Pain–autonomic interactions: a selective review

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The nociceptive and the autonomic systems are two components of an integrated central network, which are critical for adaptation and survival in response to internal or external environmental challenges. There is increasing evidence that the pain and autonomic control pathways interact at multiple levels, including the periphery, dorsal horn, brainstem, and forebrain. Nociceptive and autonomic regulatory regions of the central nervous system often respond to the same type of somatic or visceral inputs, receive convergent nociceptive and viscerosensory information, and contain groups of neurons that initiate autonomic, antinociceptive, and behavioral responses to noxious as well as visceral stimuli. Understanding the complexity of these interactions is important for an integrated approach to chronic pain syndromes. This review will focus on selective aspects of the pain–autonomic interactions at the level of the central nervous system. These include (1) some of the parallel pathways conveying nociceptive and viscerosensory information to the cerebral cortex; (2) some of the connections between the nociceptive pathways and areas that generate autonomic, endocrine, and behavioral responses; (3) the role of the periaqueductal gray matter in integration of antinociceptive and autonomic responses to stress; and (4) the role of the insular and anterior cingulate cortex in integration of nociception with high-level autonomic control. Many of these subjects have recently been reviewed [1–4]. This review will not cover the important mechanism of spinal processing of converging nociceptive and somatic information, as recently reviewed in Foreman [5].

Nociceptive and viscerosensitive inputs to the cerebral cortex

Saper, in a recent review [1], indicates that pain should be considered a visceral sensation, which monitors the integrity of all tissues and elicits visceral motor and emotional responses. This concept is supported by anatomic and functional evidence of convergence between the nociceptive and visceral sensory pathways at the levels of the dorsal horn, brainstem, basal forebrain, thalamus, and cerebral cortex; and by the increasing information about the circuits that mediate the autonomic, endocrine, and behavior responses to these convergent sensory information.

Visceral afferents can be arbitrarily subdivided into two main groups (1) afferents from viscerceptive dorsal root ganglion neurons that, together with somatic nociceptive neurons, project to the dorsal horn of the spinal cord; and (2) afferents carried by branches of the facial, glossohypogag, and vagus nerves that synapse in the nucleus of the solitary tract (NTS). The primary nociceptive and viscerceptive afferents terminate in several laminae of the spinal cord gray matter containing local, propriospinal, and projection neurons. Neurons receiving converging nociceptive and viscerosensory projection provide axons to the spinal projection tract (STT), which is the major pathway for transmission of nociceptive and visceral information to the cerebral cortex. The STT neurons are found in the superficial layer I, or marginal zone; laminae IV and V in the lateral portion of the neck of the dorsal horn; and laminae VII and VIII in the intermediate zone of the spinal gray matter [6]. For the purpose of this review, the focus will be on lamina I, but there is a large amount of information that indicates that neurons in the deep dorsal horn, particularly in lamina V, also play an important role in processing of somatic and visceral sensation. The importance of the STT projection from laminae I and V in conveying visceral sensation is underscored by the fact that more than 90% of visceral information relayed by dorsal root ganglion neurons converges on neurons that receive nociceptive afferent input. Lamina I receives small-diameter (Aδ and C fiber) input from free afferents innervating the skin, viscera, muscles, and joints throughout the body. Lamina I extends into the spinal trigeminal nucleus caudalis, which receives inputs from the face, cornea, teeth, and dura. All these afferents are activated by mechanical or thermal stress or damage, changes in temperature, muscle exercise, chemi-
cal/metabolic stimuli, or inflammatory mediators. Lamina I contains several classes of neurons: (1) nociceptive-specific (NS) neurons that receive Aδ inputs and respond only to noxious heat or mechanical stimuli within small cutaneous receptive fields; (2) multimodal nociceptive (HPC) neurons that receive C-fiber input and respond to heat, pinch, and cold; and (3) thermoreceptive-specific (COLD) neurons that respond to innocuous cooling and are inhibited by warming of the skin [6]. In addition, lamina I and, most important, lamina V contain wide dynamic range (WDR) neurons that receive direct inputs from large (Aβ) and small (Aδ) myelinated fibers and polysynaptic inputs from C fibers. These neurons respond to innocuous and noxious, somatic and visceral, inputs [7]. There is important processing of information at the level of laminae I and V, and there is abundant evidence that plasticity in the dorsal horn circuits, involving the WDR neurons, plays a critical role for mechanisms of chronic neurogenic pain [8].

The spinothalamic system has been subdivided into two main systems: a “lateral” pain system, involved in discriminative aspects of pain sensation such as localization and intensity of nociceptive stimulation; and a “medial” pain system, involved in affective and motivational aspects of pain sensation. Laminae I and V projections contribute to both systems. The specific thalamic relay for nociceptive- and thermosensitive-specific neurons of lamina I is the posterior portion of the ventromedial nucleus (VMpo) located in the posterolateral thalamus and distinguished by its calbindin fiber immunoreactivity (Fig. 1) [6]. The VMpo projects to the fundus of the superior limiting sulcus of the anterior insular cortex, in parallel with the visceral sensory projection described below. The lateral STT system also includes a projection from VMpo to the primary somatosensory area 3b in the depth of the central sulcus, and a projection from the ventral posteroinferior (VPI) nucleus (which receives inputs from laminae I and V) to the secondary somatosensory area (SII) in the parietal operculum. Area SII plays a major role in channeling somatosensory information to the amygdala and other limbic circuits. The second major target of lamina I STT neurons is the ventrocaudal portion of the mediodorsal nucleus (MDvc). The MDvc projects to area 24c in the fundus of the anterior cingulate sulcus, just anterior to the anterior cingulate motor area [9,10]. These projections, together with projections from the intralaminar and midline thalamic nuclei, constitute the “medial” pain system integrated in the anterior cingulate cortex [11]. Functional neuroimaging studies show that all the cortical projection fields of lamina I, particularly the insula and anterior cingulate, become activated by somatic noxious stimuli [12–17]. In summary, the spinothalamic system provides converging nociceptive and visceral sensory information to the cerebral cortex. This information is initially processed at the level of the spinal cord and then integrated with information conveyed at other subcortical levels.

The NTS is viscerotopically organized and consists of several subnuclei with specific inputs and outputs. The rostral third of the NTS receives oral visceral (taste) afferents; the intermediate third esophageal, gastric, and intestinal afferents; and the caudal third baroreceptor, cardiac, and respiratory afferents [18]. The NTS provides ascending projections that convey this visceral sensory information to the rostral brainstem and forebrain. Although some of the visceral sensory NTS projections reach the thalamus and hypothalamus directly, the majority synapse in the parabrachial nucleus, located in the dorsolateral pons. The parabrachial nucleus consists of several subnuclei that have unique sets of inputs, neurotransmitters, and targets [1]. Calcitonin gene-related peptide (CGRP)—containing neurons of the medial parabrachial subnucleus receive topographically organized inputs from the NTS and provide the major visceral afferent input to the thalamus [1]. The visceral sensory area of the
thalamus forms a narrow strip located just ventral to the classic somatosensory relay nuclei and corresponds to the ventroposterior parvicellular nucleus (VMpc) [19]. In the VMpc, neurons relaying taste are located medially, those receiving gastrointestinal inputs more laterally, and those relaying cardiorespiratory inputs furthest laterally. The visceral sensory thalamic neurons project to the rostral dysgranular portion of the insular cortex. The taste inputs relayed most rostrally, followed sequentially by gastrointestinal and cardiopulmonary inputs [1,19]. The insula is consistently activated by visceral stimuli in humans [20].

Thus, the areas of the thalamus receiving nociceptive and viscerceptive inputs form a shell that encases the classic somatosensory nuclei. The VMpo, which receives nociceptive and thermanocceptive spinothalamic inputs, is located just lateral to the visceral sensory thalamic nucleus; and the nociceptive projection of VMpo to the insula is located just caudal to the insular visceral sensory field. Therefore, both at the level of the thalamus and of the insular cortex, pain is represented as a topographic extension of visceral sensation [1]. This integration of visceral information with pain and temperature sensation is required for maintenance of integrity of all tissues of the body. In addition, there is potential for interactions between the visceral sensory and the "medial" nociceptive system at the level of the anterior cingulate gyrus. The parabrachial nucleus, like the dorsal horn, projects contralaterally to the midline and intralaminar thalamic nuclei, which provide input to the anterior cingulate cortex. Via these projections, nociceptive and visceral sensory inputs trigger affective and motivational responses [11].

**Spinobulbar projections of lamina I: basis for nociceptive initiation of autonomic, endocrine, and behavioral responses**

In addition to providing inputs to the thalamus, laminae I and V neurons relay sensory information to the thoracolumbar sympathetic nuclei and to several regions of the brainstem and forebrain involved in autonomic, endocrine, and antinociceptive control.

For example, lamina I neurons project to the intermediolateral, intermediomedial, and intercalate nuclei of the thoracolumbar spinal cord, which contain the sympathetic preganglionic neurons [21]. Lamina I neurons of the cervical enlargement project predominantly to the sympathetic nuclei in the T2-6 segments and those in the lumbar enlargement to the T10-12 and L3-4 segments [2]. The preganglionic sympathetic neurons are organized into distinct functional subunits each containing distinct effectors in the muscle, skin, and viscera [22]. Activation of primary sensory fibers arising from skin and muscle (as well as viscera) modulate preganglionic neuron activity through a variety of segmental somato-sympathetic reflexes [23,24]. These spinal sympathetic reflexes exhibit ipsilateral function-specific patterns of response. For example, nociceptive stimuli, relayed by HPC neurons in lamina I, stimulate discharge of muscle vasconstrictor neurons and inhibit activity of skin vasconstrictor neurons. On the other hand, innocuous cooling, which activates COLD neurons in lamina I, stimulates cutaneous vasconstrictor neurons [25].

Dorsal horn neurons project to several regions of the medulla, pons, and midbrain via several spinobulbar (ie, spinoreticular and spinomesencephalic) pathways [2] (Fig. 2). These projections provide nociceptive and visceral sensory input to brainstem neurons that initiate autonomic, endocrine, and antinociceptive responses via descending projections to the spinal cord, ascending projections to the forebrain, or both. These include the catecholaminergic groups of the lateral pontomedullary tegmentum, NTS, ventromedial medulla (including the raphe nucleus), locus ceruleus (A6 area), subcoerulear and Kölliker-Fuse nuclei (A7 area), parabrachial nucleus, and periaqueductal gray matter (PAG). Lamina I projections to the medulla are generally bilateral, whereas those to the pons and mesencephalon are predominantly contralateral.

Via direct projections to the noradrenergic A1 (caudal ventrolateral medulla), A5 (ventrolateral pons) and A7 (dorsolateral pons) groups, and to the adrenergic C1 group in the rostral ventrolateral medulla, dorsal horn neurons receiving converging nociceptive and visceral sensory inputs may trigger autonomic, endocrine, and antinociceptive responses. The C1 and A5 groups are the main source of descending catecholaminergic inputs to the intermediolateral cell column [26,27], and modulate responses of the preganglionic neurons to tonic glutamatergic excitatory inputs from the rostral ventrolateral medulla [28]. Thus, nociceptive inputs to the C1 and A5 groups may provide the basis for spino-bulbo-spinal sympathetic reflexes triggered by noxious somatic or visceral stimulation [29]. The A1 neurons stimulate release of arginine vasopressin via noradrenergic inputs to the magnocellular hypothalamic nuclei [30]. Inputs from lamina I to the A1 group may thus trigger arginine-vasopressin release in response to noxious stimulation [31]. The A6 and A7 regions provide descending bulbo-sensory noradrenergic pathways that inhibit nociceptive transmission in the dorsal horn [32]. Direct nociceptive and viscerosensory inputs from the dorsal horn may therefore provide a mechanism for feedback inhibition of pain transmission.

Spinal projections to the NTS (spino-solitary tract) provide the basis for nociceptive triggering or gating of a variety of cardiorespiratory reflexes. The NTS projects to the neuronal groups of the intermediate medullary reticular formation that initiate a variety of cardiorespiratory reflexes [18]. These include cardiovagal neurons of the nucleus ambiguus [33], sympathoexcitatory neurons of the rostral ventrolateral medulla [34], and neurons of the ventral respiratory groups [35]. Lamina I sends projections to the parabrachial nucleus, which also receives visceral sensory information, and in turn projects to the brainstem, hypothalamus, and amygdala. This spino-parabrachial connection thus provides the basis for integration of noxious, thermoreceptive, and viscerosensitive inputs with homeostatic, arousal, and emotional responses [1,3]. For example, the lateral parabrachial region, including the Kölliker-Fuse nucleus, projects to
the rostral ventrolateral medulla, NTS, nucleus ambiguus, and respiratory and preganglionic neurons of the spinal cord, all areas involved in cardiorespiratory regulation [36]. The spino-parabrachio-hypothalamic pathway provides nociceptive and viscerosensory inputs to the paraventricular nucleus and the lateral hypothalamic area, which provide descending innervation to brainstem and spinal autonomic nuclei [37,38] and to the medial preoptic and anterventral third ventricular region, which are involved in regulation of fluid and electrolyte balance, thermoregulation, and reproduction [3,39]. The spino-parabrachio-amygdaloid pathway provides a communication between nociceptive and viscerosensory dorsal horn neurons with the central nucleus of the amygdala and related basal forebrain regions [3], which together constitutes the “extended amygdala” [40]. The central nucleus of the amygdala plays a critical role in emotional responses [41] via its projections to the hypothalamus, PAG, NTS, ventrolateral medulla, and vagal nuclei. These projections are the substrate for integrated responses to emotions, such as conditioned fear, including adrenocortical and sympathetic activation, startle, and vocalization [42]. In addition to its projections via the NTS and parabrachial nuclei, lamina I (as well as laminae V and X) sends a direct spino-hypothalamic pathway that partially crosses the midline at the level of the supraoptic decussation to terminate bilaterally in the lateral, posterior, paraventricular, and suprachiasmatic nuclei.

Central interactions between antinociceptive and autonomic mechanisms circuits

Several circuits, integrated at spinal and supraspinal levels, participate in mechanisms that inhibit transmission of nociceptive information in the dorsal horn. These endogenous antinociceptive mechanisms can be activated by several influences, including stress, conditioning, circadian rhythms, exercise, sexual activity, visceral inputs, and previous exposure to nociceptive inputs. Lamina II, or substantia
gelatinosa, contains local circuit neurons that play a major role in segmental modulation of nociceptive transmission. Local excitatory interneurons use L-glutamate, and inhibitory neurons use γ-aminobutyric acid, glycine, and opioid peptides. Segmental, intersegmental, or supraspinal influences may inhibit nociceptive transmission presynaptically by decreasing release of glutamate or neuropeptides from primary afferents, postsynaptically by reducing response of NS and WDR neurons to nociceptive inputs, or both [43].

Propriospinal mechanisms contribute to spinal modulation of visceral and nociceptive sensory information. Convergence of nociceptive and viscerosensitive inputs to NS and WDR neurons [7,44] plays an important role in spinal mechanisms of antinociception. For example, NS and WDR neurons of the C1-C3 segments receive inputs from cardiopulmonary afferents and inhibit nociceptive transmission in the lumbosacral spinal cord [5]. Afferents to the C1-C3 segments carried via the vagus nerve are relayed via descending projections from the NTS and those carried by spinal nerves first relay in dorsal horn neurons of the T1-T6 segments, which then project to the C1-C3 levels via propriospinal pathways. The C1-C3 neurons activated by these cervical vagal and propriospinal cardiopulmonary afferents provide a descending antinociceptive projection to the lumbosacral segments, inhibiting transmission of both somatic and visceral pain at this level [5].

Supraspinal antinociceptive mechanisms involve descending inputs from a distributed ‘‘antinociceptive network’’ that include the paraventricular nucleus of the hypothalamus, PAG, laterodorsal pontine tegmentum, and the nucleus raphe magnus (NRM) in the ventromedial medulla [32]. These regions are reciprocally interconnected, are activated by nociceptive pathways, and contain opioid neurons, opioid receptors, or both. Stimulation of these areas produces analgesia by selectively inhibiting nociceptive transmission in the spinal cord by presynaptic or postsynaptic mechanisms. These areas receive inputs from the cingulate and insular cortices, hypothalamus, and amygdala, thereby providing a substrate for motivational or emotional modulation of pain sensation.

An important component of this network is the PAG, which plays a major role in integration of behavioral somatic, autonomic, and antinociceptive responses to stress. The PAG integrates inputs from the limbic forebrain and diencephalon with ascending nociceptive input from the dorsal horn. Neurons of the PAG are organized into distinct functional columns, each receiving distinct inputs and initiating specific patterns of behavioral, autonomic, and antinociceptive responses [4,45]. The lateral PAG receives somatotopically restricted nociceptive stimuli primarily from the skin, and its stimulation initiates behavioral and autonomic effects typical of the ‘‘fight-or-flight’’ responses. These include vocalization and other motor responses; hypertension; tachycardia; renal, mesenteric and skin vasoconstriction and skeletal muscle vasodilatation; and profound analgesia, which is independent of opioid mechanisms [4,45]. In humans, lateral PAG stimulation may reproduce unpleasant sensations of fear, anxiety, and agitation. The ventrolateral PAG receives nociceptive inputs from the muscle and viscera and is involved in a ‘‘defeat response,’’ or ‘‘hyporeactive immobility.’’ This is characterized by cessation of spontaneous motor behaviors and decreased responsiveness to external stimuli, which is associated with bradycardia and hind limb and renal vasodilatation. The analgesia evoked from the ventrocaudal PAG stimulation is of gradual onset and is mediated by opioid mechanisms [45].

The effects of PAG stimulation on pain inhibition and sympathetic cardiovascular outflow are mediated, to a large extent, by monoaminergic neuronal groups of the pons and medulla, including the dorsolateral pontine tegmentum, ventromedial medulla (including the NRM), and ventrolateral medulla. These groups receive topographically organized and functionally segregated inputs from the PAG, and project to the dorsal horn, intermediolateral cell column, or both. The lateral PAG, involved in ‘‘fight-or-flight’’ responses, projects to the dorsolateral pontine tegmentum and the rostral ventrolateral medulla. The dorsolateral pontine tegmentum contains the noradrenergic neurons of the locus ceruleus/subcerebral region (A5-A7 groups), which project to the dorsal horn, where they inhibit nociceptive transmission, in part via α2-receptor mechanisms [32]. The rostral ventrolateral medulla contains distinct subgroups of bulbospinal sympathetic excitatory neurons that receive separate inputs from the rostral (‘‘flight’’) or caudal (‘‘flight’’) zones of the lateral PAG and control specific vascular effectors [46]. The ventrolateral PAG, involved in the ‘‘defeat’’ response, projects primarily to the rostral ventromedial medulla, including the NRM and the adjacent reticular formation. The RVM also receives massive inputs from the spinoreticular tract. The NRM, like the PAG, contains ‘‘on’’ cells that are excited by noxious stimuli and inhibited by opioids and ‘‘off’’ cells that are inhibited by noxious stimuli and indirectly activated by opioids (which inhibit local GABAergic on-neurons that inhibit the off-cells) [43]. An important off-cell group of the NRM are bulbospinal serotonergic neurons, which inhibit nociceptive transmission via activation of 5-HT1 A-type receptors in the dorsal horn. The sympathoinhibition elicited by ventrolateral PAG stimulation may involve inhibitory serotonergic inputs from the NRM to the rostral ventrolateral medulla [47]. As mentioned above, projections from the C1-C3 segments carried via the vagus nerve reach the NTS and the parabrachial nucleus, and these structures provide descending projections that inhibit transmission of nociceptive inputs in the spinal cord [5].

Cortical integration of nociceptive and autonomic responses

The insula and the anterior cingulate cortex are both engaged in pain processing and both participate in high-level control of autonomic function [48–50]. Although these two areas are interconnected, they appear to operate independently as components of a parallel and distributed network that analyze different component of the pain sensation and
project to widespread autonomic areas on the brainstem and spinal cord.

The insular cortex is the final station of the “lateral pain system,” involved in discriminative aspects of pain sensation. Positron emission tomography studies in humans indicate that the insula is strongly activated by noxious heat and cold stimuli as well as innocuous cold and warm stimuli. Lesions that interrupt this critical lateral ascending pathway produce analgesia and thermoanesthesia. In a significant proportion of cases, these lesions also produce, with variable delay, the appearance of ongoing pain in the ‘deafferented’ region, including the thalamic pain syndrome [51]. As mentioned previously, the agranular insula receives viscero-sensory projections that, together with the nociceptive- and thermoreceptive-specific projections, provide the insula with a topographic representation of all sensations related to maintenance of bodily homeostasis and integrity. The agranular insular cortex projects to many components of the central autonomic network, including the central nucleus of the amygdala, lateral hypothalamic area, parabrachial nucleus, and NTS [49,50]. The insula is activated by visceral stimuli in humans, including those from the baroreceptors [20]. Stimulation of the insular cortex in various species, including humans, elicits changes in arterial pressure, heart rate, respiration, gastrointestinal motility and secretion, salivation, pupillary dilatation, and piloerection [52,53]. The cardiovascular responses depend on an obligate relay in the lateral hypothalamic area [53].

The anterior cingulate cortex receives inputs from the “medial pain system,” relayed via the MDvc as well as the intralaminar and midline thalamic nuclei. The role of the anterior cingulate in processing of pain sensation has been recently reviewed [11]. It has been suggested that the primary function of the medial pain system is to predict and avoid noxious stimuli. Functional neuroimaging studies show that the anterior cingulate cortex is strongly activated by noxious heat and noxious cold but not by innocuous stimuli [54]. Anterior cingulate activation is uniquely associated with a sensation of burning, ice-like pain elicited by thermal grill illusion of pain [13]. These experiments use a grid of innocuous hot and cold stimuli that together produce the perception of painful burning. Hypnotic alterations of stimulus unpleasantness influence the anterior cingulate cortex [11].

The anterior cingulate cortex includes two of the four subdivisions of the cingulate gyrus [11]; the perigenual areas 25, 24, and 32; and the midcingulate areas 24’ and 32’. These two subdivisions of the anterior cingulate gyrus seem to be involved in different aspects of processing of pain sensation. The perigenual area is involved in affective experience, whereas the midcingulate cortex is in motivation and goal orientation in response to noxious stimuli [11]. These two subdivisions of the anterior cingulate also differ in their effector mechanisms in response to the experience of pain. The perigenual area 25 is referred to as the “visceral motor cortex.” It projects to the lateral hypothalamic area and to the medial preoptic, paraventricular, dorsomedial, and tuberomammillary nuclei. It is also the main source of cortical afferents to the parabrachial nucleus, NTS, nucleus ambiguus, ventrolateral medulla, and intermediolateral cell column [49,50]. Stimulation of areas 25 and 24 elicits a variety of visceromotor responses, including increases or decreases in blood pressure, heart rate or respiration; mydriasis; piloerection and facial flushing; salivation; nausea; vomiting; and bowel or bladder evacuation [55,56]. Stimulation of the dorsal perigenual area 24 produces fear, pleasure, and agitation [11].

On the other hand, the midcingulate cortex is involved with mental imagery and motor representation [11]. It includes the “anterior cingulate motor area” located in the depths of the cingulate sulcus. This area projects to the ventral horn and to other motor areas of the frontal lobe and thereby controls skeleton motor responses [11].

Conclusion

Chronic pain is a manifestation of plasticity within the central and peripheral nociceptive pathways. The evidence reviewed indicates that the interactions between the nociceptive and the autonomic systems are complex, and involve a variety of central antinociceptive, autonomic, emotional, and behavioral control mechanisms. An integrated approach to the care of patients with chronic pain syndromes requires an awareness of these multilevel interactions, which could provide the basis for innovative pharmacological, physical, and behavioral therapy approaches.

References

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