Neurol Sci (2013) 34 (Suppl 1):S41–S46
DOI 10.1007/s10072-013-1391-z

PATHOPHYSIOLOGY OF MIGRAINE

Nociception and autonomic nervous system

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Abstract The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Pain may also be experienced in absence of noxious stimuli and together with temperature and other bodily feelings constitute the interoception redefined as the sense of the physiological condition of the entire body, not just the viscera. The main characteristic of these feelings is the affective aspect. Emotion, motivation, and consequent behavior connected with these feelings characterize their homeostatic role. This implies an interaction between neural structures involved in pain sensation and autonomic control. The aim of this review is to focus on pain perception, mainly on pain matrix structures' connections with the autonomic nervous system.

Keywords Pain · Autonomic nervous system · Pain matrix · Central autonomic network

Introduction

Nociception, which is initiated by the activation of peripheral nociceptors, may be defined as the activity in the peripheral and central nervous system elicited by mechanical, thermal, or chemical stimuli having the potential to inflict tissue damage [1]. However, nociception is not synonymous with pain, which is experienced as a conscious percept. Indeed, nociception can trigger brain responses without necessarily causing the feeling of pain [2–4]. On the other hand, pain can occur in the absence of nociceptive input [5].

Pain, temperature, and other bodily feelings are distinguished from touch for their inherent association with emotion. Pain belongs to the interoception and touch to exteroception and recent findings on the functional anatomy of the lamina I spinothalamocortical system indicate that interoception should be redefined as the sense of the physiological condition of the entire body, not just the viscera [6].

Neuroanatomy of pain perception

Afferent pathways

The major class of nociceptors are Aδ and C small diameter afferent fibres that innervate all tissues of the body and reach mainly the lamina I, i.e., the most superficial layer of the spinal and trigeminal dorsal horn and the lamina V. The lamina I neurons arise from the progenitors of autonomic interneurons placed in the lateral horn and migrate in their superficial dorsal position during a ventromedial rotation of the entire dorsal horn, which occurs simultaneously with the arrival of the small diameter afferents [6, 7]. This course of development supports the view that the small-diameter afferents and lamina I constitute a cohesive homeostatic afferent system [6, 8, 9]. The ascending projections of lamina I project strongly to the sympathetic cell columns of the thoracolumbar spinal cord, thus forming a spino-spinal loop for somato-autonomic and viscera-autonomic reflexes [10, 11]. Next, they project to the main

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homeostatic integration sites in the brainstem. Pain-related information ascends in the contralateral spinothalamic tract, but there are also direct connections to the medulla and brainstem via the spinoreticular and spinomesencephalic tracts and to the hypothalamus via the spinohypothalamic tract [12]. Lamina I and caudal trigeminal nucleus project to the nucleus of the solitary tract (NTS) and then to parabrachial nucleus (PBN) that is the main integration site for all homeostatic afferent activity [8]. However, the integrative role of lamina I, NTS, and PBN in the homeostatic afferent pathway is clearly consistent with the dense projections of PBN to the periacqueductal gray (PAG), the "mesencephalic motor center" (discussed in the section "Descending pathways"), and to the hypothalamus "the diencephalic homeostatic motor center". Afterwards, the integrated homeostatic afferent information reaches the posterior part of ventromedial nucleus and the ventral caudal part of the mediodorsal nucleus of the thalamus and finally the anterior cingulate cortex (ACC) considered as the limbic motor cortex and the insula considered as the limbic sensory cortex [8].

Cortical control of nociception: the pain matrix

In the last decades, a very large number of studies have aimed at better understanding how the cortex processes nociceptive stimuli and how the experience of pain may emerge from this processing. In humans, most of these studies have relied on non-invasive functional neuroimaging techniques to sample, directly or indirectly the neural activity triggered by various kinds of nociceptive stimuli showing that nociceptive stimuli elicit responses in several subcortical and cortical brain structures [13–21]. The responses in some of these structures are observed consistently across studies, and seem to be correlated with the perceived intensity of pain. Thus, they have been hypothesized to be preferentially involved in experiencing pain and structures such as the primary (SI) and secondary (SII) somatosensory, the cingulate and the insular cortices are often referred to as belonging to the so-called "pain matrix", i.e., a network of cortical areas through which pain is generated from nociception [16–20].

In other words, nociceptive input would generate a conscious percept of pain through the activity it elicits in the network constituting the "pain matrix", and, hence, measuring the activity within this network would constitute a direct and objective measure of the actual experience of pain [22]. The pain matrix is subdivided into medial and lateral pain systems; this distinction, which is based on the projection sites from medial or lateral thalamic structures to the cortex, is probably an oversimplification of the networks involved but it is a useful means for grouping brain regions that appear to have similar roles in pain perception [12]. For instance, the lateral pain system (S1, S2) seems principally involved in discriminating the location and the intensity of painful stimuli [23, 24], whereas the ACC [25, 26] is involved in the affective (cognitive–evaluative) component of pain. The insula, however, encodes both the intensity [6, 12, 27] and the laterality [28, 29] of painful and non-painful thermal stimuli, but may also have a role in affective pain processing [30–33]. The insula is situated at the interface of the cognitive, homeostatic, and affective systems of the human brain, providing a link between stimulus-driven processing and brain regions involved in monitoring the internal milieu [34]. Like other feelings from the body, pain normally consists of both a sensation and a motivation. The cortical region associated with such motivation seems to be the ACC and it can be regarded as limbic motor cortex because of its association with autonomic and emotional control [6]. Thus, activation of ACC is associated with motivation, and activation of the insula is associated with feeling, which together form an emotion [6]. It is actually difficult to provide a unique and consensual definition of the "pain matrix" since each area belonging to the "pain matrix" is not only involved in the perception of pain, but also form an ensemble of interplaying parts that cannot be reduced to a mere cortical and subcortical "representation" of pain. Indeed, several studies have shown that the activity of the so-called "pain matrix" (1) can be clearly dissociated from the perception of pain intensity [4, 35–41], (2) is strongly influenced by factors independent of the intensity of the nociceptive stimulus [37, 39, 42, 43], and (3) can be evoked by non-nociceptive and non-painful stimuli [44–49]. Importantly, these experimental observations do not question the involvement of the cortical activity in the emergence of pain. Rather, they question the notion that the cortical activity involved in the generation of pain is necessarily and specifically reflected in the "pain matrix".

Descending pain modulatory system

The descendent pain modulatory system regulate pain signalling in the nervous system and has a tonic regulatory influence from the brain to the spinal dorsal root level [12]. The effector structure of the amygdala nuclear complex is the central nucleus, which via its connections with the bed nucleus of the stria terminalis, hypothalamus, and brainstem, initiates autonomic, endocrine, and motor outputs that are critical for the expression of emotional responses including conditioned fear in response to pain [50, 51]. The hypothalamus has a central role in the integration of autonomic and endocrine responses necessary for the homeostasis and adaptation to internal or external stimuli and it includes the posterior hypothalamic and lateral

hypothalamic areas involved in arousal, autonomic control, and pain modulation.

The next area of the nociceptives pathways is the PAG. The stimulation of this structure may provide long-term effective pain relief in selected patients [52, 53]. The PAG receives afferents from the central and from the peripheral nervous systems. The lateral and dorsolateral PAG columns receive somatotopically organized inputs from superficial nociceptors relayed by the superficial lamina of the spinal and spinal trigeminal nucleus. In contrast, the ventrolateral column receives convergent input from both the superficial and deep dorsal horn relaying nociceptive afferent information from visceral, muscle, and C-fiber skin nociceptors as well as visceral inputs from the nucleus of the NTS and sacral spinal cord. Functional neuroimaging studies in humans indicate that PAG activation by nociceptive inputs is modulated by attention, emotion, expectation of pain and expectation-related placebo analgesia [54–61]. Experimental studies using chemical microstimulation indicate that the different columns of the PAG organize different coping strategies to pain and other stressors [62–66]. The lateral and dorsolateral PAG initiate flight or fight responses associated with tachycardia, hypertension, and redistribution of blood flow, i.e., sympathoexcitatory responses mediated by neurons of the ventrolateral medulla (VLM), which activate sympathetic preganglionic neurons controlling cardiovascular effectors [65–68]. In contrast, neurons of the ventrolateral PAG column initiate sympathoinhibitory responses (hypotension and bradycardia) that are associated with immobility and hyporeactivity to the environment. The vasodepressor responses are mediated by neurons of the ventromedial medulla (VM) and nucleus raphe pallidus, which inhibit the sympathoexcitatory neurons of rostral VLM. PAG is a critical component of the pain modulation network that exerts a dual control, inhibitory or excitatory, on nociceptive transmission in the dorsal horn and trigeminal nucleus. The balance between inhibition and facilitation of nociception is dynamic and can be altered in different behavioral, emotional, and pathologic states [63, 69]. The PAG exerts its pain modulatory effects primarily via its descending projection to the rostral VM (RVM). The RVM exerts a bidirectional control on spinal nociceptive processing via two types of cells: off-cells and on-cells. Off-cells are activated by opioids and inhibit nociception; on-cells are inhibited by opioids and promote nociceptive responses.

Functional organization of autonomic nervous system

The autonomic nervous system is structurally and functionally positioned to interface between the internal and external milieu, coordinating bodily functions to ensure homeostasis and adaptive responses to stress.

Afferent fibers consist of lightly myelinated Aδ fibers and unmyelinated C-fibers conveying to visceral afferent neurons. Afferent neurons are located in vagal, glossopharyngeal, facial, and spinal ganglia. They project to NTS and then to PBN directly or via the preganglionic neurons in the dorsal horns.

Central control of the sympathetic and parasympathetic outputs involves several interconnected area distributed throughout the neuraxis. This central autonomic network (CAN) has a critical role in moment to moment control of visceral function, homeostasis, and adaptation to internal or external challenges.

The functions of the CAN are organized in four hierarchical levels that are closely interconnected: spinal, bulbopontine, pontomesencephalic, and forebrain levels [70, 71].

The spinal level mediates segmental sympathetic and sacral parasympathetic reflexes and is engaged in stimulus-specific patterned responses under the influences of the other levels. The sympathetic output is critical for maintenance of arterial pressure, thermoregulation, and redistribution of regional blood flow during stress and exercise. The sympathetic output originates from preganglionic neurons located in the thoracolumbar spinal cord at the T1–L2 segments primarily in the intermediolateral cell column. The parasympathetic outputs are represented by a cranial component originating from the nuclei of III°, VII°, IX°, X° cranial nerves and a sacral component originated from neurons located in the lateral gray matter at the S2–S4 segments.

The bulbopontine (lower brainstem) level is involved in reflex control of circulation, respiration, gastrointestinal function, and micturition. It includes the NTS and the ventrolateral reticular formation of the medulla and medullary raphe.

The pontomesencephalic (upper brainstem) level integrates autonomic control with pain modulation and integrated behavioral responses to stress. The pontomesencefalic areas controlling autonomic output are the PAG involved also in the coordination of the micturition reflex and control of respiration and the PBN involved in interoception, but also participating in the control of respiratory, cardiovascular and gastrointestinal functions.

The forebrain level includes the hypothalamus, which is involved in integrated control of autonomic and endocrine responses for homeostasis and adaptation and components of the anterior limbic circuit, including the insula, ACC, and amygdala, which are involved in integration of bodily sensation with emotional- and goal-related autonomic responses [72].

Nociception and CAN interactions

It is evident from the above description of the functional anatomy of pain perception and CAN that they largely correspond and that there is a strong integration of nociceptive and visceral information at the levels of the dorsal horn, NTS, PBN, A1/C1 groups, thalamus, hypothalamus, amygdala, insular cortex and between lamina I neurons (originating from the progenitors of autonomic interneurons) and the sympathetic cell columns of the thoracolumbar segments [6, 51].

Spinal and trigeminal nociceptive pathways provide collaterals that converge at every level with projections of the brainstem visceral pathways. The NTS receives taste, oesophageal, gastric, intestinal, and respiratory afferents but it also receive nociceptive information from the dorsal horn and the trigeminal nucleus caudalis (TNC). Some NTS neurons respond to both nociceptive and visceral input. Trigeminal and spinal inputs to different columns of the PAG elicit specific autonomic, motor, and pain modulatory responses determined by the nature of the pain stimulus and the subjective reaction to it (behavior). The PBN receives most of the ascending NTS projection, but also converging nociceptive and viscerosensitive input from lamina I. The PBN projects to the majority of the CAN structures including the central nucleus of the amygdala, thalamus, hypothalamus, PAG, and medulla [51]. The superior salivatory nucleus is activated by medullary reflexes via the TNC and NTS and by descending hypothalamic influences triggered by environmental stimuli. The thalamic areas receiving visceral inputs from the PBN is adjacent to that receiving nociceptive and thermoceptive spinothalamic and trigemino-thalamic pathways. The posterior hypothalamus (Hypocr/Orxs neurons) and the paraventricular nucleus are sites of integration of trigeminal, visceral, environmental, and circadian information and are involved in the integration of autonomic, antinociceptive, and pain modulatory responses [73]. The insula is the primary viscerosensory cortex and is also the primary cortical area receiving pain and temperature informations.

In summary, the activity of the cortical and subcortical areas classically observed in response to nociceptive stimuli constitutes a network involved in detecting salient sensory events in order to prioritize their access to attentional and executive functions. Through biasing operations, the main function of the proposed salience detection system [74] would be thus to facilitate the processing of behaviorally significant (e.g., potentially threatening) sensory input and to select the appropriate response, regardless of whether this input is conveyed through nociceptive pathways. This view does not imply that the cortical processing underlying the salience detection system does not contribute to the experience of pain. On the contrary, it highlights the fact that such a system subtends one of the most important functions of the nociceptive system, namely the ability to detect salient changes and, possibly, to integrate them into a peripersonal representation of our body. In other words, the salience detection system would represent a network by which we react to a wasp when viewing the wasp approaching the hand, but even before being stung by it [74].

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

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