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When pain is useful? - a neuroscience approach

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Abstract

Normally, the amount of pain reflects the degree of injury. Acute pain decreases as the injury heals.
If the pain remains after a normal period for the injury to heal, it becomes chronic pain. Acute pain is a symptom; chronic pain is a disease itself. Chronic pain leads to: depression, stress, weakened immune system, loss of appetite and weight, insomnia. It never has a useful biological function and impedes on the quality of life.

Keywords: acute pain; nociception; chronic pain; sensitization; behavioral approaches;

1. Introduction

The goal of this article is to familiarize the reader with neuroscience data helpful in the management of psychological impact in patients with acute and chronic pain conditions.

The International Association for the Study of Pain (IASP - International Association for the Study of Pain, 2011) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. A notable feature of this definition is the rejection of the position that the pain is caused by stress or tissue damage, with the observation that it is associated with damage, leaving room for

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multiple causes, mediators and moderating structures belonging to the central nervous system (Hale & Hadjistavropoulos, 1997; Gatchel et al., 2007). This definition highlights the two essential components of pain:

- Sensory - discriminative component, i.e. location, duration, intensity, quality. The nociceptive sensation refers to forebrain and diencephalic responses to factors that stimulate nociceptors (peripheral structures situated not only in skin but also in deeper tissues, that respond in a multi-modal nature to potential harmful stimuli) and experienced by a person as pain;
- Affective - motivational component which provides the unpleasant nature of pain. Therefore pain is always subjective, associated with meaning, evaluation, learning and emotional reactions; the same stimulus may be mildly painful to one person and agonizing to another.

This dual aspect of pain nature requires correlation between terms used in psychology to their equivalent in terms of neuroscience. First, as shown above, pain is not equivalent to nociception. Nociception is the neural processes of encoding and processing only noxious stimuli (and no other stimuli) that can lead to the perception of pain. Secondly, when we refer to the perception of pain disorders, we should distinguish between hyperalgesia and hypersensitivity. Hyperalgesia represents an increased response to a stimulus which is normally painful (Stranding, S. et al., 2008). Primary hyperalgesia is felt at the site of injury and is due to peripheral sensitization (sensitization of primary afferents). Secondary hyperalgesia is felt away from the site of injury and is due to central sensitization (sensitization in the central nervous system – CNS, starting with dorsal horn neurons in the spinal cord). Another pain perception disorder is called allodynia, meaning resentment of pain sensation under the action of stimuli that in normal circumstances should not cause pain. It should only be used when the test stimulus is not capable of activating nociceptors. Currently, the only established example of allodynia is pain from dynamic brushing of the skin (e.g., a cotton wisp dragged across the skin). This is done by activation of normally non-nociceptive afferents (e.g., Aβ fibers) to produce pain. While allodynia represents a replacement of a non-painful sensation (tactile, thermal or proprioceptive – muscular) by pain sensation, hyperalgesia represents an increased pain sensation related to a noxious stimulus.

2. Gross anatomy basis

The dual sensory / affective nature of pain is explained by the fact that nociceptive stimuli are transmitted (in all mammals CNS!) to the telencephalon (brain) by two main pathways - the lateral and the medial supraspinal nociceptive pathways (Stranding, S. et al., 2008).

The lateral ascending pathway generates in the cerebral cortex the sensory discrimination of the pain - location, duration, quality, intensity. It is formed by large diameter fibers – the neospinothalamic and neotrigeminothalamic tract, so is fast, somatotopically organized and has small receptive fields. It project to ventral posterior-lateral (VPL) and ventral posterior-medial (VPM) thalamic nuclei; thalamic neurons then project to sensory cortex.

The medial ascending pathway project in many more areas of the brain: reticular formation – including medial and intralaminar thalamic nuclei, periaqueductal gray of mesencephalon, hypothalamus and limbic system – anterior cingulate, insular, prefrontal cortex and therefore gives pain its emotional status. It is formed by thin fibers, it is multisynaptic and therefore slow, has no somatotopic organization but large receptive fields. The main tracts involved in the medial ascending pathway are paleospinothalamic, paleotrigeminothalamic, spinoreticular and spinotectal (spinomesencephalic). Because in mammals the hypothalamus and periaqueductal gray are strongly connected with amygdala, they are critical areas that can spark the expression of both behavioral and autonomic components of aggressive behaviour induced by pain (hence the expression to behave like a “wounded beast”) (Thibault, P. et al., 2008). However, in humans (Homo sapiens sapiens) and bonobo chimpanzee (Pan paniscus) thick connection between the amygdala and the ventral anterior cingulate cortex, which helps control aggression impulses, makes them less aggressive and more empathic in pain condition than their close relatives in primate species (Stranding, S. et al., 2008).

3. Neuronal basis

Different cutaneous afferents encode different types and intensities of stimuli, which is specificity encoding. Low threshold afferents (Aβ and low threshold Aδ fibers) encode innocuous stimuli (e.g., touch, pressure, warm, cool).

They do not encode into the noxious range. Nociceptors do not encode innocuous stimuli and start firing when the stimulus becomes noxious.

Most visceral afferents encode both innocuous and noxious intensities of stimulation; intensity encoding. As the intensity of a visceral stimulus increases into the noxious range, the same primary afferent will continue to encode the intensity.

Cutaneous afferents have discrete projections into the spinal cord dorsal horn. Their terminal arborization extends to 1-2 segments and is confined in the mediolateral and dorsoventral planes. This discrete termination lets cutaneous stimuli be precisely localized on the body surface forming a somatotopic map.

Visceral afferents enter the spinal cord and extend 5-10 spinal segments dropping collaterals along this rostrocaudal extent sending projections throughout the mediolateral and dorsoventral extent, with some collaterals projecting to the contralateral side. This diverse central projection of visceral afferents results in poor localization of visceral stimuli.

The spinal cord gray matter is divided into laminae based on the size and density of neurons. While some laminae are hard to differentiate from others, laminae I, II and IX are very obvious. The size of laminae changes along the long axis of the spinal cord. There is no lamina VI in the thoracic segments. Laminae I-V are considered the dorsal horn (site of sensory processing). Laminae VIII and IX are the ventral horn, concerned with motor output. Lamina IX is the motoneuron pool. Lamina X is the area around the central canal and involved in viscerosensory processing. Based on the terminal distribution of primary afferents, one can predict that the superficial dorsal horn (laminae I, II) and lamina V are involved in processing nociceptive information. Laminae III and IV processes innocuous stimuli.

Aβ fibers transmit innocuous stimuli: brush, touch, pressure, nonnoxious temperature, proprioception. Most Aδ and C fibers transmit noxious stimuli.

In addition, primary afferents that innervate a specific region of the body, for example the toes, will project to a specific area of the spinal cord (lumbar segments). If all the dorsal horn neurons in this area receive input from the toes, and adjacent to this are dorsal horn neurons that receive input from the medial ankle, etc., a map of the body on the surface on the spinal cord begins to emerge: that is the somatotopic map. This map gets preserved at many levels in the nervous system allowing precise localization of the stimulus on the body.

The dorsal horn is composed of 5 types of neurons: the central projections of primary afferents, two types of interneurons (inhibitory and excitatory), projection neurons to upper CNS structures and descending fibers from neurons located in brain stem and diencephalon that modulate neural impulse transmission in the spinal cord.

Interneurons are local circuit neurons. They can receive monosynaptic input from primary afferents or descending fibers. Their axons are generally contained within the same segment as the cell body where they modulate activity of projection neurons. Inhibitory interneurons contain inhibitory transmitters (e.g., GABA, glycine, enkephalin) and inhibit activity of projection neurons either directly by hyperpolarizing the neuron or indirectly by synapsing on the presynaptic terminal of primary afferents inhibiting transmitter release. Excitatory interneurons are also contained within a single segment. They contain excitatory transmitters (e.g., glutamate, substance P) and directly or indirectly increase activity in projection neurons.

Descending fibers from the brainstem or telencephalon modulate activity in dorsal horn neurons either directly or indirectly (via presynaptic actions). Descending modulation can be inhibitory or excitatory.

The most common scheme used to describe dorsal horn central projection neurons is based on their response to cutaneous stimuli:

- Low threshold (LT) neurons receive input from nonnociceptive afferents. LT neurons are most numerous in laminae III-V;
- Wide Dynamic Range (WDR) neurons receive input from nociceptive and nonnociceptive afferents. WDR neurons are most numerous in deeper laminae, IV-V;
- Nociceptive specific (NS) neurons receive input from nociceptive afferents. NS neurons are most numerous in the superficial dorsal horn and are connected by other interneurons in deeper laminae.

3.1. Peripheral sensitization and allodynia

In primary afferent nociceptor signaling, activation means neural or multimodal receptor membrane depolarization by a noxious stimulus, generating an action potential in the primary nociceptive fiber. Sensitization means an increased excitability of nociceptive neuron, generating an action potential as a response to subthreshold stimuli. It results from modulation of cellular proteins leading to changes in ion channel activity with a subsequent increase in excitability of the primary afferent nociceptor. Sensitization of a primary afferent leads to peripheral sensitization and has the following characteristics: decrease in threshold, increase in suprathreshold response and increase in spontaneous activity. Activation does not always lead to sensitization and sensitization can occur without nociceptor activation.

3.2. Central sensitization

Compared to peripheral sensitization, peculiar aspect of central sensitization is the expansion of receptive field. Under normal conditions, pinch in an area of skin (that can be mentioned as area I) activates the normal afferent fiber, exciting a neuron (mentioned as neuron 1) of the spinal dorsal horn, leading to the perception of pinch. A similar process occurs for a neighboring skin area (area II) activating the afferent fiber, and another dorsal horn neuron (neuron 2). The afferent fiber from area II also has a collateral branch that synapses on a distal dendrite of neuron 1, but it has no effect on the excitability of that neuron, it forms a silent synapse in the subliminal fringe. Following injury to the area I receptive field, the first afferent fiber becomes sensitized (peripheral sensitization). The increased afferent input increases the excitability of the neuron 1, making it hyperexcitable (central sensitization). Now a pinch to the area II skin evokes a response in the neuron 1, effectively expanding its receptive field. In addition, the perception of pinch in the area II skin is perceived with greater intensity than normal (neuron 1 is sensitized so any pinch will produce a greater response than normal: hyperalgesia; and there are more dorsal horn neurons transmitting information about this pinch supraspinally) evoking hyperalgesia. Since the skin in area II is normal, there is no peripheral sensitization, so the hyperalgesia is termed secondary hyperalgesia and is centrally mediated.

3.3. Allodynia

In the natural environment, injury (e.g., a cut, a burn, chemical irritation) induces peripheral sensitization which increases afferent input to the spinal cord. The resulting increase in transmitter release leads to a long lasting depolarization of the postsynaptic membrane, similar to windup, but also further activation of metabotropic and ionotropic receptors leading to kinase activation. Phosphorylation of receptors and ion channels further increases ion influx and neuronal excitability. This increase in excitability expands the receptive field of the dorsal horn neuron (input to the subliminal fringe now becomes suprathreshold) leading to secondary hyperalgesia. That is, the increased perception of pain to a noxious stimulus, hyperalgesia occurs away from the site of injury in undamaged tissue. This situation is referred to as central sensitization. Because hyperalgesia is evoked from normal tissue, this cannot result simply from peripheral sensitization and must occur within the spinal cord. Furthermore, this form of plasticity outlasts the initiating stimulus; it can last for hours or days while the initial injury discharge lasts for only seconds or minutes. When this activation lasts for hours to days to weeks, there is a change in gene expression. Certain receptors, ion channels and cellular proteins get up or down regulated, altering the normal excitability of the dorsal horn neuron. This leads to persistent hyperalgesia and allodynia and if it persists beyond the normal healing time of the injury as occurs with nerve injury, this becomes chronic pathological pain.

4. Descending inhibitor systems

The brain can temper pain. Soldiers and athletes perceive less pain than might be expected from an injury. On the other hand, patients with fibromyalgia or irritable bowel syndrome appear to experience pain in the absence of any identifiable cause.

Limbic structures project directly and indirectly to the periaqueductal gray, which projects to reticular formation nuclei (like nucleus reticularis magnocellularis and dorsolateral pontine tegmentum nuclei). These nuclei project to the spinal cord to inhibit nociceptive processing. These descending projections modulate activity in spinal projection neurons either directly by projecting onto dorsal horn neurons, or indirectly by presynaptic inhibition. Opioids work at several levels of this system, each engaging to ultimately inhibit activity in dorsal horn projection neurons (Melzack & Wall, 1988).

But the nucleus reticularis magnocellularis also facilitates nociceptive processing contributing to chronic pain. Importantly, this circuit shows how different areas of the brain can access the descending system. An individual's state of mind can alter the balance of descending inhibition and facilitationn (Stranding, S. et al., 2008). Distraction can attenuate pain while hypervigilance can exacerbate pain.

5. Conclusions

Nociceptive pain is protective. It is due to rapid synaptic transmission by glutamate binding AMPA receptors.

Windup is an increase in the gain of dorsal horn neurons due to slower, longer lasting depolarization of the cell membrane. It is NMDA receptor dependent. Temporal summation is the psychophysical equivalent.

Central sensitization is a longer lasting change in excitability of dorsal horn neurons. Peptides, neurotrophins and glutamate all contribute to increasing cellular excitability. Phosphorylation of ion channels and receptors prolongs the effect resulting in hyperalgesia and allodynia. Longer lasting stimuli (e.g., nerve injury) alter gene expression further prolonging hyperexcitability.

Loss of inhibitory modulation (disinhibition) can permanently increase hyperexcitability leading to chronic pain.

Stress is interesting - acute stress can attenuate pain but chronic stress can exacerbate pain.

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