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# MEDITATORS INVOLVED IN TRANSMISSION AND MODULATION OF CHRONIC PAIN

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## *Summary*

This article presents a review of the neurotransmitters and neuromodulators in chronic pain states. Chronic pain, which is associated with prolonged tissue damage or injuries to the peripheral or central nervous system, results from a number of complex changes in nociceptive pathways. The tissue damage evoke interactions between neural and non-neural tissues which are important in producing hyperalgesia by changing membrane excitability and cell phenotype with expression of new molecules, including neurotransmitters, enzymes and chemical receptors. But the transmission of nociceptive information is modulated at the level of spinal cord and at the midbrain level according to the release of various mediators and complexity connections between different area of CNS.

In chronic pain states, an increased neural excitability can be reduced with receptor selective drugs that block central chemical mediators or that control ectopic activity.

**Key words:** Pain, chronic; Pain transmitters; Pain modulators

## **Introduction**

“The astronauts will probably land on Mars in another decade. Unmanned spacecraft the eight billion miles to the farthest borders of our solar system, taking more than eight years to reach that most remote of planets, Pluto. But when man himself ventures out into the most distant reaches of limitless space, he can be certain of only one thing – even there he will still have to face his ancient implacable enemy, pain.

For pain is as old as life itself and as new as your last heartbeat, and life and pain are inseparable, joined together for all eternity. Prehistoric man endured the hurt of arthritis and toothaches, of broken bones and infected ones, of childbirth and disease; and so will man of the twenty-first century”(1).

The Nobel laureate Albert Schweitzer, physician who practiced in the African jungle for two decades, wrote «We must all die. But that I can save him from dazs of torture, that is what I feel as my great and ever new privilege. Pain is a more terrible lord of mankind that even death itself»(2).

Pain is a personal and complex sensory experience that is difficult to describe to another person. In fact, pain is an unpleasant sensory and emotional

experience associated with actual or potential tissue damage or described in terms of such damage (3). Certainly, one of the great paradoxes in pain is that it can be both, a symptom and a disease. As a symptom, acute, transient pain is associated with tissue damage and is a necessary safety signal for survival, protecting us from many of the dangers in our personal world. The chronic, intractable pain is associated with tissue damage, inflammation or neuropathologies, and is a destructive disease turning the sufferer inward until his whole life begins to revolve around his pain (3). Moreover, in chronic pain states there is a superimposition of many other processes onto the basic events of nociception, which alters the relationship between stimulus and the response and affects the ability to modulate the resultant pain state (4). Chronic pain is a complex synthesis of biologic, psychologic, behavioral and neurohormonal – chemical factors (5). There are essentially three sensory centers in modulation of pain (5): the 1st center contains the peripheral receptors with fibers mediating impulses through the dorsal roots to the dorsal horn of the cord; the 2nd center is at the midbrain level and involves the thalamus, reticular system and hypothalamus; the 3rd center contains the cerebral cortex, where the pain is localized and qualified.

In chronic pain, a rudimentary understanding of the complexity of events that occur in nociceptive pathways is beginning to emerge. Some of these events occur in precise time windows during the development and consolidation of the pain state, and can range from changes in the excitability of fine afferent nerves to drastic alterations in their cellular phenotype with the expression of new molecules, including neurotransmitters, enzymes and chemical receptors (5,6).

Chronic central alterations in neurochemistry of pain produce hypersensitivity which enhances and prolongs relatively low levels of afferent input and allows normally innocuous stimuli to become painful. After a peripheral nerve injury, structural changes include loss of spinal interneurons, inappropriate rearrangements of afferent nerve processes in the spinal cord (7) and proliferation of sympathetic fibres into sensory ganglia which are not normally innervated to any significant degree (8,9).

### ***Modulation of receptor's field***

After a peripheral injury a complex cascade of events is initiated. The initial insult results in the activation of the arachidonic acid cascade, which leads to the formation of prostaglandins and leukotrienes. These products are released from tissue and act to sensitize primary afferent terminals (10). Prostaglandins such as PGE<sub>2</sub> and PGI<sub>2</sub> can act directly on the peripheral terminals of nociceptors (11).

The original injury also results in the enzymatic conversion of kininogen into bradykinin (12-14). Prostaglandins (15,16) and leukotriens (17) act in concert with bradykinin to produce an enhanced activation of the primary afferent terminal.

Bradykinin's effects in the periphery are not nonspecific but are mediated by B2 bradykinin receptors, which are located on the terminals of primary afferent neurons (18,19). However, B1 receptors are expressed during prolonged inflammation and make a significant contribution to the hyperalgesia (20,21).

Other inflammatory products including cytokines, such as interleukin1,6 and 8 (IL) and tumor necrosis factor alfa (TNF-alfa), also induce hyperalgesia by facilitating induction of B1 receptors, stimulating prostanoid production, and activating of sympathetic neurons.

5-Hydroxytryptamine (5-HT) is released from platelets and mast cells and produces mild and transient pain by direct activation of sensory neurones via 5-HT3 receptors. 5-HT also induces a direct sensitization of nociceptors via 5-HT1 and 5-HT2 receptors (22,23). A possible basis for sensitization by 5-HT, as well as by bradykinin and prostanoids, is a reduction of the slow inhibitory afterpotential that follows the action potential in some sensory neurones. The inhibition is due to cAMP generation and a reduction of the inhibitory K current. The overall effect is to increase the likelihood that the neurone will respond to a relatively weak stimulus with a train of action potentials rather than with a single spike. Histamine is released from mast cells and evokes the sensations of itch at low concentrations and pain at higher concentrations (24). Probably, these effects are produced by activation of histamine H1 receptors which increase membrane Ca-permeability and the release of tachykinins and calcitonin gene-related peptide (CGRP), resulting in further complex interactions including vascular changes and mast cell degranulation. These inflammatory mediators stimulate vascular endothelial cells to release the vasodilator nitric oxide (NO). NO is important for intercellular communication in peripheral tissue and in the CNS, including nociceptive pathways. This is usually achieved via the activation of guanylate cyclase and the production of cGMP (25). NO does not directly alter sensory neurone excitability, but acts indirectly in the antinociceptive effects of acetylcholine and morphine and promotes tachyphylaxis to bradykinin (26). However, peripheral NO mechanisms may be involved in neuropathic pain since nitric oxide synthase (NOS) is induced in sensory ganglia following peripheral axonal section. Furthermore, both pain and ectopic discharges that occur in peripheral fibres are reduced by NOS inhibition (27). How NOS inhibition alters nerve excitability is unclear, but changes in peripheral blood flow may contribute to this effect.

### *Interaction between neural and non-neural tissue*

The activation of afferent nerves induces an axon reflex and the release of sensory neuropeptides (substance P, neurokinin A, and CGRP). These peptides also change the excitability of sensory nerves nearby postganglionic sympathetic fibres.

They also activate immune cells, alter local blood flow and induce the release of other active substances by plasma extravasation. A number of other peptides, such as a nerve growth factor (NGF), which are normally secreted by target tissues to regulate growth and maintain cellular phenotype of sensory and sympathetic neurones, can be increased by inflammation and nerve damage (28,29). Chemical pain transduction involves interaction with membrane receptors that are coupled to ion channels and the 2<sup>nd</sup> messenger system, resulting in changes of membrane excitability and cell phenotype. In this environment many chemical stimuli are available to initiate cascade of signals. In fact, there is enormous potential for signal amplification and modulation, as well as an opportunity for synergism between neural and non-neural tissues (30). Such interactions are important in producing hyperalgesia.

### *Changes in afferent nerves*

Activation of the primary afferent nerve terminals begins the transmission of nociceptive information. It is the release of nociceptive neurotransmitters from these primary afferent fibres that activates the second-order dorsal horn neurons.

Substance P, neurokinin A (NKA), CGRP, somatostatin and cholecystokinin are all present in small diameter unmyelinated primary afferents that terminate in the dorsal horn (31). In addition to neuropeptides, excitatory amino acids, such as glutamate and aspartate, which act on N-methyl-D-aspartate (NMDA) receptors, also play a distinct role in nociceptive transmission (31-35). Glutamate is co-localized with substance P in the dorsal root ganglion cells and in the central terminals of primary afferent fibres (36). A role for substance P may be to promote the release of excitatory amino acids from the spinal cord, leading to enhanced synaptic transmission. Glutamate mediated transmission is of fundamental importance in the hyperexcitability that is induced in the spinal cord and other central pathways in chronic pain (37). Spinal NMDA receptors are critical for producing "wind up" in the spinal cord. This is characterized by an increase in the excitability and discharge frequency of neurones in the dorsal horn (38). NMDA and peptide receptor mechanisms may also account for the spinal hyperexcitability following

peripheral nerve injury, during which normally innocuous mechanical stimuli, such as light touch, may evoke a feeling of intense pain (5). However, in neuropathic pain, further contribution to central hyperexcitability may occur through loss of inhibitory interneurons by excessive glutamate release (39).

### ***Modulation and transmission in CNS***

Numerous receptor systems have been localized at the dorsal horn of the spinal cord such as opioid, adrenergic, serotonin, GABA, cholinergic, adenosine, neuropeptide Y, calcitonin, somatostatin, neurotensin. Many of these receptor systems may function as specific modulators of nociceptive transmission (40-42).

Although numerous neuropeptides, such as enkephalin, neurotensin and somatostatin are found within the hypothalamus (41,43-46), the functional significance of these neurotransmitters in pain processing is not known.

Because the hypothalamus is highly integrated with limbic structures, the modulation of pain message by emotional states (especially in chronic pain) or prior experiences probably occurs at this level. The hypothalamus may be the activation site of migraine and cluster headaches (47). The posterior thalamus, which contains cells that regulate autonomic function, is closely related to the anterior hypothalamus, which contains the suprachiasmatic nuclei. These nuclei control the principal circadian functions in mammals (46). This may explain the rhythmicity of many pains, including the time related cluster headaches and other pains (46,47).

The hypothalamic pacemaker is mediated by the serotonergic system (47). As in the hypothalamus, numerous neuropeptides and neurotransmitters have been localized within the periaqueductal gray substance (PAG) including enkephalin, dynorphin, neurotensin and substance P (48-52). This region of the midbrain is well characterized site of descending inhibition (53-58). The PAG was the first brain site implicated in morphine produced analgesia (59).

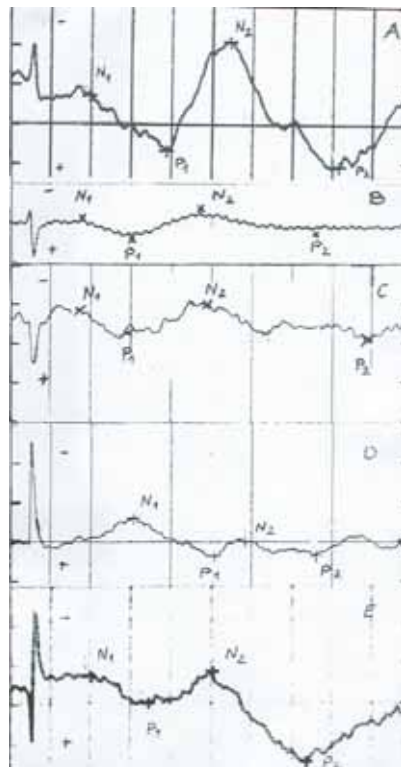
Activation of the PAG will inhibit nociceptive reflexes and second-order neurons. Although the locus coeruleus (LC)(60) is considered to be primarily a noradrenergic nucleus, some 5-HT is also present in the locus coeruleus along with numerous peptides (61-63). The locus coeruleus sends noradrenergic projections to the other brain regions (64) and activation of the LC will inhibit the firing of dorsal horn neurons and, also, nociceptive reflexes (65,66). The LC contains high density of opioid receptors (67,68) and morphine increases the activity of LC neurones. The nucleus raphe magnus is a 5-HT containing nucleus (61) that also contains a variety of other neurotransmitters (45,50). The largest input into the nucleus raphe magnus arises from the PAG and nucleus raphe magnus sends reciprocal serotonergic and nonserotonergic input into the PAG.

The role of the nucleus raphe magnus in descending inhibition has been characterized at the level of spinal transmission and spinal reflexes (54,55,57,69-73).

It is certain that major role in modulation, in fact suppression of pain transmission, has the density of opioid receptor distribution. A high density of all three receptor types ( $\mu$ ,  $\kappa$ ,  $\delta$ ) are present in the dorsal horn of the spinal cord, thalamus, PAG and rostral ventral medulla sites. The same receptors are present on both spinal cord pain transmission neurons and upon the primary afferents that relay the pain message to them (74).

The tooth pulp evoked potentials (TPEP's), obtained as a response on electrical stimulation of tooth, represent a nociceptive pathway from receptor to the cortex (Fig.1).

**Fig 1.** Tooth pulp evoked potentials as an «objective index» of pain sensation:  
N1 - the first negative wave showing the first synaptic junction (substantia gelatinosa of nucl.caudalis pontis);  
P1 - the first positive wave showing nociceptive pathway through lemniscus medialis;  
N2/P2 - the second negative and the second positive waves showing nociceptive pathway at the thalamo-cortical level.



A - control registration  
B - registration 30 minutes after the administration of 50 mg tramadol per os  
C - registration one hour after the administration of 5 mg diazepam per os  
D - registration one hour after the administration of 7.5 mg flormidal per os  
E - registration one hour after the administration of 100 mg phenobarbitone per os.

In this case, a receptor - nociceptor is tooth pulp which is innervated solely by A-delta and C fibres, and although contradictory reports are available, it is generally accepted that the great majority of these fibres are of the nociceptive type. As TPEP's demonstrate only the pain response (nociceptive response), their use in clinical practice is permitted as an "objective" index of pain sensation (74) and in the diagnosis of orofacial pain syndrome (74,75). However, according to the registered TPEP's, it is possible to determine the level on which the pain transmission is changed, and to find out, in experimental environment, the effects of receptor selective drugs (74,76). The native opioid peptides - endogenous opioids, exogenous opioids and central acting analgesics (Fig.1 - B) produce analgesia via three receptor types that are closely linked with AMP system and changes in Ca and K flux (77). It is well known that gamma amino butyric acid (GABA) is the most important inhibitory neurotransmitter at all levels of the neuraxis, including the spinal cord, hypothalamus, hippocampus, substantia nigra, cerebellar cortex and cerebral cortex.

That is the reason why benzodiazepines (diazepam and flormidal) (Fig.1 - C and D) and phenobarbiton (Fig.1 - E) change the pain response. In fact, benzodiazepines potentiate GABA-ergic neurotransmission by increasing the efficiency of GABA-ergic synaptic inhibition via membrane hyperpolarization, which leads to a decrease in the firing rate of neurons (76), while barbiturates also facilitate the actions of GABA by increasing the duration of the GABA-gated channel openings (78,79).

Furthermore, chronic pain behavior has added complexities, since human reactions can be modified by the environmental or sociological setting, and because of all of these facts, the treatment can begin with the acknowledgement that chronic pain is mechanistically diverse and is the outcome of multisystem dysfunction.

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