of spinal nociceptive input to the CVLM

is also integrated with the information derived from widespread brain areas [24]. The CVLM receives strong input from areas participating in somatosensory processing, and autonomic and motor controls. More than just providing a mechanism of feedback integration, the reciprocal spino-CVLM loop is likely to play a complex role on the protective homeostatic function of the pain system.

Chronic pain and the brainstem–spinal dorsal horn communication

Importance of controlling nociceptive input to the brain

Acute pain and transient ALLODYNIA and HYPERALGESIA (see glossary) associated to inflammation, chronic pain and disease are crucial examples of the importance of pain for organism protection (Fig. 1). Conversely, other situations require analgesia to preserve organism integrity and surviving, which indicates that pain suppression is as important to the organism as pain perception [2]. Fear and acute stress, for example, strongly inhibit pain as it could be incompatible with the need of running from eminent danger. Accordingly, the AMY and the PVN, areas responsible for emotional processing of fear and initiation of the physiological response to stress, respectively, have shown to modulate pain [25,26].

Recent data indicate that the analgesic action triggered by PVN stimulation changes the activity of ON and OFF cells also present in the RVM and CVLM [21,27], which is exerted through a descending serotonergic and noradrenergic pathway inhibiting spinal nociceptive neurons (unpublished). These PVN actions upon the medulla oblongata and spinal cord are paralleled by a correspondent inhibition of pain-like behavior [21,27]. The AMY exerts also a fine control upon RVM ON and OFF cell activities, and the data collected indicate that the AMY is also implicated in pain facilitation [26,28]. Finally, the ACC, a key area in the processing of the motivational-affective dimension of pain was also shown to have a descending nociceptive facilitating action, which is mediated by two relay medullary centers, the RVM and the DRt [13] (Fig. 2a). All these data strongly implicate medullary pronociceptive and antinociceptive centers reciprocally connected with the spinal dorsal horn, as relay stations for the pain modulatory actions triggered by forebrain areas regulating pain experience. Importantly, the induction of chronic pain can change the modulatory action of the forebrain upon brainstem neurons and, consequently, upon and spinal neurons and nociceptive transmission (Fig. 1b). This was recently demonstrated for the PVN, as its actions upon RVM and CVLM ON and OFF cells and spinal convergent nociceptive neurons changed after the development of arthritis [21,27]. Thus, prolonged pain states are capable of changing the physiological homeostasis of the forebrain–brainstem–spinal cord neuronal network implicated in pain modulation.
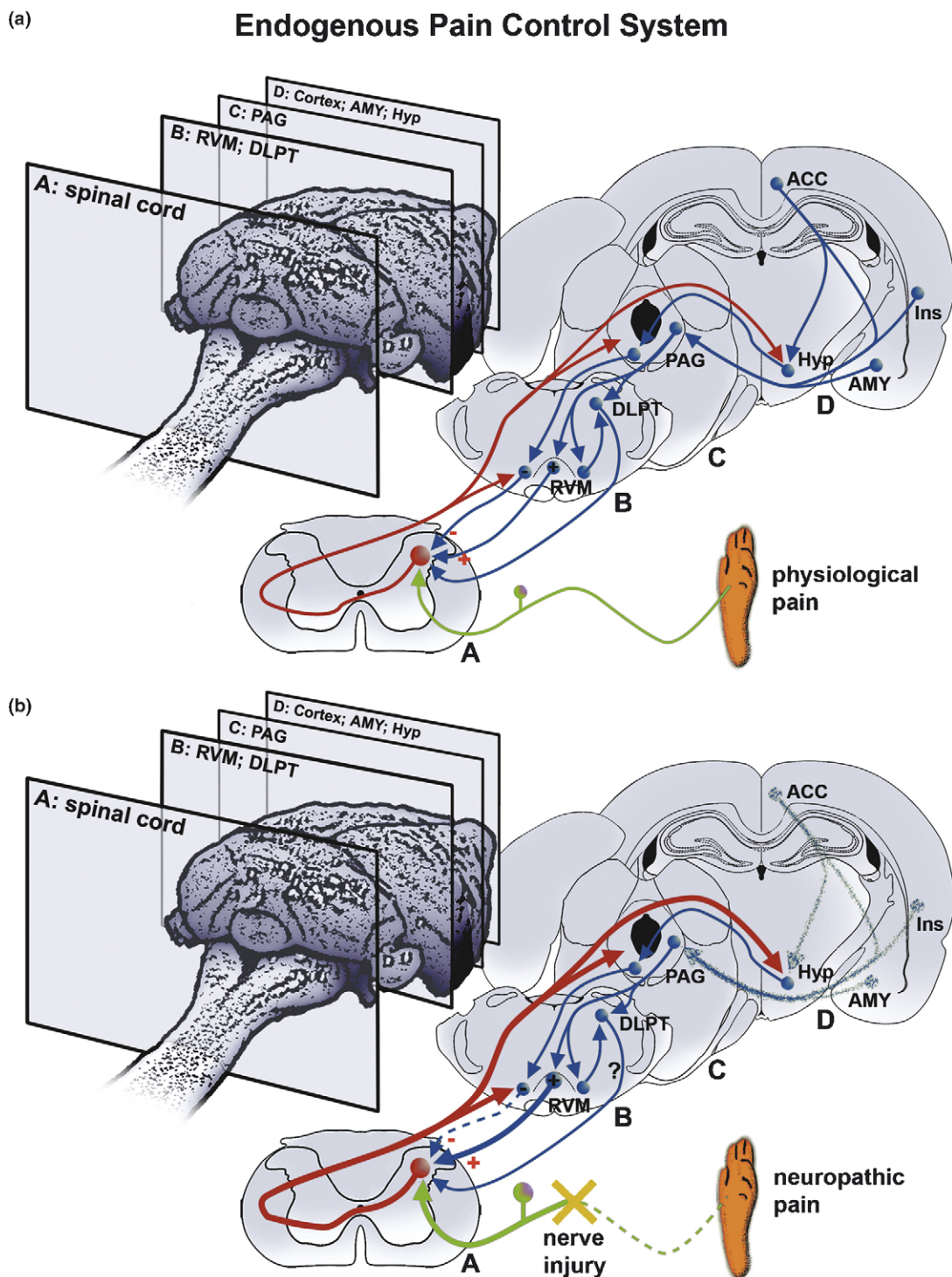
Figure 1. Schematic representation of the supraspinal endogenous pain control system following physiological (a) and chronic (b) pain. Ascending pain pathways (red arrows) convey nociception to different targets along the brain, including the major brainstem pain modulating areas. Descending neuronal projections (blue arrows) between brain areas relevant for descending pain control extend from the forebrain to the spinal cord dorsal horn. Under physiological conditions (a) the RVM contains nociceptive neurons that project to the spinal dorsal horn and facilitate (+: ON-cells) or inhibit (−: OFF-cells) spinal nociceptive transmission arriving from peripheral nociceptors (green arrow). Pain chronification (b) resulting from peripheral (large green arrow) and central (large red arrows) sensitization induces changes in the endogenous pain control system, which may include disruption of the antinociceptive system (−: dashed blue arrow) and exacerbation of pronociceptive mechanisms (+: large blue arrow). Changes induced at forebrain levels are less known and are represented by blurred blue arrows. It should be noted that the RVM plays also a role in the noradrenergic descending control mediated by the locus coeruleus (DLPT). The three-dimensional rat brain profiles at the left of 1a and 1b represent the levels of the brain coronal sections A–D. A–D are central nervous system sections adapted with permission from the Paxinos and Watson Atlas [41] and represent the spinal dorsal horn (A), the medulla oblongata and pons (B), the mesencephalon (C) and the

Table 1. Medullary-spinal circuitries: roles in pain perception and potential future therapies for chronic pain treatment

Brainstem–spinal circuit	Strategic approach to the circuit	Expected outcome of intervention at the circuit	Who is working in the circuit	Potential therapies	Advantages/ disadvantages of these therapies	Refs
DRt–spinal	- DRt chemical or electrical stimulation or inhibition - DRt local administration of drugs	Pronociception - increased (DRt stimulation) or decreased (DRt inhibition) pain behaviour	Almeida, A et al. [3,16,19] Tavares, I et al. [33,35] Villanueva et al. [15,20]	- Gene therapy (GT) - Intracerebral lesioning (ICL)	(GT): Induction of local production of opioid drugs/very preliminary studies (ICL): Potential block of pronociception in chronic pain processing/ Location between two respiratory areas	[3,15,16, 19,20, 33,35]
ACC–DRt–spinal	Stimulation/lesioning the ACC and DRt, respectively	Pronociceptive modulation mediated by he limbic system	Zhang, L et al. [13]	?	?	[13]
CVLM–spinal	- Local chemical or electrical stimulation or inhibition - Local administration of drugs - C-fos visualization of nociceptive neurons	Antinociception – decreased pain behaviour	Tavares, I et al. [6,22–24] Pertovaara, A and Almeida, A [21]	- Gene therapy	Induction of opioid production by CVLM-spinal neurons/very preliminary studies and motor and respiratory side effects	[6,21–24]
NTS–spinal	- NTS lesioning - proinflammatory cytokines	Sickness-induced hyperalgesia	Watkins, LR and Maier, SF [17]	?	?	[17]
RVM–spinal	- Local administration of drugs - Destruction of substance P spinal neurons - Excitatory transmitter release	Pronociception and/or Antinociception	Porreca, F et al., [5,9,32] Dickenson, A, [7] Fields, H, Heinricher, M, [11] Dubner, R et al. [31]	- Ablation of opioid RVM cells - Cholecystokinin antagonists - NMDA antagonists - Serotonergic pain-facilitating pathways	- Reduction of neuropathic pain/neuronal death - Prevention of opioid tolerance	[5,7,9,11, 31,32]
AMY–RVM–spinal	- Local administration of opioids	Antinociception mediated by the limbic system	Heinricher et al. [26]	?	?	[26]
PVN–RVM–spinal	- Local chemical stimulation or inhibition - Local administration of drugs	Stress-induced analgesia	Pertovaara, A and Almeida, A [27]	?	?	[27]

Role of the brainstem in the development of chronic pain

Chronic inflammatory or NEUROPATHIC PAIN (see glossary) results from prolonged nociceptive barrage to the central nervous system and the resulting neuroplasticity of peripheral and central components of the nociceptive system. Central and PERIPHERAL SENSITIZATION (see glossary) increase neuronal excitability along the ascending and descending pain pathways, which may disrupt the fine balance between pronociceptive and antinociceptive pain modulatory actions descending from the brain [4,29]. The reciprocal anatomical connections between the medulla oblongata and the spinal cord should play a role on neuronal plasticity of brainstem and spinal dorsal horn areas and in the impairment of pain behavior in chronic pain syndromes. Accordingly, the RVM and PAG are involved in human central sensitization [30], whereas in the rat the RVM is implicated in the maintenance of central sensitization in persistent inflammatory, neuropathic and visceral pain states [9,31] (Fig. 1b). The RVM is also responsible for the increased release of nociceptive neurotransmitters by peripheral nociceptors in the spinal dorsal

forebrain (diencephalon and telencephalon), (D). Abbreviations: ACC, anterior cingulate cortex; AMY, amygdala; CVLM. caudal ventrolateral medulla; DRt, dorsal reticular nucleus; Hyp, hypothalamus; DLPT, dorsolateral pontine tegmentum; Ins, insular cortex; PAG, periaqueductal gray matter; RVM, rostral ventromedial medulla.
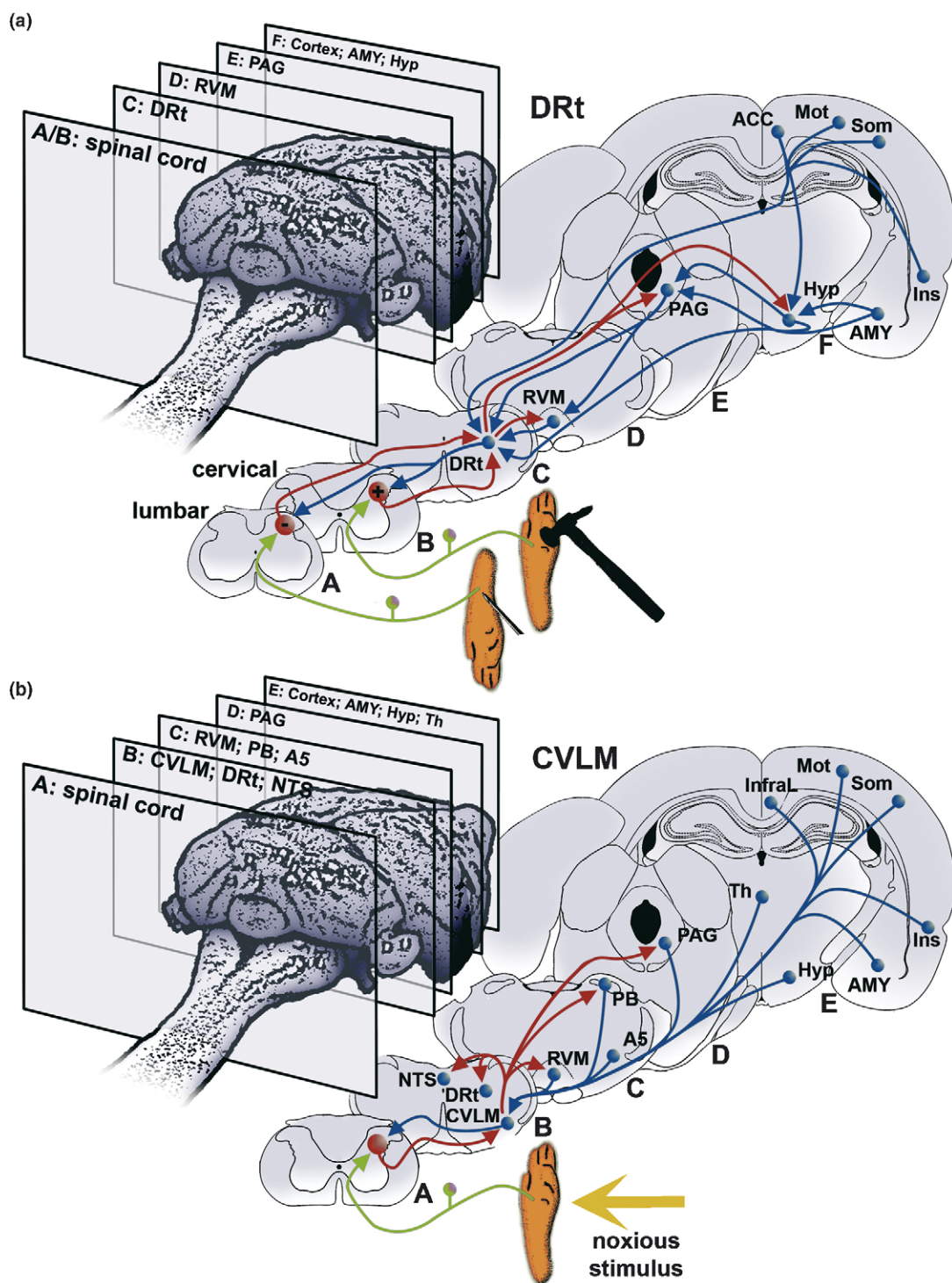
Figure 2. Spino-bulbo-spinal and brain neuronal network underlying the DRt (a) and the CVLM (b) involvement in pain modulating circuitries. In what concerns the DRt (a) note the reciprocal connections with the spinal dorsal horn, Hyp, PAG and RVM. The DRt has a pronociceptive action upon the spinal nociceptive transmission arriving from the front paw dermatome submitted to strong noxious stimulation (+ in the neuron located at the spinal level stimulated by hammering the forepaw) [3]. Moreover, it appears to mediate the inhibition of heterotopic nociception (− in the neuron located at the spinal level stimulated by pricking the hindpaw dermatome), a phenomenon known as diffuse noxious inhibitory control (DNIC) (see reference [15] for details). The limbic system projects massively to the DRt. In what concerns the CVLM (b), note the large afferent projections from several cortical, subcortical and diencephalic areas of the brain and the reciprocal connections with the PAG, parabrachial nuclei, RVM and spinal cord. Ascending connections are represented in red, descending projections are in blue and nociceptors are depicted in green. A–D are central nervous system sections adapted with permission from the Paxinos and Watson Atlas [41] and represent the spinal dorsal horn (A), the medulla oblongata and pons (B), the mesencephalon (C) and the forebrain (diencephalon and telencephalon, D). Abbreviations: A5, A5 noradrenergic cell group; ACC, anterior cingulate cortex; AMY, amygdala; CVLM. caudal ventrolateral medulla; DRt, dorsal reticular nucleus; Hyp, hypothalamus; Infral, limbic cortex; Ins, insular cortex; Mot, Motor cortex; NTS, nucleus tractus solitarius; PAG– periaqueductal gray matter; PB, parabrachial nuclei; RVM, rostral ventromedial medulla, Som, somatosensory cortex; Th, thalamus.

horn during experimental neuropathy [32]. Moreover, superficial dorsal horn projection neurons expressing neurokinin-1 receptors (NK1-R) (see glossary), which are activated by excitatory neurotransmitters released by peripheral nociceptors, control spinal excitability and pain sensitivity through brainstem serotonergic facilitatory pathways descending along the dorsolateral funiculus [7,8]. Interestingly, the expression of NK1-R in spinal neurons projecting to brainstem areas involved in pain modulation differs with the target as the expression of NK1-R in the spino-CVLM pathway is stronger than that in the spino-DRt, which appears to exhibit mainly GABA$_B$ receptors [33].

The role of the two reciprocal bulbospinal loops centered at the DRt and VLMlat in inflammatory and chronic inflammatory pain is only beginning to be addressed. In both pain models the activity of the DRt was shown to be increased [34]. During arthritis, a strong decrease in the expression of GABA$_B$ and μ-opioid receptors in DRt and CVLM nociceptive neurons was demonstrated ([35], unpublished), which might account for a lower efficacy of drugs acting upon these receptor systems. Accordingly, the intensity of nociceptive neuronal activation at the CVLM is negatively correlated with nociceptive activation of lamina I neurons (unpublished). Finally, we have recently demonstrated an involvement of both spinomedulllary loops in the differential expression of NK1 and GABA$_B$ receptors in spinal nociceptive neurons during secondary hyperalgesia induced by arthritic pain (unpublished). These data demonstrate the importance of controlling the cross talk between the brainstem and spinal cord in pain perception. Accordingly, the endogenous antinociceptive pain control system is disrupted in a dysfunctional pain syndrome like fibromyalgia and may account for the generalized hypersensitivity shown by these patients [10].

Conclusions

The brainstem concentrates all regions directly modulating the ascending nociceptive transmission from the spinal dorsal horn and mediates the pain control orders triggered by the forebrain areas responsible for coordination of the final pain perception. Moreover, the brainstem (and the medial thalamus) is also the main recipient of the spinal nociceptive information concerning the motivational-affective dimension of pain. This indicates that the brainstem and spinal cord are privileged areas for assuming the permanent homeostasis of the nociceptive system and its integration with other body functions through a continuous balance mediated by reciprocal feedback loops.

Can a better knowledge of the brainstem-spinal crosstalk be used in future therapies for pain control? On the basis of the extensive connections of pain control centers and on their involvement in several body functions, the search for neuronal specific targets of manipulation should be envisaged (Table 1). Gene therapy with vectors that target specific neurons and deliver therapeutic transgenes, like opioid precursors, in an inducible and sustained manner could be important in the future. The reciprocal bulbospinal loops implicated in pain control could be targeted by spinal administration of viral vectors that migrate to the caudal medulla. Thus, future therapies aimed at specifically increasing the serotonergic and noradrenergic descending control and the opioidergic, GABAergic and glycinergic 'pain' inhibiting action at the spinal level may prove effective in providing analgesia. On the contrary, neuroinflammatory factors involving not only neuronal networks but also glial cells and the immune system are actually under intense research in studies involving mainly chronic neuropathic pain models. However, no data are available on how the reciprocal networks between the brainstem and spinal cord are affected by the immune and glial changes accompanying prolonged inflammation and chronification of pain. Finally, a potential therapeutical target involving crosstalk between the brain and spinal cord could be the development of more specific drugs for modulating wind-up and long term potentiation (LTP) in spinal neurons following pain syndromes [36]. These two mechanisms induce increased/prolonged activity of nociceptive neurons/excitatory synapses and are implicated in central sensitization at both the brain and dorsal horn levels. Thus, they are both potentially present in supraspinally projecting spinal nociceptive neurons and nociceptive brainstem neurons modulating spinal nociceptive transmission. Reinforcing the necessity of exploring this hypothesis, endogenous spinal opioid receptors were shown to play a role in the endogenous spinal opioid mechanisms involved in wind-up [37], whereas GABA and NMDA RECEPTORS (see glossary) participate in spinal LTP induction and maintenance [38,39]. Future studies at the molecular level concerning the identification of specific characteristics of the pain neuronal network and improvement of membrane receptor cellular biology [40] are needed to develop well localized targeting strategies to control pain. However, although promising and exciting, the power of controlling the feedback interactions between the brain and spinal cord in terms of pain mechanisms is conceptually and technically complex and far from being achieved [38].

Acknowledgements

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