Supraspinal Modulation: Something to be Remembered

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ABSTRACT

Pain has always been a challenging issue in patients with acute and chronic conditions. Pain results from activation of sensory receptors specialized to detect actual or impending tissue damage. However, a direct correlation between activation and nociceptors and the sensory experience of pain is not always apparent. Emotional state, the degree of anxiety, attention and distraction, past experiences, memories, and many other factors can either enhance or diminish the pain experience. Many active agents are used to block and alleviate pain sensation in acute and chronic settings. When an inadequate treatment for acute pain and neuralgia occurred, it would induce complex processes involving both central and peripheral sensitization contributing to persistent post-surgical pain and worsening neuralgia that would lead to chronic pain issues.

The important thing to be considered is that this pain process is an intertwined, interconnecting and sustainable process that could not be cut abruptly. Our aim is to remind professionals to accept that the pain pathway is not straightforward but rather a convoluting idea that can evolve and expand. Imagining areas could be defined one day through high technology advances and would lead us into defining the depth of this beautiful and complex pathway.

INTRODUCTION

Supraspinal modulation should not be defined merely on the process of modulation stage in pain pathways, but also involving other interconnecting tracts and nuclei which are placed in several places above the medulla. The supraspinal area was deemed as fictitious, incoherent, and imaginary. In other hand, several animal and receptors experiments conducted by biomolecular scientists have found different results. The exact region may not be concluded yet, but there are certainly complex processes occurring in upper pain pathways above the modulation stage consisting of the brain cortex and its related nuclei. These processes would be more active during continuous sensitization starting from central sensitization and altered descending pain facilitation in pain processes which would lead to persistent pain and eventually chronic pain.

The idea of elaborating this supraspinal modulation theory is to build a solid combination of ideas and proven experiment results to occupy the mind of pain physicians and to be enlightened on the bigger perspective of pain pathways and management. Experiments and clinical trials are still ongoing and we have to be prepared to adopt the new advancements and technologies developed by other experts and scientists.

Central Sensitization

There are many pathways that can lead to altered processing in the late phase that can cause central sensitization (CS). Ascending processes are usually the result of injury of psychophysical causes in which the nociceptive neurons are modified and the pain signal becomes sensitized. Descending processes usually are the result of modifications to supraspinal input. Moreover, pain blocks the proper functioning of catecholamines arising from the locus coeruleus, which project to the peri-aqueuductal grey (PAG) and then to the dorsal horn in the spine, diminishing the descending inhibitory effect on nociception.1

Many of those with central sensitization are also chronically stressed prior to the onset of pain. The theory of allostasis provides an explanation for these disorders that is strongly associated with hypocortisolism and dysregulation of the sympathetic nervous system, as well as serotonergic, opioid, and immunological functions. The receptiveness of the autonomic nervous system to physical and psychosocial stressors supports the homeostatic qualities of the pain system. Autonomic nervous system and psychosocial influence would be defined clearly in pain through the emotional motor system (EMS) mechanism.1, 2

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Nociceptive Neurons
A-α and A-β fibres are large-diameter touch neurons responsible for registering proprioception and the ‘normal touch’ sensation. A-δ fibres are medium-diameter nociceptive neurons that transmit noxious mechanical, thermal, and chemical stimuli. C-fibres are unmyelinated, small nociceptors that are responsive to nociceptive input. When a stimulus evokes a signal that falls outside of a ‘normal range’, the signal exceeds the threshold and the nociceptors are activated.1

Modulation of Sensation
There are two principal mechanisms in the modulation of sensation: selective attention and endogenous pain inhibition, that would be further explained in diffuse noxious inhibitory control (DNIC). The combination of these two mechanisms allows the brain to focus the attention on sensations arising from particular body region while tuning out sensory input from all other regions. Brain regions that are important in selective attention systems are the dorsolateral prefrontal cortex and the anterior cingulate cortex.1-2

The rostral portion of the anterior cingulate cortex represents the visceral motor cortex with projections to a network made up of hypothalamic nuclei, amygdala, and PAG. The output of this network reaches nuclei within the brain stem (rostral ventral medulla, locus coeruleus, raphe nuclei) with important roles in the regulation of pain modulation, arousal, and vigilance. This network has been referred to as the emotional motor system (EMS) and related to a specific set of parallel motor pathways governing somatic, autonomic, antinociceptive, and endocrine responses to stressors.1-2

Emotional Motor System (EMS)
Two components of the EMS play a crucial role in modulation of the pain experience in the context of conditioned fear: the amygdala and the PAG. The amygdala receives information about visceral stimuli not only from the visceral motor cortex, the lateral and basolateral nucleus of the amygdala receives projections from the thalamus, nucleus parabrachial, and nucleus gigantocellularis. The latter input reaches the amygdala via noradrenergic projections from the locus coeruleus. The central nucleus of the amygdala sends projections to the lateral and ventrolateral portion of the PAG, mediating opioid and non-opioid mediated analgesia. The connections between the lateral and basolateral nucleus of the amygdala and the central nucleus contain glutamnergic synapses involving both N-methyl-D-aspartate (NMDA) and non-NMDA receptors. The NMDA receptor is involved in the development of long-term potentiation, an important mechanism in the development of emotional memory in the amygdala.1-2

Pain Pathways
The two major ascending pain pathways in mammals are the spinothalamic and the spinoparabrachial tracts. The thalamus and parabrachial nucleus receive information from projection neurons in various laminae of the dorsal horn and then relay this sensory information to cortical and amygdalar regions where the information is decoded as a painful stimulus.1

Pain Modulation
Pain modulation is a degree to which a person reacts to pain which involves pain perception variability and influenced by endogenous and exogenous mechanism. The pain signal facilitation includes peripheral and central sensitization. The central sensitization has already been defined clearly above. While the pain signal inhibition includes spinal/segmental inhibition with its gate control theory, supraspinal modulation, which is the main topic of our discussion, and also pain modulation by opioid neurotransmitter could play some roles in pain modulation too.1

Pain modulation likely exists in the form of a descending pain modulatory circuit with inputs that arise in multiple areas, including the hypothalamus, the amygdala, and the rostral anterior cingulate cortex (rACC), feeding to the midbrain PAG region, and with outputs from the PAG to the medulla.1

Supraspinal Modulation
Supraspinal modulation is one path of pain pathway that would be happened during pain modulation. It is a specific system in the pain pathway that blocks pain transmission in the central nervous system which consists of the PAG and periventricular areas, raphe magnus nucleus (RMN), and pain inhibitory complex (PIC). The PAG and periventricular areas of the mesencephalon and upper pons surround the aqueduct of Sylvius (periaqueductal) and portions of the third and fourth ventricles (periventricular). On the other hand, raphe magnus nucleus is a thin midline nucleus located in the lower pons and upper medulla, and the nucleus reticularis paragigantocellularis, located laterally in the medulla. The PIC is located in dorsal horn of spinal cord and consists of multiple short encephalineric neurons that terminate on central endings of pain conducting afferent fibres.1-3,5

The analgesia occurs in the thalamus, hypothalamus and cerebral cortex by sending neuronal
Signals to the PAG area. The PAG projects neurons contain aspartate and glutamate that stimulate raphe magnus nucleus. Then RMH projects serotonergic neurons, this in addition to noradrenergic neurons projects from adjacent medulla to dorsal horn. They will block pain signals by activating PIC. When this complex is stimulated, encephalin is released and leads to pre- and postsynaptic inhibition of pain transmission.1,3-5

**Opioid Receptor Modulation**

Besides the neurons and areas in supraspinal modulation, this process also related to opioid receptor modulation. The opioid peptides consist of endorphin, encephalin, dynorphin, and endogenous morphine. Neurons using endorphin or encephalin are found in PAG where they inhibit GABA-ergic interneurons that normally suppress the anti-nociceptor neurons. Encephalin is used by interneurons in lamina II responsible for inhibiting the lamina-I nociceptor-specific spinothalamic neurons. Dynorphin could be found in hypothalamus, PAG, reticular formation, and dorsal horn, while endogenous morphine is in terminals forming synapses with neurons having µ-opioid receptors in pain modulation.1,2,5

**Brain Pain Matrix**

Other researchers have used imaging studies to suggest that the pain matrix constantly activates the brain areas by noxious stimuli. These areas often include the rACC, posterior cingulate cortex (pCC), somatosensory cortex 1 and 2, the insula, amygdala and thalamus, and the PAG. The pain matrix concept conceptually represents a collection of brain regions that are involved in neurological functions, including cognition, emotion, motivation, and sensation as well as pain.1,3

**On-Off Cells of Rostral Ventromedial Medulla**

Descending projections from the RVM course through the DLF to the spinal dorsal horn and form synaptic connections with primary afferent terminals and second-and third-order neurons that transmit nociceptive signals to supraspinal sites as well as with interneurons and thus are well situated to modulate nociceptive inputs. Studies by Fields and colleagues led to the identification of a population of RVM neurons that increase firing just prior to the initiation of nociceptive reflex (known as on-cells) and another population of neurons was found to decrease firing (known as off-cells). Both of them were sound to project to the spinal dorsal horn, indicating possible exerting modulatory influences on nociceptive inputs.1

**Serotonergic Role of Pain Modulation**

Stimulation of the PAG or RVM cause release of serotonin in the spinal cord, and intrathecal administration of 5-HT agonists elicited antinociception, whereas intrathecal 5-HT antagonists attenuated SPA from the RVM. Such studies led to the assumption that RVM provided descending serotonergic pain modulation from RVM. The effect of spinal serotonin can be either inhibitory or facilitatory, depending on the receptor subtype activated. Although several observations indicate an important serotonergic role for pain modulation, the precise spinal mechanism involved remains unclear.1,3-5

**Adrenergic Receptors in Pain Modulation**

There are also findings that suggest a contribution of norepinephrine in antinociception associated with descending inhibition. While neither PAG nor RVM contain noradrenergic neurons, both regions communicate with noradrenergic sites related to pain modulation including A5 (locus coeruleus), A6, and A7 (Kölliker-Fuse) nuclei. Activation of α-adrenergic receptors has been shown to inhibit nociceptive transmission at the level of the spinal cord through presynaptic activity, inhibiting release of excitatory neurotransmitters from primary afferent terminal, as well as through postsynaptic sites.1,3-4

**Stress-induced Analgesia (SIA) Associated with Antinociceptive Effects**

Other mechanisms in pain modulation by mediating suppression of pain by stress have been intensively studied. Stress-induced analgesia (SIA) is associated with elevated PAG levels of B-endorphin, and microinjection of µ-receptor antagonists into the PAG or RVM abolished SIA. Opioid microinjection into the amygdala elicits antinociception that is blocked by lidocaine in either the PAG or RVM. These led to the conclusion that SIA can be opioid sensitive and mediated through descending inhibitory pathways from amygdala, the PAG, and through RVM projections to the spinal cord.1,4

**Descending Pain Facilitation**

Activation of descending facilitation after peripheral nerve injury has been associated with pronociceptive changes in the spinal cord. Peripheral nerve injury resulted in enhanced capsaicin-evoked release of calcitonin gene-related peptide (CGRP) from primary afferent fibres in spinal cord sections and upregulation of spinal dynorphin to pathological levels. Manipulations that abolished descending facilitation also abolished dynorphin upregulation and
enhanced release of CGRP. Recent studies revealed that increased concentration of spinal dynorphin can stimulate neurons through increased calcium influx, unexpectedly mediated through the bradykinin receptors. Blockade of spinal bradykinin receptors inhibited behavioural signs of neuropathic pain, visceral pain, and diminished central sensitization.1,3-5

Diffuse Noxious Inhibitory Control (DNIC) Role in Chronic Pain Syndromes
Recent concept of DNIC was formulated from observations made with recordings of spinal dorsal horn units in anesthetized rats in response to peripheral stimuli applied to various parts of the body. Importantly, DNIC was not demonstrated in dorsal horn units that responded solely to noxious, proprioceptive, or innocuous inputs, indicating a requirement for convergent neurons receiving both noxious and innocuous stimuli.1,4

Novelty of Drugs as Targets of Pain Management in Supraspinal Modulation
The concept of supraspinal modulation which consists of a descending pain modulatory system provides many targets for the development of analgesic drugs or adjuncts that enhance the effects of existing analgesics. Opioids act throughout the neuraxis and can relieve pain through activities at cortical and subcortical sites, as well as by activating descending pain inhibitory circuits. Accordingly, α2-adrenergic receptor agonists have been shown to produce antinociception as well as to potentiate the antinociceptive effects of opioids. Moreover, by increasing spinal noradrenergic activity, tricyclic antidepressants and other selective noradrenergic reuptake inhibitors enhance the analgesic effect of opioids and show clinical efficacy against neuropathic pain. It was recently shown that the clinical efficacy of gabapentin may be due to its activation of descending noradrenergic systems and release of norepinephrine in the spinal cord. The cyclooxygenase (COX) inhibitors exert an analgesic effect by inhibition of prostaglandin E-2 (PGE2) synthesis, this reducing peripheral and central sensitization. Recent studies also indicate that inhibition of COX in the PAG promotes an opioid-mediating descending pain inhibition.1,3-5

Advances in Imaging and Technological Studies for Pain Modulation
The advent of neuroimaging studies and technological advances allowing increased spatial and temporal resolution has contributed greatly to our changing perceptions of how pain is integrated and modulated in the central nervous system. Early animal studies described a linear system of pain modulation from the PAG through the RVM and descending to the spinal cord in which envision a complex pain matrix that includes important cortical and subcortical regions and elements of the limbic system as well as midbrain and medullary sites. The concept of a top-down pain modulation system accounts for, or contributes to, pain relief as seen with the placebo effect, stress, DNIC, and the actions of pain-relieving drugs, such as opioids, NSAIDs, reuptake blockers, and possibly gabapentinoids. These modulatory pathways help to explain how personal experience and emotional state, as well as societal beliefs, may alter the experience of pain.1-3

CONCLUSION
Supraspinal modulation, which was theoretically explained many years ago, was not only a theory but has developed into many studies and research targets. We have to accept that we could not adhere to solid and stiff theory and conventional pain management anymore. Pain management would not only be the scope of pain physician but also open up to better challenges for biomolecular scientists, neuroimaging researchers and even psychosocial experts. Collaborative works and projects in this unique supraspinal modulation would lead us to other aspects, other stages of pain pathways, other receptors, new neurotransmitters that would ask for many shared thoughts, ideas and improved theories. The ‘fictional’ supraspinal modulation surely would not be fictitious anymore and could be defined in a progressive objective and therapies.

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