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Research Article

Ascending Nociceptive Afferent Systems

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Abstract

Chronic pain is a significant public health problem affecting up to 40% of the European population. Although understanding of the pathomechanisms underlying chronic pain has increased over the past decades, the exact mechanisms leading to the development and maintenance of chronic pain remain unknown. Nevertheless, the identification of the underlying pathomechanism is a prerequisite for more successful approaches to the treatment of chronic pain.

Keywords: nociceptive; afferent systems; nervous system

Introduction

Chronic pain is a significant public health problem affecting up to 40% of the European population. Although understanding of the pathomechanisms underlying chronic pain has increased over the past decades, the exact mechanisms leading to the development and maintenance of chronic pain remain unknown. Nevertheless, the identification of the underlying pathomechanism is a prerequisite for more successful approaches to the treatment of chronic pain [1].

There is often a discrepancy between the supposed peripheral pain generator and the severity of chronic pain. This discrepancy or non-linearity in the input-output relationship can be partially explained by the imbalance of endogenous pro- and antinociceptive modulation of pain. Patients with chronic pain often show a shift towards pronociceptive modulation in neural networks, possibly due to central sensitization. Although the existence of central sensitization has been demonstrated in animal models, it cannot be directly assessed in humans. From a clinical point of view, "human-assumed" central sensitization is usually reflected in advanced patterns of pain and widespread hypersensitivity. In addition, several experimental approaches have been proposed to indirectly study the hypersensitivity of central pain networks in humans, including experimental pain addiction. In particular, pain habituation is reflected as a decrease in response after repeated painful stimulation and can be assessed using various subjective and objective indications, such as pain assessments and pain-related brain potentials. In addition, addiction to sympathetic skin reactions associated with pain (SSR) can be used as another objective indication, using a complex multilevel interaction between nociceptive and autonomous systems. The value of studying multiple indications of pain addiction lies in the fact that it allows for a more comprehensive study of nociceptive processing [1]. An overall decrease in pain habituation in patients with chronic pain will occur compared to HC, which will be most pronounced in the subgroup of patients with "human" central sensitization, regardless of the etiology of pain. Moreover, we hypothesized that patients with reduced pain habituation would report more widespread/intense pain and higher rates of depression, anxiety, and pain catastrophization [1].

The involvement of the reticular formation of the brain stem (RF) in the transmission and modulation of pain is well known. We have come a long way since the first anatomical studies that demonstrated that RF is projected into the thalamus, functional approaches that show that RF manipulation alters behavioral nociceptive responses, and imaging studies in humans that indicate RF activation in response to pain. Studying the role of RF in pain is difficult for anatomical and functional reasons. Anatomically, RF is defined as a cluster of neurons with several morphological configurations and without a clear connection pattern. Functionally, and in addition to the sensory component of pain, RF is involved in a variety of functions that include arousal, motor reactions, cardiovascular control, and visceral functions. This anatomical and functional complexity of the Russian Federation has turned neuroscientists away from a global study of Russia's involvement in pain processing, and most of the research has focused on specific areas of the Russian Federation. Taking into account the concept that pain control cannot be studied separately from other brain functions, as well as the internal feature of the RF as an excellent brain network, it is possible that the RF is an outstanding example of a "dynamic pain connectome" [2].

Most sensory systems include parallel sensory information pathways that encode various characteristics of a stimulus, as well as participate in controlling sensor movement. The rodent vibrissus system is no exception. Ascending signals in the vibrissus system travel along two main trigeminothalamic pathways: (1) the lemniscus pathway, which originates in the main nucleus of the trigeminal nerve (PrV), passes through the ventral posterior medial nucleus (VPM) of the thalamus and projects into the primary somatosensory cortex; (2) The paralemniscus pathway, which originates in the rostral part of the interpolar nucleus of the trigeminal nerve (SpVIr), passes through the posterior group (Po) of the thalamus and projects into the somatosensory cortical regions and into the motor cortex of the vibrissae[3].

The lemnisk pathway transmits tactile information, as well as information about the relative phase of the vibrissae in the wave cycle. The role of the paralemnisk pathway remains mysterious. It has been suggested that this pathway conveys information about the kinematics of the swing, but more recent studies have shown that the encoding of the swing along the paralemniscal path is relatively weak. It has also been suggested that the paralemniscus pathway is activated specifically by pain stimulation, but it has never been shown that interpolar cells that respond to vibration deflection are also activated by pain stimulation. Thus, the general function of the paralemnisk path remains unresolved [3].

Classical pathways use the ventral thalamus, whose neurons project into the primary auditory cortex, while nonclassical pathways use the medial and dorsal nuclei of the thalamus, which project into the secondary auditory cortex and associative cortex, thus bypassing the primary cortex [7].

DNLL neurons are not only non-selective, but their responses to species-specific screams are simple in the sense that information processing is linear, and reactions triggered by even complex signals can be predicted using the excitatory tuning of the neuron. These features can be demonstrated by folding the region of the excitatory response of a neuron, a range of frequencies that cause discharges with a fixed intensity, with the spectral characteristics of each signal [8].

The spinothalamic tract is a sensory tract that carries nociceptive, temperature, rough touch and pressure from our skin to the somatosensory area of the thalamus. It is responsible for our rapid withdrawal response to a painful stimulus, such as touching a hotplate. The spinothalamic tract consists of two adjacent pathways: anterior and lateral. The anterior spinothalamic tract carries sensory inputs about rough touch. The lateral spinothalamic tract carries information about pain and temperature. These two sections of the spinothalamic tract run next to each other indistinctly. The spinothalamic tract is a part of the anterolateral system, which also encompasses the spinoreticulothalamic tract and the spinotectal tract. Three types of sensory fibers are associated with the spinothalamic tract: type III fibers, unmyelinated C fibers, and myelinated A-delta fibers. Peripheral receptors associated with the spinothalamic tract pathway are nociceptors, thermal receptors, and thermal nociceptors. Nociceptors are connected to A-delta and type III fibers, which are small, slightly myelinated axons for transmitting rapid, acute pain. Thermal receptors and thermal nociceptors are connected to the A-delta and C fibers, which are small, unmyelinated axons that transmit slow burning pain [11]. Nociception provides a means of neural feedback that allows the central nervous system to detect and avoid harmful and potentially destructive stimuli in both active and passive settings. The sensation of pain is divided into four major types: acute pain, nociceptive pain, chronic pain, and neuropathic pain. Nociceptive pain arises from tissues damaged by physical or chemical agents, such as trauma, surgery, or chemical burns, while neuropathic pain arises from diseases or injuries mediated directly by sensory nerves, such as diabetic neuropathy, shingles, or postherpetic neuralgia. Nociceptive signals cease with the cessation of the stimulus, dephosphorylation and suppression of the receptor, or after the influx of calcium through open membrane proteins causes the nociceptive nerve terminal to collapse and become immune to repeated stimulation in both neural and secretory mechanisms. The destruction of the nociceptor after stimulation confirms the conclusion that harmful stimuli adapt quickly, and their conscious perception quickly weakens as soon as their peripheral activity stops [12]. Supraspinal regions of the brain alter nociceptive signals in response to various stressors, including stimuli that raise the pain threshold. The medulla oblongata has previously been involved in this type of pain control, but the neurons and molecular circuits involved have remained elusive. Once activated, these neurons produce bilateral direct inhibition, which weakens nociceptive responses through a pathway involving blue spot and norepinephrine in the spinal cord. This pathway is sufficient to reduce injury-induced thermal allodynia and is necessary for counter-stimulus-induced analgesia to harmful heat [13].

Nociceptors are plastic in their physiology and in no case return to normal function after injury. An increase in sensitivity and a decrease in the stimulus threshold are often recorded after injury, when, for example, lower mechanical pressure can now cause nociceptor activity, whereas intact nociceptors require higher pressure. This phenomenon is called sensitization and is often observed during inflammation [14].

Research methods.

The results and their discussion.

The involvement of the spinoreticulothalamic pathway as the main ascending pathway for nociceptive transmission to the brain is well known. In general, this multisynaptic pathway originates from neurons located mainly in the plates of the spinal cord IV–V and VII–VIII target areas of the medullary and pontine RF, which have collaterals of the spinothalamic tract. The role of RF as a relay to the medial thalamus has emerged, which has given RF an interesting perspective on its involvement in motivational-affective components of pain. As for the regions of the RF that directly receive nociceptive information from the spinal cord, our research group conducted extensive neuroanatomical studies on tracking tracts, which showed that spinal neurons projecting to VLM or DRt are strongly activated in response to several types of nociceptive stimuli [2].

The reticular formation is closely related to the coordination of motor reflexes of the brain stem. The important role of its various departments inthe development and control of eye movements and chewing reflexes has been established.

Afferent impulses from the visual and vestibular systems, which closely interact in certain structures of the brainstem in order to maintain a clear image on the retina and maintain the balance of the head and trunk, converge not only on the vestibular nuclei, but also on the reticular formation. The main structures on which such convergence was found are the medial nuclei of the ponto-mesocephalic reticular formation, the giant-cell reticular the nucleus and periangular nuclei, also referred to as reticular. In turn, these structures are monosynaptically and dysynaptically connected via interneurons of the oculomotor or vestibular nuclei to motor neurons of the external muscles of the eye [4].

The involvement of RVM as the most important relay station against pain-modulating actions arising from PAG is well known. In animal studies, RVM has been shown to play a peculiar bidirectional role in controlling spinal cord pain, namely balancing inhibitory (antinociceptive) and facilitating (pronociceptive) effects in the spinal cord. One of the most well-established neurobiological mechanisms of bidirectional RVM control is the existence of two classes of neurons in RVM. OFF-neurons

are involved in pain suppression, and their electrophysiological responses are suspended when the animal exhibits nocifensive behavior. On the contrary, OH neurons are involved in pain relief because their electrophysiological activity increases immediately before the nociceptive withdrawal reflex appears. In addition to the two types of neurons, RVM also contains neutral neurons that exhibit electrophysiological activity unrelated to the identified animal behavior. The coexistence of antinociceptive and pronociceptive systems in human RVM has been studied only recently. This delay in evaluating the estimated translational prospects for the existence of OFF- and ON-neurons is mainly due to the limitations of imaging techniques when studying small areas such as RVM. Initial imaging studies that assessed RVM activation in healthy volunteers confirmed activation of this region of the FR in response to nociceptive stimulation in healthy volunteers. More recently, using a whole-brain imaging protocol optimized for the brain stem, it became possible to demonstrate various clusters of activity in RVM of healthy volunteers that correspond to antinociceptive and pronociceptive activity of OFF- and ON-neurons, respectively. The translational prospects of this recent imaging study should be evaluated in the future, namely to analyze whether activation of the pronocic components of RVM increases in patients with chronic pain, similar to the well-known results in animal models [2].

In addition to the spinothalamic pathways, the nociceptive input from the spinal cord goes back in parallel to many other areas of the brain. Anatomical studies on monkeys revealed spinal projections to the pontomedullary reticular formation, parabrachial nucleus, locus coeruleus, periaqueducal gray, upper mound, reticular formation of the midbrain, pale globe, central nucleus of the amygdala and hypothalamus. Many of these areas are projected into the thalamus or other areas that provide further transmission of nociceptive information [5].

The dendrites of thalamocortical neurons define the main group of 6-8 neurons. Afferents of different pathways (for example, the medial lemniscus in the VBc) determine several synapses at once in a large number of dendrites of this group of neurons. This principle of organization ensures the synchronous activation of the entire group of neurons under the influence of the same afferent hall, which provides the possibility of accurate signal transmission. And such properties of neurons in relay nuclei as minimal adaptation to intracellular currents and the absence of significant differences in the thresholds of the membranes of the initial segment and soma also ensure the preservation of linear connections with the input-output characteristic of the relay nucleus [6].

Multiple areas of the cerebral cortex receive parallel input from the thalamus and are located just one synapse away from the direct spinal nociceptive input. Moreover, these areas of the cerebral cortex are closely interconnected, which ensures a parallel flow of information. According to this anatomical organization, human studies show that classical somatosensory regions such as SI and SII are activated in parallel with harmful stimulation. In addition, the intracranial EEG shows that areas such as the posterior insular lobe, SII, middle cingulate cortex, and amygdala are also activated in parallel. Next, other areas without direct spinal nociceptive input are activated - the anterior insular lobe, frontal operculum, preclinium, and dorsolateral prefrontal cortex. Finally, areas such as the posterior parietal cortex and the perigenual cingulate cortex are activated last of all.In accordance with this parallel distribution of nociceptive inputs to the thalamus and the cerebral cortex, a wide range of human brain regions show a gradual increase in activation in response to a gradual increase in the intensity of harmful stimuli. These include the bilateral parts of the thalamus, the contralateral SI, the bilateral SII, the bilateral posterior insular lobes, the bilateral anterior insular lobes, the bilateral anterior cingulate gyri, and the bilateral sections of the putamen. Moreover, these areas are activated depending on the perceived intensity of the pain. This widespread dissemination of intensity-related information is notable because it covers areas ipsilateral to stimulation, as well as areas such as the anterior cingulate cortex, which are usually associated with affective rather than sensory-discriminating processing [5].

Parkinson's disease (PD), multiple systemic atrophy (MSA), and progressive supranuclear palsy (PCP) are neurodegenerative diseases characterized by very similar motor symptoms, which makes it difficult to differentiate them in their early stages, despite the presence of pronounced molecular pathology. A number of magnetic resonance imaging (MRI) techniques have been used to identify areas of brain pathology in Parkinsonian syndromes. Previous imaging studies have revealed pathological changes in the white matter with some involvement of the cerebral cortex [9]. We studied the specificity of neuronal responses to active movement and touch in three parallel trigeminal pathways by recording from 67 individual neurons located in the corresponding thalamic stations in rats under anesthesia. The facial nerve was stimulated at a frequency of 83 Hz for 100 ms to induce protraction (forward movement of all whiskers), and then left without stimulation for 100 ms to allow passive retraction. Thus, repetitive whipping movements were induced with a frequency of 5 Hz, which is within the natural whipping speed, in trains lasting 2 seconds and intervals between trains of 3 seconds. During the sensory blocks (consisting of 12-24 sequences each), a pole with a diameter of 2 mm, located at a distance of 70-90% of the length of the whisker, was vertically positioned on the trajectory of the main whisker of each registered neuron. Not a single object was represented in the free-air blocks [10].

The path of the spinothalamic tract to the cerebral cortex begins with the ganglia of the dorsal roots, which consist of pseudounipolar neurons with peripheral (distal) and central (proximal) axonal processes. These ganglia of the spinal roots lie next to the spinal cord and represent a first-order neuron of the spinothalamic tract pathway. The axons of the central process of first-order neurons enter the spinal cord through the entry zone of the lateral spinal roots to enter the Lissauer tract and synapses with second-order neurons in a gelatinous substance located in the gray matter of the spinal cord. The axons of second-order neurons cross the spinal cord on the opposite side two segments above the entrance level through the anterior white commissura, unlike the path of the posterior medial loop, which crosses in the brainstem. The intersecting fibers of the second neuron enter the anterolateral part of the spinal cord, and then enter the brain stem in the form of a spinal loop. The spinothalamic tract rises in the ventrolateral part of the cerebrospinal white matter along the entire length of the spinal cord. The anterolateral system in the rostral medulla oblongata runs between the inferior olive nucleus and the nucleus of the cerebrospinal trigeminal tract, whereas in the bridge and midbrain the anterolateral system runs dorsolaterally to the medial loop [11]. Nociceptive neurons are a component of the peripheral nervous system. Nociceptive neurons arise from neural crest stem cells that migrated from the neural tube before it closed. More precisely, nociceptors develop from a dorsal population of neural crest stem cells in neural crest tissue. Although the transcription factors necessary for nociceptive differentiation remain unknown, all nociceptive neurons express the tropomyosin receptor kinase A to nerve growth factor [12].

Pain stimuli are detected by peripheral nociceptive neurons, which then transmit signals to higher brain centers to create appropriate sensory perceptions and regulate physiological and behavioral responses. These reactions can be modulated by descending circuits, which implies a change in the activity of spinal cord neurons. These downstream circuits often produce context-dependent effects, where pain modulation is likely

to have an adaptive advantage. For example, pain responses are suppressed during purposeful activities such as feeding, whereas injury can lead to pain relief, which can be adaptive to ensure optimal tissue repair and regeneration [13].

Harmful stimuli are defined as those that can or do cause tissue damage, such as high mechanical pressure, extreme temperatures (<10°C and >40°C in mammals), and chemicals such as acids. Many studies have now revealed many somatosensory nociceptors from both the periphery and from internal organs and deep tissues. Unlike touch and pressure receptors, nociceptors have free nerve endings and usually consist of two types of fibers: small myelinated A-delta fibers and smaller unmyelinated C fibers. Electrophysiological and anatomical studies make it possible to determine these types of fibers by myelination (or lack thereof), fiber diameter, and conduction velocity. The diameter of the C fiber is relatively smaller and conducts more slowly than the A-delta fiber. A number of types of nociceptive C-fibers have been identified in mammals, which are sensitive exclusively to mechanical action or additionally react to cold or heat, or are called "dumb" because they react to heat only in the case of sensitization [14].

The modulation of pain is believed to be controlled by multiple brain nuclei. Spinal-projecting neurons in the ventral blue spot and in the rostral-ventral medulla oblongata release norepinephrine and serotonin, respectively, and they modulate the activity of nociceptive spinal circuits. In addition to norepinephrine and serotonin, the ventral blue spot and the rostral-ventral medulla oblongata release other transmitters that affect nociceptive responses, and other brain nuclei can also alter nociceptive signaling, including through corticospinal and bulbospinal pathways [13].

Pain is the most common sign that leads to the diagnosis of cancer and remains the most frightening symptom for patients throughout the course of the disease. Cancer pain is not a homogeneous and clearly understood pathological process. There is a wide range of different types of cancer that require individual assessment and treatment. In addition, not every pain in cancer patients is caused by an active tumor. The physiological mechanisms of cancer pain are generally described as nociceptive, inflammatory, or neuropathic. The main approach to cancer pain treatment is based on the World Health Organization's Cancer Pain relief method. This approach is based on the concept of matching the strength of analgesia to the severity of pain, ranging from basic analgesics to strong opioids. Other approaches include adjuvant analgesia, corticosteroids, radiotherapy, and interventional procedures [15]. Opioid receptors modulate pain pathways at both presynaptic and postsynaptic levels to exert analgesic effects. Presynaptically, they block calcium channels on nociceptive afferent nerves, thereby suppressing the release of neurotransmitters that promote nociception (such as glutamate and substance P). Their postsynaptic effect includes the opening of potassium channels that hyperpolarize cell membranes, suppressing spike activity (by increasing the necessary action potential to generate nociceptive transmission [16]).

The sensation of pain is characterized by enormous interindividual variability. A variety of biological and psychosocial variables contribute to these individual differences in pain, including demographic variables, genetic factors, and psychosocial processes. For example, gender, age, and ethnic differences in the prevalence of chronic pain conditions have been widely reported. Moreover, these demographic factors were associated with a response to experimentally induced pain. Similarly, both genetic and psychosocial factors contribute to clinical and experimental responses to pain. It is important that these various biopsychosocial influences interact with each other in a complex way, forming the sensation of pain. It has been found that some genetic associations with pain vary depending on gender and ethnicity. Numerous epidemiological data show that chronic pain is more common among women than among men. These results relate to chronic pain in general, but gender differences in the prevalence of specific pain conditions have also been reported. Indeed, women are at greater risk of the most common chronic pain conditions, including migraines and tension headaches, lower back pain, fibromyalgia and widespread pain, temporomandibular joint disorders, irritable bowel syndrome, and osteoarthritis. Some studies have examined gender differences in the severity of acute and chronic pain, and in general, any gender differences identified were inconsistent and small in magnitude [17].

Thalamic pain syndrome is a chronic and disabling neuropathic pain disorder observed after a cerebrovascular incident of the thalamus. This is an unfortunate outcome after a cerebrovascular accident. The pain experienced by the patient is centralized, neuropathic, and associated with changes in temperature. Patients often suffer from hyperalgesia and allodynia. The prevalence of thalamic pain syndrome after stroke is relatively high, accounting for up to eight percent of cases. Thalamic pain syndrome is a type of centralized pain. With centralized pain, the source of the pain area comes from the central nervous system. Central pain sensitization occurs when the patient's nervous system is constantly in a state of high activity. The constantly activated state reduces sensitivity to action potentials. Increased activation of the action potential leads to increased neural signaling. Patients become hypersensitive to pain. This state of heightened alertness is commonly known as hyperventilation; clinically, it is known as temporal summation. Traditional treatments for chronic pain and central pain include antidepressants, convulsants, and opioid analgesics. A systematic review and meta-analysis have shown limited evidence for the use of amitriptyline, opioids, anticonvulsants, transcranial magnetic stimulation, and acupuncture in the treatment of central post-stroke pain [18].

The opioid epidemic has led to serious research into the use of opioids to treat pain. Opioid drugs are effective because of the expression of opioid receptors throughout the body. These receptors respond to endogenous opioid peptides, which are expressed as polypeptide hormones that are processed by proteolytic cleavage. Endogenous opioids are expressed throughout the peripheral and central nervous system and regulate many different neural circuits and functions. One of the key functions of endogenous opioid peptides is to modulate our responses to pain. The ventrolateral circulatory gray matter integrates information from cortical and subcortical regions to modulate a variety of different behavioral responses, including defensive responses to pain, threat, and stress, as well as cardiovascular and respiratory control, lactation, and feeding [19]. Opioid receptors and endogenous opioids are inextricably linked to nociception and pain. The endogenous opioid system, which consists of three G-protein coupled receptors, namely the μ-, δ- and κ-receptors and their corresponding ligands β-endorphin, enkephalin and dynorphin. In mammals, these receptors and substances are located mainly in areas involved in conducting and processing nociception and pain, and endogenous substances provide analgesia in the central and peripheral nociceptive systems. Peripheral opioid receptors are found primarily in primary sensory neurons, but these receptors are largely inactive until the neurons are innervated by harmful stimuli. Opioids are one of the two main classes of analgesics, and, for example, they have a peripheral antinociceptive effect on inflammation. Morphine, the most well-known drug, acts mainly through the m-opioid receptors and is used in the treatment of severe pain conditions. However, side effects such as tolerance, respiratory depression, and constipation reduce their effectiveness, and other opioid medications are being developed [14]. Opioid resistance describes the inability to obtain adequate pain relief with therapeutic doses of opioid analgesics. Risk factors for opioid resistance (potentially leading to problematic opioid use) in people with

cancer have been reported and include young age, neuropathic pain, and low alkaline phosphatase activity [16].

The dopamine center of the midbrain includes a key network for reward, significance, motivation, and mood. Data from various clinical and preclinical settings indicate that the dopamine circuit of the midbrain is an important modulator of pain perception and pain-induced anxiety and depression. Clinical studies over the past 40 years show that the comorbidity between chronic pain and depression is close to 50%. Chronic pain conditions contribute to a number of neuroendocrine adaptations in all CNS networks that modulate mood and cognition, including the mesolimbic dopamine circuit. In humans, maladaptation in the plasticity of the nucleus accumbens is associated with depression and other mood disorders [20].

Inflammatory reactions include cell breakdown, release of cellular contents, and degranulation of mast cells. Ion channels are affected in such a way that nociceptors become sensitized. This increased sensitivity of the painful area is thought to be beneficial because it promotes behaviors that protect the area and promote healing. However, in clinical settings, this can go wrong and lead to neuropathic pain, when previously harmless stimuli now cause pain (allodynia) and/or hyperalgesia, when previously painful stimuli become more painful. Evidence of sensitization has been collected in non-mammalian animals [14].

Conclusions.Neuropathic pain is associated with sensitization of spinal neurons, an active-dependent expression of hypersensitivity of spinal neurons. Electrophysiological studies indicate the contribution of DRt to the maintenance of spinal sensitization during neuropathic pain. Recent studies conducted by our group indicate that noradrenergic modulation of DRt contributes to the relief of DRt pain during neuropathic pain. We have shown that nociceptive stimulation increases the release of norepinephrine in DRt, which enhances pain relief from DRt by activating α1-adrenergic receptors. Reducing the release of norepinephrine in DRt using a viral vector derived from HSV-1, which selectively reduced the synthesis of norepinephrine in the noradrenergic afferents of DRt, significantly weakened the behavioral manifestations of neuropathic pain for almost 2 months. Our studies also show a violation of the inhibitory feedback function of α2-adrenergic receptors in the DRt during neuropathic pain, which probably further contributes to increased noradrenergic input into the DRt during neuropathic pain. Increased noradrenergic neurotransmission in the DRt, which enhances pain relief from this area, raises an important question related to the treatment of neuropathic pain with antidepressants that inhibit norepinephrine reuptake. Norepinephrine reuptake inhibitors are known to induce analgesia due to spinal action, but our results also show that they can enhance pain relief from the brain, thus counteracting their analgesic effects in the spinal cord.

Irreversible changes should also be considered during the installation of chronic pain, as it has been demonstrated that PVM suffers from neurodegeneration during the installation of neuropathy. In the initial phases of neuropathy, RVM demonstrates plastic changes in terms of its involvement in downward modulation, namely by increasing the activity of ON-neurons contributing to pain, and vice versa for OFF-neurons, along with increased pain effects in the spinal cord mediated by local 5-HT3 receptors. Collectively, these changes lead to increased relief of descending pain, which may explain the setting of chronic pain. During the progression of pain and due to the continuous barrage of nociceptive input from the spinal cord, local RVM circuits are disrupted with the appearance of massive damage by oxidative stress and hyperactivation of glial cells. Subsequent neuroinflammation can lead to neurodegeneration associated with the loss of neurons, which is a non-plastic effect of installing chronic pain in RVM. Neuroplastic changes in key downstream modulating regions of pain have been shown to be crucial for the onset and maintenance of chronic pain. The research collected here strongly suggests that changes occurring in the RVM-VLM-DRt triad during chronic pain are also fundamental for its maintenance. In addition, our results emphasize the need to take into account the changes occurring at the RF levels in order to develop effective treatments for chronic pain [2].

The main function of the spinothalamic tract is to transfer pain and temperature through the lateral part of the pathway and rough touch through the anterior part. The spinothalamic tract pathway is an imperative sensory pathway for human survival, as it allows a person to escape from harmful stimuli by transferring information about pain and temperature from the skin to the thalamus, where it is processed and transmitted to the primary sensory cortex. The primary sensory cortex interacts with the primary motor cortex, which is located next to it, to generate rapid movement in response to potentially harmful stimuli. In addition, the spinothalamic tract plays a role in responding to pruritogens, making us itch. Interestingly, itching suppresses the response of neurons in the spinothalamic tract to the effect of histamine [11]. Every day, patients seek medical help after injuries related to high fever, extreme cold, significant mechanical force, or exposure to harmful chemicals. Patients are aware of their injuries only because of the functional nociceptors that are located throughout the body. Nociceptors convert acute pain into inflammatory pain when the duration of the stimulus persists, and nociceptors release their pro-inflammatory markers, sensitizing local, responsive cells [12]. Comparative studies have provided fundamental information about the conservative mechanisms underlying nociception and the properties of nociceptors. Many electrophysiological and anatomical aspects of nociceptors are identical in different animal taxa; thus, invertebrate models have provided exciting insights into the physiology and molecular biology of nociception. Expanding research on animals with simpler nervous systems may allow faster progress in understanding the basic science of nociception and lead to the discovery of new drugs. Although empirical evidence is growing, groups of vertebrates other than mammals have not been studied sufficiently [14]. Pain is one of the most burdensome symptoms in people with cancer, and opioid analgesics are considered the primary treatment for cancer pain. There is a need to critically review how we use opioids to treat pain in cancer patients beyond the terminal stage of life [16]. Demographic factors such as gender, race/ethnicity, and age are easily quantifiable personal characteristics that are associated with pain and can have important public health implications. However, these factors do not directly affect pain by themselves, but rather serve as a proxy for many underlying processes that modulate pain. Genetic factors are also important variables of individual differences, but they have a distinct advantage because they reflect certain biological pathways that potentially directly affect pain. Psychosocial factors also contribute to individual differences in pain, and in addition to their value as risk markers, many psychological processes are amenable to change and thus may be important targets for intervention. It is important that these numerous biopsychosocial variables interact in a complex way, affecting pain, and several examples of such interactions were discussed above (for example, the interactions of gene X and gene X and psychology) [17].

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