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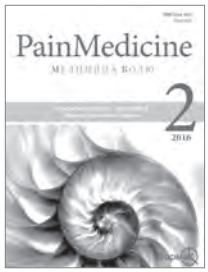

Pathophysiology of Chronic Pain

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Abstract. *Acute pain hurts and most often is the result of tissue injury. Chronic pain also hurts. Although those who suffer from chronic pain also tend to associate the onset with an injury, illness, or surgical procedure; the root cause is far more complex. Chronic pain most often does not follow dermatomal distributions associated with any injury, disease or surgical procedure. And more often than not, chronic pain sufferers also suffer from various forms of depression and/or anxiety. The process of central sensitization resulting from tissue injury has been elucidated, as has many of the molecular changes within the brain that perpetuate chronic pain. Genetics, epigenetics, environmental stressors, and emotional stressors all play roles to varying degrees in the development of the chronic pain state. This article explores how synaptic memories form in the brain as a result of both physical and emotional traumas (multiple hits) resulting in progression to chronic pain, because of failure of the brain's descending modulatory mechanisms to prevent or control "the pain".*

Key words: *epigenetics, memory, central sensitization, chronic pain.*

Antigonish is a Canadian town in Antigonish County, Nova Scotia where there was a house reported to be haunted. American educator and poet Hughes Mearns in 1899 wrote a poem entitled *"Antigonish*" about this home [1].

The last verse goes:
Last night I saw upon the stair,
A little man who wasn't there.
He wasn't there again today
Oh, how I wish he'd go away...

Although Mearns was not a physician, he could very well have been describing what patients with chronic unremitting pain experience. Ochoa quotes this verse in an editorial he wrote in 1993.(2) Ochoa's purpose was to point out the elusiveness of the understanding in 1993 of the mechanisms of "neuropathic" pain syndromes. He states further in his editorial, *"As long as therapeutic failure is ignored, theory will rest on deception because, to a large extent, the theory on which therapy is based is circularly based upon anecdotes of successful therapy."* [2].

Patients do not wake up one morning and notice they are suffering from chronic pain. Often patients ascribe their pain to a recent or past surgery, like ***"post lumbar back surgery."*** Other times the cause of the pain may be more enigmatic, like fibromyalgia (FM) or chronic interstitial cystitis [3, 4, 5]. Vierck states in his review of Fibromyalgia (FM) that the voluminous literature on FM includes suggestions that hypothalamo-pituitary-adrenal (HPA) dysfunction is causal for FM pain, an evolving concept [6].

Unfortunately, when peripheral changes are observed, they often are considered as consequences, rather than a source of abnormal central processing. This seems logical, because FM pain and sensitization are spatially distributed and involve peripheral tissues that have not been injured overtly.[6] Turk et al state that few people have "pure" fibromyalgia (FM), and their example patient described "diffuse body pain, neck pains, headaches, and limited neck motion," all likely sequelae of a cervical "whiplash" injury.[5] However, the patient also suffered from depression, fatigue, nonrestorative sleep, and deconditioning [5].

Bonica and Loeser recognized that for health professionals Pain remains one of the most pressing issues of society [7]. Acute and chronic pain afflicts millions of people around the world, and pain is the most frequent cause of suffering and disability that impairs quality of life.[7] Perkins and Kehlet, in their meta analysis study of chronic pain as a surgical outcome (at least 1 year) [8] found that the incidence of chronic pain for the following relatively common surgical procedures was:

1. Limb amputations (30–81%),
2. Thoracotomy (47%),
3. Breast surgery (phantom, scar, arm, neck, shoulder) (11–57%),

4. Gallbladder (3–56%) and
5. Inguinal hernia (0–37%).

They also studied associated risk factors and found that *poorly controlled pain* and *psychologic vulnerability* when present preoperatively and postoperatively, were highly correlated with the development of chronic pain.[8] Deumens et al found similar results and explored the possible mechanisms for post surgical chronic pain [9].

In 2002 there were approximately one million back surgeries being performed in the United States annually, with approximately 40–70% of patients remaining with residual back pain depending on which study was cited [10]. Chronic pain after total hip arthroplasty (THA) seems to be a significant problem in at least 12.1% of patients [11], and 13% of patients report moderate to severe pain at 1 year post total knee arthroplasty surgery (TKA), in spite of an absence of clinical or radiologic abnormalities [12].

Those of us who treat patients with chronic pain are aware that this problem is still current in 2016. In this review paper, it is our intention to explore the underlying molecular mechanisms and influencing factors (genetic, epigenetic, environmental, and psychosocial) that lead a patient from acute pain to the suffering associated with chronic pain, "The Journey of Multiple Hits."

Until 1979, when the International Association for the Study of Pain (IASP) defined "Pain" as "an unpleasant sensory and emotional "experience" associated with actual or potential tissue damage." Pain was considered the result of tissue injury, or if no tissue injury could be found, the pain must be psychological in nature [13]. A list of pain terms was first published in 1979 [13]. In 1994, "Chronic Pain" was defined as persistent or episodic pain of a duration or intensity that adversely affects the function or well-being of the patient, attributable to any nonmalignant (or malignant) etiology [14].

The task force noted that "Pain" is always subjective, and each individual learns the application of the word through experiences related to injury in early life; and injuries in early life include "psychological and emotional" traumas [14]. It goes without saying that those stimuli which can result in the experience of somatic pain are also liable to damage tissue, and manifest as an unpleasant emotional experience." But in order to make that association, particularly with respect to potential tissue damage, memory of similar experiences must be present. The "experience of pain" therefore requires "cognitive function," and memory. If the patient regards his/her experience as painful, it should be accepted as pain. This definition avoids tying the experience of pain to the stimulus or source of nociception [15].

Furthermore, the American Academy of Pain Medicine has attempted to classify pain on a neurobiologic basis; nociceptive pain is eudynea, and maladaptive pain is Maldynea [16]. In their report, the authors recognize that in some pain states there is no recognizable peripheral source, the pain itself does not promote healing, but that structural and chemical changes have taken place in the brain that perpetuate the experience of pain [16].

Siddell and Cousins previously reported that repetitive ongoing nociceptive inputs result in a host of consequences that impact on the patient, ranging from changes in receptor function both peripherally and in the brain, mood dysfunction, inappropriate cognitions, and social disruption. These changes that occur as a consequence of continuing nociceptive inputs argue for the consideration of persistent pain as a disease entity in its own right, rather than just a symptom of a diagnosable disease [17, 18].

Noxious stimulation from peripheral receptors is transmitted across synapses in the dorsal horn of the spinal cord and internuncial neurons, and then to different areas of the brain according to the type of stimulation. Nociceptive stimulation is processed in the brain stem and brain, and the final experience of pain is dependent on the cognitive function of the cortex, the mood of the patient and other memories, affected by and affecting fear, anger, anxiety, and depression [19]. As will be shown further, these evaluative areas of the brain involve the amygdale, hippocampus and perirhinal cortex among others [20] (Figure 1).

The brain responds to noxious stimuli through the nervous, endocrine, and immune subsystems, which communicate dynamically using the language of common chemical substances [21]. These major language elements are peptides, hormones, neurotransmitters, endocannabinoids, and cytokines [21]. These substances are pleiotropic in that they exert different effects depending on context (e.g., phase and location) [21]. Circulation, diffusion, migration, and autonomic nervous system activity are the processes of information transmission [21]. These systems have constant reciprocal communication, and tend to react to a stressor in a highly orchestrated manner, as a single unit [21] (Figure 2).

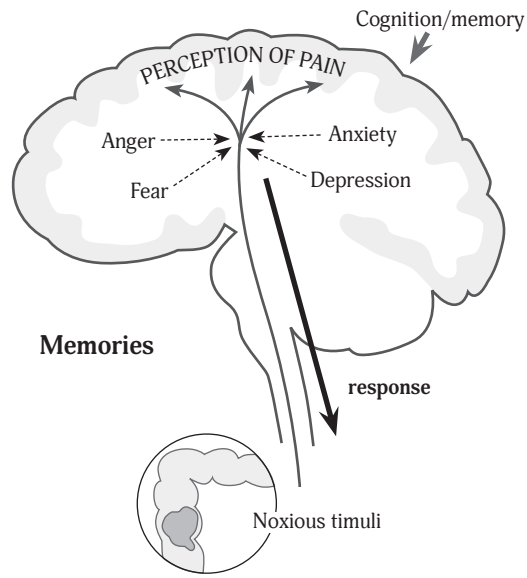


Figure 1. Evaluative areas of the brain involve the amygdale, hippocampus and perirhinal cortex among others.
(*Fitzgibbon D., Chapman C.R., Cancer pain: Assessment and Diagnosis. Chapter 35 In: Bonica's Management of Pain 3rd edition, Loeser J chief editor, Lippincott, Philadelphia, 2001)* [20] (modified)

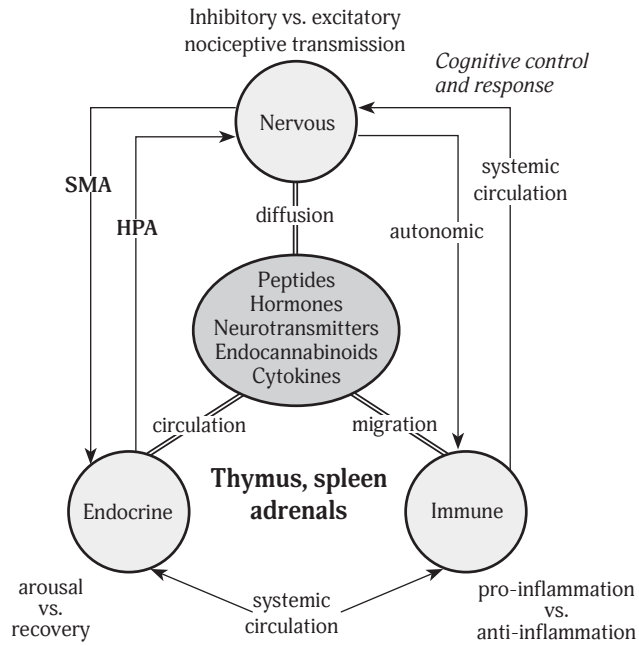


Figure 2. The relationship between the three systems described previously [21, 29].
(Modified from Chapmanert C.R., Tuckett R.P., and Song C.W.)

In humans, a healthy stress response, through activation of the hypothalamo–pituitary–adrenal axis (HPA), will initiate a cascade of adaptive responses aimed at enhanced cognitive performance and modified cardiovascular and immune functions [22]. Activation of the HPA axis and the sensation of acute pain after tissue damage are two highly functional and protective responses necessary for survival, that allow the individual to focus attention toward the tissue damage, and if necessary take evasive action (fight or flight), or seek help [22]. This is coordinated with the sympatho-adrenomedullary axis (SMA) which releases adrenaline when activated [23].

In contrast, in states of chronic stress and chronic pain the HPA axis becomes dysfunctional resulting in either hyper or hypocortisolemia. Either of these conditions can result in changes in mood, pain, and depression [22]. Thus as indicated previously, acute tissue injury activates an ensemble of interdependent nervous, endocrine, and immune processes that operate in concert and comprise a "supersystem." Some chronic pain conditions result from the "supersystem" dysregulation. Individuals vary and are vulnerable to dysregulation due to the unique interactions of genetic, epigenetic, and environmental factors and experiences in the past that characterize each person [21]. This could be referred to as the "Theory of multiple hits" as described by Buchheit, Van de Van, and Shaw [24].

Phylogenetically, the immune and central nervous systems display striking similarities. Both systems show a remarkable degree of cell diversity. Both possess memory characteristics that do not exist in other systems. Both systems serve functions of adaptation, defense, and homeostasis. Both relate the organism to an often-hostile environment [25]. This view of immune-neuro-endocrine interactions as a "supersystem" network allows us to assume that the degree of activity of the network can be changed by stimuli acting at or generated from any of its components, e.g. antigens at the level of the immune system, psycho-social stimuli at the level of the CNS, and cumulative epigenetic responses. This will have consequences for both immune responses, behavior, "and the pain experience." [26].

There are tests such as the McGill Pain Questionnaire that can separate out affective from somatic components, which can assist with therapy [27]. It is also well known that depressed patients can manifest chronic pain conditions that are poorly localized to any peripheral source [28]. Further along in this review we will be exploring how peripheral injury can lead to central sensitization at the spinal cord level with subsequent changes in the brain, and how these brain alterations can feedback to the body, enhancing the pain experience instead of moderating or modulating the pain experience.

In chronic pain states there is often the absence of the "normal" physiologic indicators of acute pain such as tachycardia, hypertension, and diaphoresis. Yet there may be hyperpathia, allodynea, hyperalgesia in the absence of any physical findings of tissue injury. Patients can be smiling and at the same time tell you they are experiencing excruciating pain. As depicted in Figure 3, it becomes clear immediately that there is a fundamental difference between acute pain and chronic pain.

The sympathetic response permits the brain to monitor the external world continuously, manipulate and integrate input information, then output appropriate information to particular brain areas [29, 30]. The sympathetic nervous system is involved in coordinated regulation of body functions under different conditions [31]. It is clear that under non-pathological conditions, stimulation of the efferent sympathetic nervous system does not cause pain because these neurons have no effect on the receptive properties of primary afferent neurons [31]. If efferent sympathetic stimulation lead to afferent sympathetic mediated pain, then all animals would be in "pain" any time the body experienced stress. In fact the opposite actually occurs.

It has been shown, for example, that the mild stress of exercise causes neurogenesis, or the creation of new neu-

Figure 3. "The Scream" with smiling eyes.
(Modified from "The Scream" a painting by Edvard Munch 1910)

rons. The new neurons are created in the hippocampus, the center of learning and memory in the brain [32]. At a cellular level, it is possible that the mild stress generated by exercise stimulates an influx of calcium, which activates transcription factors in existing hippocampus neurons. The transcription factors initiate the expression of the Brain-Derived Neurotrophic Factor (BDNF) Gene, creating BDNF regulated proteins that act to promote neurogenesis [33, 34].

Thus the generation of BDNF is a protective response to stress, and BDNF acts not only to generate new neurons, but also to protect existing neurons and to promote synaptic plasticity: the efficiency of signal transmission across the synaptic cleft between neurons, generally considered the basis of learning and memory [32, 33, 35]. However, BDNF's effects are more than protective, they are also reparative. For example, in a comparison between sedentary and active mice, scientists found that active mice regenerated more sciatic axons post-injury than sedentary mice. This effect was not observed when the active mice were injected with a neurotrophin-blocking agent, indicating that exercise stimulates injured neurons to regenerate axons via neurotrophin-signaling mechanisms, (BDNF) [35, 36].

This reparative effect is particularly relevant to humans because the brain starts to lose nerve tissue beginning at age 30. Aerobic exercise reinforces neural connections by increasing the number of dendrite connections between neurons, creating a denser network, which is then better able to process and store information [35, 36, 37]. Under conditions of injury however, the concerted actions of the sensory and sympathetic systems are disrupted, leading to abnormal sensations and dysregulation of peripheral tissues [38, 39].

How does this happen? The sympathetic nervous system (SNS) and pain interact on many levels of the neuraxis. In healthy subjects, activation of the SNS in the brain usually suppresses pain mainly by descending inhibition of nociceptive transmission at the spinal cord. Furthermore, some experimental data even suggest that the SNS might control peripheral inflammation and nociceptive activation [40]. However, even subtle changes in pathophysiology can dramatically change the effect of SNS on pain, and vice versa.

In the periphery, inflammation or nociceptive activation can reverse descending inhibition, to spinal facilitation, and the awareness of all these changes will induce anxiety, which further amplifies pain perception, affects pain behavior, and depresses mood. Unraveling the detailed molecular mechanisms of how this interaction of the SNS and pain is established in health and disease will help us to treat pain more successfully in the future [41].

Some patients who suffer even minor injuries develop long lasting pain conditions with significant psychological suffering. Complex Regional Pain Syndrome (CRPS) Type I is such a condition. Previously known as reflex sympathetic dystrophy among other names, physicians traditionally ascribed CRPS to dysfunction or hyperactivity of the sympathetic nervous system. Terms such as sympathetic maintained pain (SMP) and sympathetic independent pain (SIP) are used to describe the patient's condition based mainly upon the patient's response to procedures and interventions that blocked sympathetic innervation to the affected limb [42].

Wahren and Torebjörk concluded that sympathetic effects on allodynia are peripheral in nature [43].

Koltzenberg, Torebjörk and Wahren (1994) concluded that it was necessary to use a multi axial approach to classifying neuropathic pain syndromes, e.g. classifying disorders by sensory abnormalities in the nature of ongoing pain, presence or absence of thermal, chemical, or mechanical hyperalgesia [44]. This is not unlike the conclusions of Veldman and his associates [45].

Meller and Gebhart presented data which demonstrated that thermal hyperalgesia was dependant on activation of NMDA receptors, opening of calcium channels, production of PKC, generation of nitric oxide synthase (NOS), and accumulation of nitric oxide (NO). Mechanical hyperalgesia, on the other hand, resulted from AMPA and metabotropic receptor activation, influx of calcium, generation of phospholipase A_2, cyclooxygenase, and Arachidonic acid [46].

Mechanical hyperalgesia was probably the predominant clinical feature associated with tissue damage and or inflammation [46]. Primary hyperalgesia was therefore a peripheral event, whereas secondary hyperalgesia was a central event (the result of wind-up). Meller and Gebhart also felt it was probably not possible to develop a single drug or treatment that could relieve both mechanical and thermal hyperalgesia [46].

There is evidence that after nerve injury such as sciatic nerve ligation, noradrenergic axons sprout into the dorsal root ganglion (DRG) and that stimulation can activate primary afferents by stimulation of the cell bodies [47, 48, 49]. This could lead to allodynia and hyperalgesia [31, 50] It is believed that adrenoceptors either appear de novo, or are uncovered and/or upregulated in response to tissue injury or nerve injury [51]. The new adrenoreceptors might also be produced or generated in the cell body and translocated towards the peripheral terminal as well as towards the central terminal [52]. Prevention of regeneration may occur due to scarring at the original lesion site [31].

Nociceptive inputs from peripherally injured sites, whether mechanical, thermal, cold, or chemical injury, enter the spinal dorsal horn through transmission in primary afferent fibers that synapse onto transmission interneurons [53]. As shown in Figure 4, the projection fibers ascend through the contralateral spinothalamic tract and travel to the thalamus and are distributed to various parts of the brain for cognitive evaluation of pain. Descending pain modulation is mediated through projections to the peri-acquaductal grey (PAG), which also receives inputs from other sites, including the hypothalamus and communicates with the rostral ventro-medial medulla (RVM), which includes the nucleus raphe magnus (NRM) as well as other medullary nuclei that send descending projections to the spinal dorsal horn through the dorsal lateral funiculus (DLF), [17] (Figure 5). The locus coeruleus (LC) also receives inputs from the PAG, communicates with the RVM, and sends descending noradrenergic inhibitory projections to the spinal cord. [55–66].

As shown in figure 4, the NRM receives descending afferents not only from the PAG, but also from the paraventricular

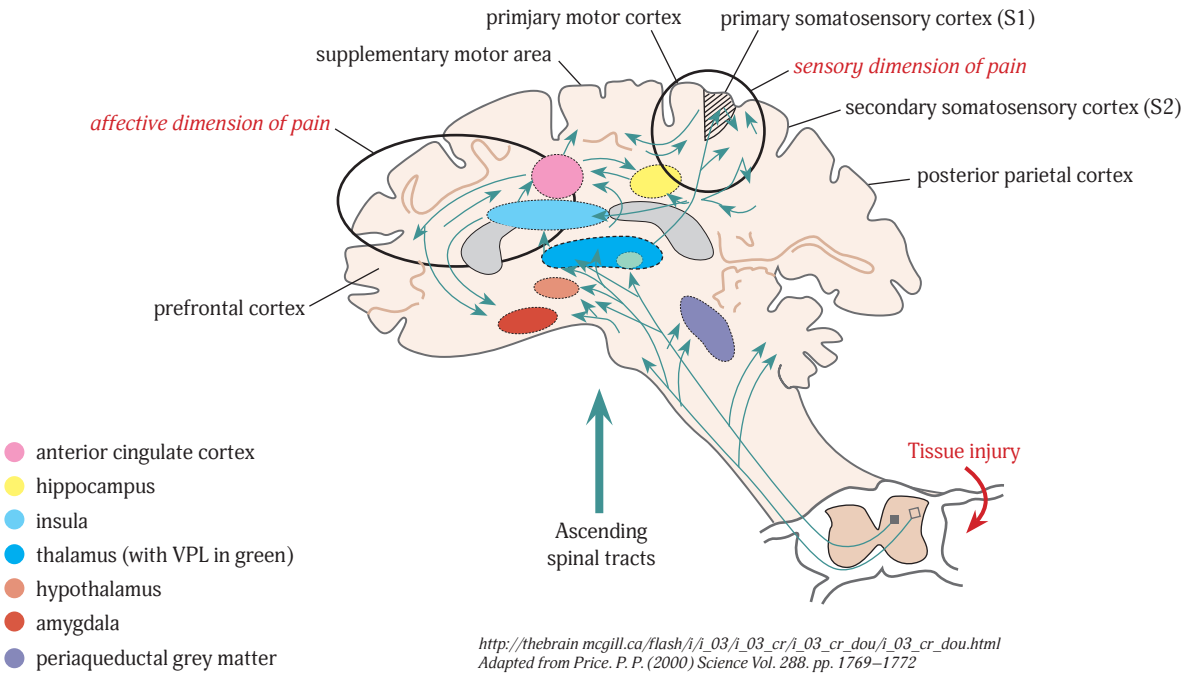


Figure 4. The "Pain matrix".
(Modified from Price D.D. [66] and Peyron R., Laurant B., Garcia-Larrea L. [67]). Editorial comment: redesigned for publishing purposes

hypothalamic nucleus, central nucleus of the amygdala, lateral hypothalamic area, parvocellular reticular nucleus and the prelimbic, infralimbic, medial and lateral precentral cortices. All of these brain areas influence the main function of the NRM, which again is part of the (RVM) [55, 66, 67].

Efferent PAG connections to the NRM are activated when stimulated by opioids (endogenous or exogenous) [56], (Figures 5, 6). The NRM sends projections to the dorsal horn which either inhibit of facilitate nociception. The NRM also releases serotonin when stimulated. Raphe-spinal neurons

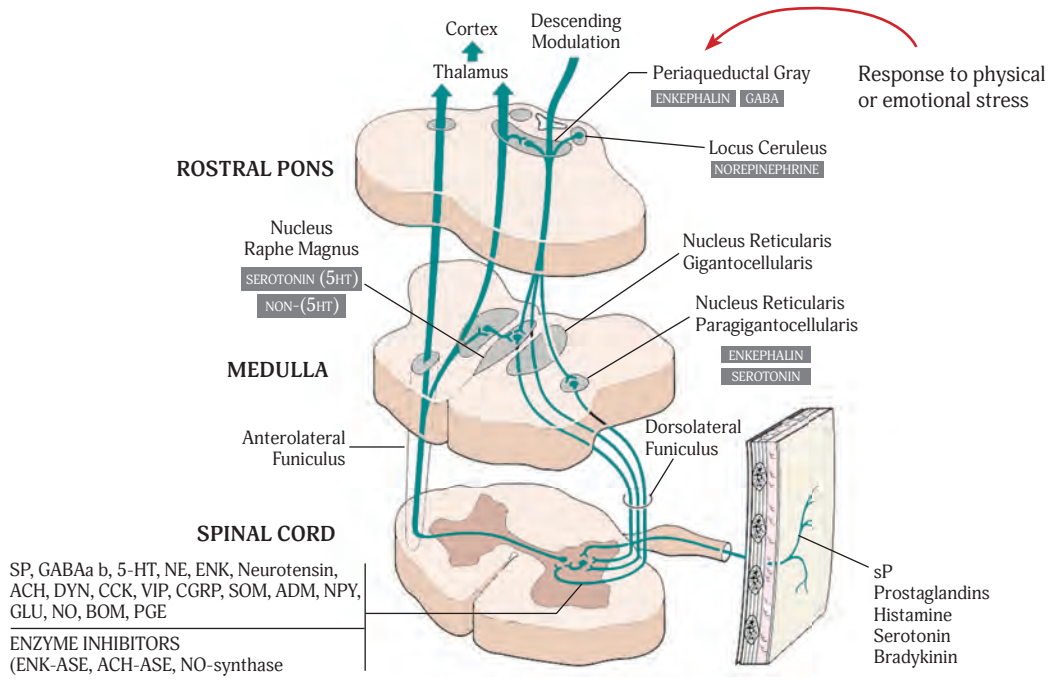
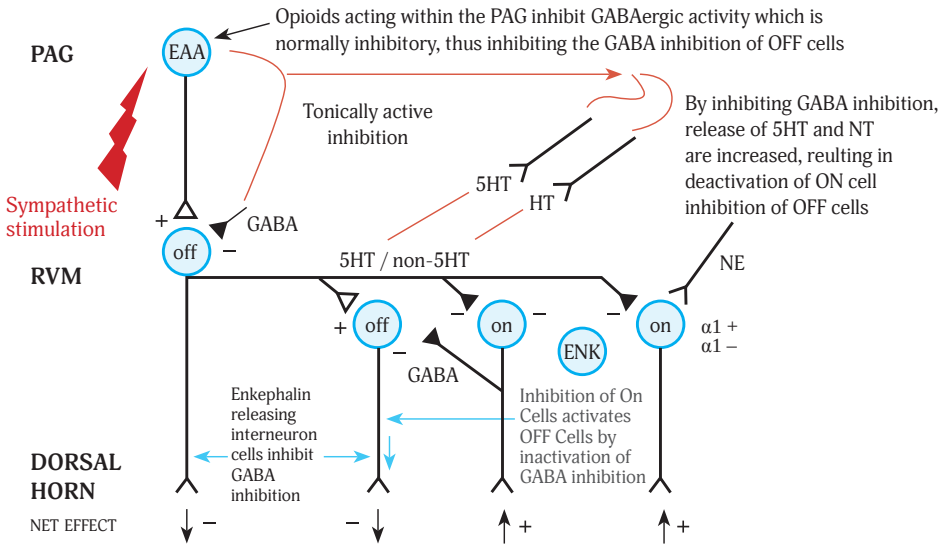


Figure 5. Efferent PAG connections to the NRM are activated when stimulated by opioids (endogenous or exogenous).
(Modified from Siddall P.J. and Cousins M.J. [68]). Editorial comment: redesigned for publishing purposes



Fields et al, Annual Rev Neurosci, 1991, 14:219-45 (modified) Fields, et al in Bonica's Management of Pain, 3rd edition, 2001, page 133 (modified)

Figure 6. Schematic of relationship of the PAG to the RVM and modulation of dorsal horn nociception. *(Modified from Fields)* [57, 58] *Editorial comment: redesigned for publishing purposes*

project to enkephalin releasing interneurons in the dorsal horn of the spinal cord [57].

As shown in figure 6, in the absence of stress stimulation, the RVM sends projections to the dorsal horn of the spinal cord, which can either facilitate (On Cells) or inhibit (OFF Cells) nociceptive input as described by Fields et al. [58]. Therefore, the RVM can both positively and negatively modulate nociceptive inputs and provide for an endogenous pain regulatory system [69]. All of this seems to indicate that the NRM must also be part of the endogenous opiate system, and acts to inhibit pain in the spinal cord. So why does this endogenous analgesic system fail in chronic neuropathic pain?

Aristotle (384–322 BC) taught that the Brain had no direct function in sensory perception, and that the Heart was the seat of emotions [7]. The Aristotelian concept of the five senses, and pain as a "passion of the soul" felt in the heart, prevailed for 23 centuries [7].

2000 years after Aristotle and nearly 400 years ago, René Descartes proposed a model of pain perception that characterized pain as a purely physical phenomenon, devoid of psychological influence. As depicted in his drawing (figure 7) (Descartes), an injurious stimulus would be transmitted to the brain, and that the response to this "Hurt" would be proportional to the intensity of the stimulus and was separate from cognitive control of the "Mind." [69]

But what Descartes did not appreciate was that the biopsychomotor model of pain suggests that in addition to the sensory component of the pain system, it will be important to consider two main intra-individual behavioral systems: the communicative behavior system and the protective behavior system. This is shown in the modified version of Descartes' L'Homme as modified from Sullivan.

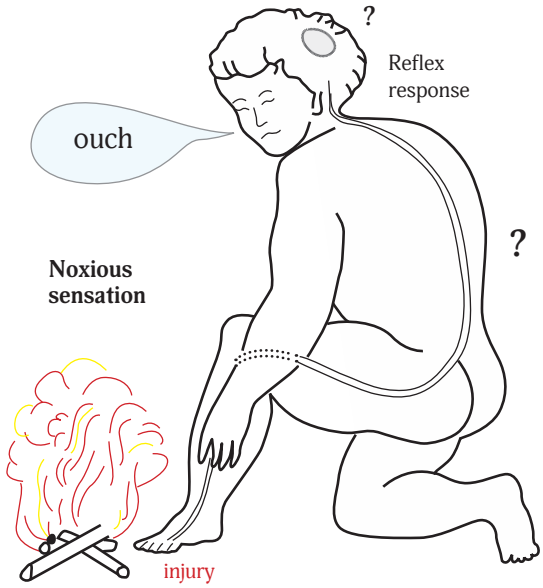


Figure 7. René Descartes' model of pain perception taken from De Homine, Leyden: Moyardis and Leffen 1662 *(modified from Sullivan) [69]*

In their article Watson and Williams, analyze the Noble Prize winning work of Sir John Eccles in defining how "The Mind" responds to stimuli of all kinds and defines the response of the body and the emotions [70]. Watson and Williams report that Eccles' approach to the problem is found in his (Eccles) concept of "mental units": Eccles proposed [71]. The hypothesis that all mental events and experiences, in fact the whole of the outer and inner sensory experiences, are a composite of elemental or unitary mental experiences at all levels of intensity. Each of these mental units is reciprocal-

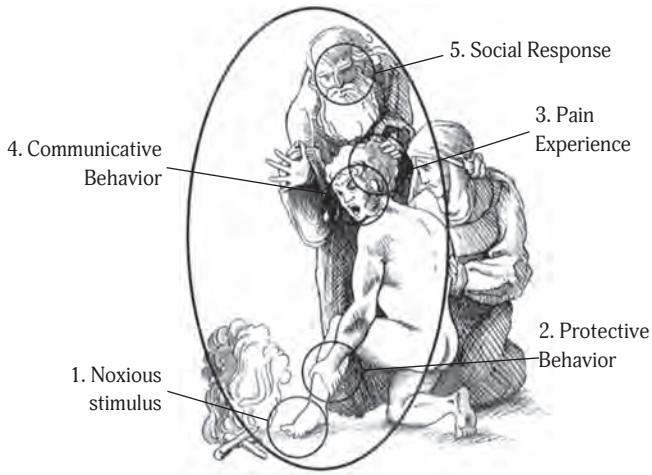


Figure 8. A biopsychomotor model of pain. The noxious stimulus produces not only the reflexive withdrawal, but also the cognitive experience of pain resulting in a change in behavior which increases the probability of survival but also illicit a social response. Without an adaptive behavioral response, Sullivan concludes there would be no use for a nociceptive system, much like a fire station without firemen [69]. Even the fear of getting burned would result in the same response if the individual had experienced a burn injury in the past. *(Modified from Sullivan)*

ly linked in some unitary manner to a dendron [(a bundle of dendrites)].

Appropriately we name these proposed mental units 'psychons.' Psychons are not perceptual paths to experiences. They are the experiences in all their diversity and uniqueness. There could be millions of psychons each linked uniquely to the millions of dendrons. It is hypothesized that it is the very nature of psychons to link together in providing a unified experience [72].

As described by Eccles: "[The word "self"] will be used to connote an experienced unity that derives from a linking by memory of conscious states that are experienced at widely different times and spread over a lifetime. Thus, in order that a 'self' may exist there must be some continuity of mental experiences and, articularly, continuity bridging gaps of unconsciousness. For example, the continuity of our 'self' is resumed after sleep, anaesthesia, and the temporary amnesias of concussion and convulsions" [70]. Quantum theory allows the possibility that conscious mental acts can influence brain behavior [71, 72, 73]. This is an important concept that will be addressed further in this review.

As presented previously, the IASP has defined "Pain": but what is the actual experience of pain?

If the presumption is that "pain" is something that "hurts," then we immediately recognize that there are many types of "pain."

1. A broken arm hurts (acute pain);
2. A sun burn hurts (allodynia, hyperalgesia);
3. A kidney stone hurts (visceral pain);
4. A heart attack hurts (ischemic pain);
5. An amputated leg hurts (phantom pain);
6. A death in the family hurts (broken heart);
7. Chronic pain hurts all the time (with or without continued pathology).

As stated earlier, pain is therefore always subjective, and requires cognitive function to be experienced. Engel in his classic paper written in 1959 introduced the concept of "pain memories," in that the experience of pain permits the individ-

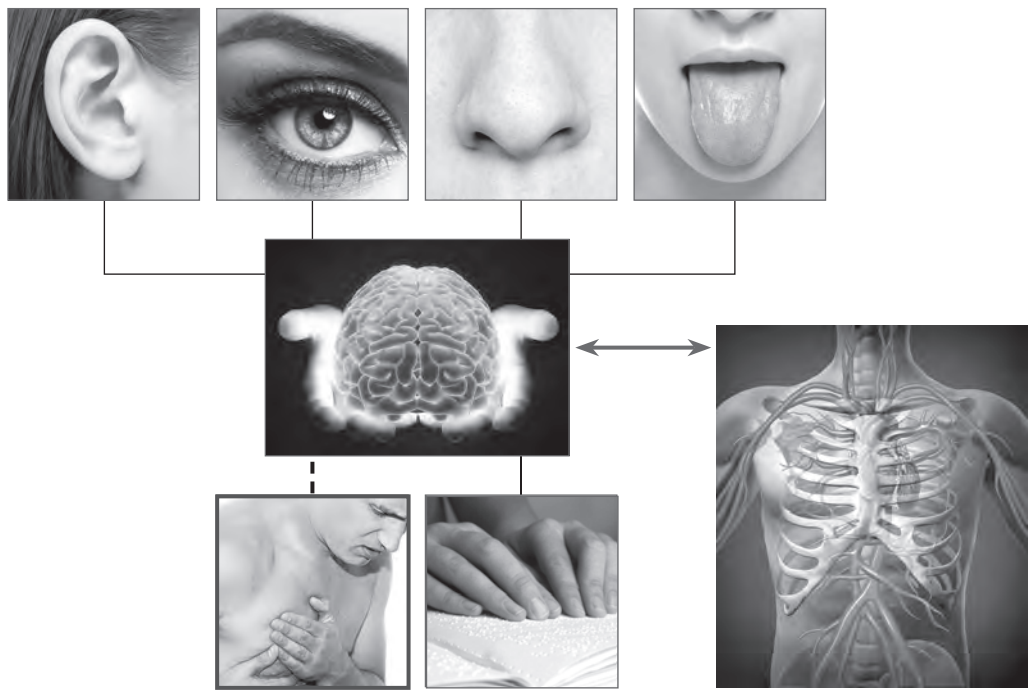


Figure 9. The 5 senses plus pain. Editorial comment: redesigned for publishing purposes

ual to recognize bodily injury or environmental situations that can cause injury and therefore cause pain [28]. This is similar to the Sullivan's modified biopsychomotor model of pain [69].

In figure 9, the classic 5 senses, vision, hearing, taste, smell, and touch are shown, all serve to teach the brain about its' environment. The brain receives information and interprets that information based on its' memories of similar stimuli received from similar parts of the body as harmful (painful) or pleasurable, and reacts accordingly.

However, there is a 6th sense. The ability to sense tissue injury is the most important of our senses. Children born without the ability to sense tissue injury usually die before their teens because they are unable to protect themselves. They have no experience of pain [74].

In their review, Tau and Peterson report that during prenatal life genes are responsible for creating the architecture of the brain and nervous system [75]. The same genes are located in every cell of the body, but it is the Epigenetics of those genes that will determine how each cell will function. The cortex is the last to develop and very immature at birth. At birth, there is an excess of neurons, but they are not inter-connected. From the moment of birth onward, the brain actively constructs an internal model of the external world (through input from the senses), a picture of how the world works, and stores this information as memories, (Epigenetics). During the 1st month of life, 40,000 synapses per second are formed in the brain. This is genetically regulated for the first 3 years of life, (referred to as synaptic overgrowth connections). After this, the density remains constant though some continue to form and grow (neurogenesis) and some die (apoptosis) [75].

During pre-adolescence another increase in synaptic formation occurs. From adolescence until age 25, the brain becomes a reconstruction site. Connections important for self-regulation (in the prefrontal cortex) are being remodeled. This is important for a sense of "wholeness" [76]. But it also causes personal turbulence and is susceptible to stress (i.e., abuse) and toxins (like alcohol and drugs) during these years which affects the rest of one's life. These multiple "hits" reinforce the synapses of memory. The mind changes the brain (throughout life). Where brain activation occurs, synapses happen. When one pays attention and focuses the mind, neural firing occurs and brain structure changes (synapses are formed). Human connections impact neural connections, ongoing experiences and learning include the interpersonal ones [27, 77].

Event memories are recorded in the hippocampus and separated according to importance and detail to facilitate recall. To avoid interference, the finest scale memories are distributed at the back of the hippocampus and the coarser memories at the front of the hippocampus [78]. Fear memories seem to be encoded in the lateral amygdola [79].

Cortical Memory

Verney in his comprehensive review article presents the current understanding of memory formation [80]. He cites the work of Eric Kandel who during his Nobel Prize acceptance lecture described memory as "the pattern of functional interconnections of cells." Short-term memory involves increased levels of neurotransmitters at the synapses, the communication sites between nerve cells, and long-term memory requires changes in the levels of proteins in the synapse [81]. This seems to be the extension of Eccles' work on the concepts of dendrons and psychons. [70, 71, 72].

There are about 160,000 Km of nerve fibers that make up the white matter of the adult brain that connect the various components of the "mind," giving rise to everything we think, feel, and perceive [82]. Each Neuron has about 10,000 synapses in a volume of 1000 cubic microns. Each neuron makes connection with only 1 other specific neuron. Wedden and Wald have mapped the brains of six people, charting the activity of 20,000 protein-coding genes at 700 sites within each brain [82]. They estimate that 84% of all the genes in our DNA become active somewhere in the adult brain. In each of the 700 sites the neurons switch on a distinct collection of genes [82].

In comparing two regions of the brains, they compared 1000 genes that are already known to be important for neuron function, and they found that those genes were active in each brain in the same locations. Thus, it seems that the brain has a genetic landscape with special combinations of genes carrying out tasks in different locations. The secret of many diseases of the brain, including chronic pain, may be hiding in that landscape, as certain genes shut down or switch on abnormally, Epigenetics [82].

Epigenetics is the study of transgenerational inheritable traits that do not stem from mutations to the underlying DNA structure that influence phenotypic expression, and are potentially reversible. Epigenetic influences may reflect environmental pressure on an individual or on an individual's ancestors [83]. Such changes in gene expression occur through the methylation of DNA, the post-translational modifications of histone proteins, and RNA-based silencing of those histones [84]. Epigenetic influences not only stem from the environment; like genetic influences, they may interact with the environment. Unlike genetic influences, they are unstable and may alter with environmental change including in principle therapeutic intervention [83, 85].

MicroRNAs (miRs) are endogenous, noncoding RNA molecules that act to regulate nearly every cellular process through inhibition of target messenger RNA expression. The mature microRNA then combines with the RNAinduced silencing complex and interacts with its target to induce gene silencing through target mRNA degradation or translational repression, which may result in a Chronic Pain state [86].

Thus, these newly identified noncoding RNAs govern gene expression. Peripheral noxious stimuli can drive expressional changes in these noncoding RNAs and these changes are associated with pain hypersensitivity under chronic pain conditions [87]. Lutz et al present current evidence for the mechanism of peripheral inflammation and nerve injury inducing changes in the expression of two types of noncoding RNAs, microRNAs and Kcna2 antisense RNAs, in pain-related regions, particularly in the dorsal root ganglion which will have importance in our later discussion of central sensitization [87].

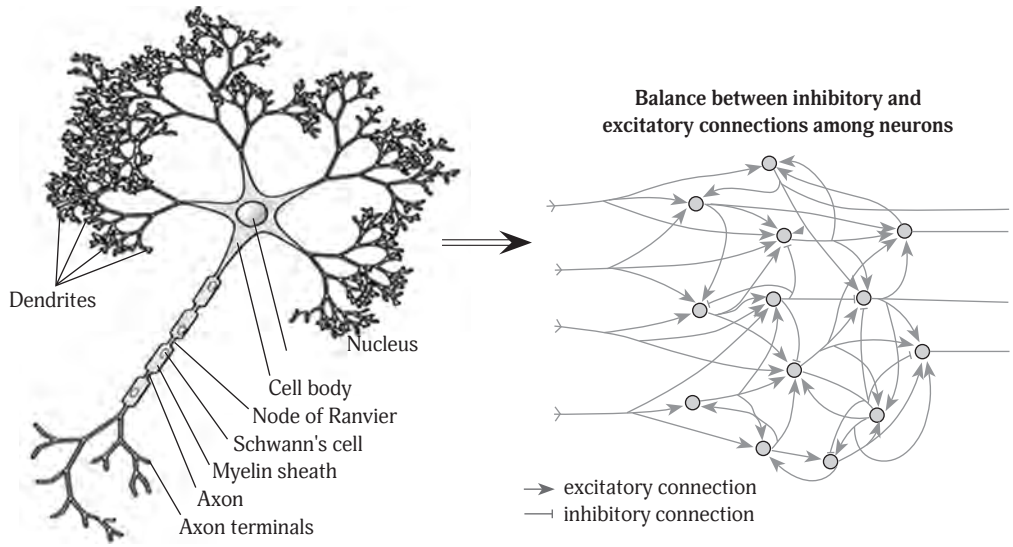


Image in the public domain uploaded from: http://upload.wikimedia.org/wikipedia/commons/7/72/Neuron-figure-notext.svg, the original image from Nicolas Rougier. (Stiles J, Jernigan TL. The basics of brain development. Neuropsychol Rev. 2010; 20(4): 327–348.)[89]

(Atmanspacher, Harald, "Quantum Approaches to Consciousness", The Stanford Encyclopedia of Philosophy (summer 2015 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/sum2015/entries/qt-consciousness/>.)[90] modified

Figure 10. Schematic drawing of a neuron and the balance of excitatory and inhibitory connections. *Editorial comment: redesigned for publishing purposes*

Genetic and epigenetic factors may affect individual differences in pain sensitivity through synthesis and function of proteins affecting the plasticity of the CNS with tissue remodeling after injury, appearance of catecholamine metabolizing enzymes such as catachol-O-methyl transferase (COMT), and production of pro-inflammatory cytokines. Altered pain sensitivity may also be due to differences in genetic opioid receptor subtypes, and therefore the efficacy of opioids and other analgesic drugs in individual patients [83].

However, information must reach the cells of the central nervous system and the brain in order to form the synapses that lead to the participation of those cells in protein production. Synapses grow stronger because of the incoming signals from all our senses, initiating the production of specific proteins in the cells, BDNF for example [88]. These proteins not only build up the synapse but also encode memories. As Verney points out, physical exercise leads to greater muscle mass through a production of new proteins, so do experiences build memories in synapses, potentially whole neural networks and brain regions [80].

We know a lot about the anatomy of nerve fibers and the brain. In figure 10, the gross anatomy of a neuron is depicted, and the balance between inhibitory and excitatory connections among neurons [89, 90]. Each neuron has a single large axon. At the distal tip of the axon is a growth cone that serves to guide the axon to targeted brain regions. Once the axon reaches the target site, synapses, or points of connection, form between the axon and the target neuron. The synapse allows electrochemical signals to be transmitted to the target neuron. Each neuron also has a complex arbor of dendrites that receive information from other neurons. When an activating signal arrives at a synapse, there is a release of chemical transmitter which activates the postsynaptic receptor of a neuron which can be inhibitory or stimulating based on the balance of the incoming signals [90].

The back of brain is mainly involved in receiving signals of perception. The top of brain governs movement, and the front of brain is where thinking occurs. Nevertheless, in order to carry out their respective functions, these brain regions must first receive information upon which to respond. Mandal points out that the thalamus is a vital structure lying deep within the brain that has several important functions [91].

There are extensive nerve networks that send signals all around the structures of the brain including the cerebral cortex. As shown previously in figures 4 and further in figures 10 and 11, the thalamus is involved in sensory and motor signal relay and the regulation of consciousness and sleep. Aside from sense of smell, all other sensory processes involve a thalamic nucleus receiving a sensory signal which is then directed to the relevant cortical area. The thalamus also plays a role in controlling the motor systems of the brain which are responsible for voluntary bodily movement and coordination [91].

As stated earlier, the most current neuroscientific view is that memories are encoded in nerve cells and their synapses by the production of particular proteins. Both short-term and long-term memories reside in different parts of the brain. If you were to stimulate one area of the brain such as the occipital cortex at the back of the brain with a tiny electrical probe you would trigger visual memories; the left temporal area at the side of the brain might produce speech sounds, words, phrases, etc. Related memories are stored in adjoining synapses. The larger the area stimulated the more complete the memory becomes [92].

In the process of transmission, synapses grow stronger as a result of the incoming signals initiating the production of

specific proteins in the cells.92 These proteins not only build up the synapse but also encode memories. Just as physical exercise leads to greater muscle mass through a production of new proteins, so experience builds memories in synapses, potentially whole neural networks and brain regions [93, 94, 95, 96, 97].

The frontal cortex can tap into the sensory information immediately for use as a short-term, or working, memory. New neural connections then grow in the hippocampus and areas of the medial temporal lobes. These new connections strengthen the brain's existing circuitry – changing the number of synaptic connections – which leads to long-term memory. When permanent changes in the neural connections are maintained throughout the brain, the long-term memory remains [94, 95, 96, 97, 98].

Information, depending on its type, takes up permanent residence in brain regions involved in processing the original experience. Which region of the brain is involved depends on the type of experience. If the information is spatial, then the hippocampus region will be involved; if the information is emotional, then the amygdala will have the primary involvement of processing. The hippocampus and cortical brain regions then help with long-term memory retrieval when sensory information or emotions trigger that memory [94, 95, 96, 97].

The hippocampus is part of the limbic system. This system is located in the brain's medial temporal lobe, near the center of the brain. The hippocampus is involved in the storage of long-term memory, which includes all past knowledge and experiences. In particular, the hippocampus plays a primary role in declarative memory, the type of memory involving things that can be purposely recalled, such as facts or events. The hippocampus is not involved with short-term memory or procedural memory types (memory of how to do motor actions, like walking). These are primarily handled by the cortex and the cerebellum. Those that have lost function or had removed major portions of the limbic system but still have the hippocampus, have only long-term memory and cannot record any new memories or functions [99].

The reticular formation is a set of interconnected nuclei that are located throughout the brain stem. Its dorsal tegmental nuclei are in the midbrain while its central tegmental nuclei are in the pons, and its central and inferior nuclei are found in the medulla (Figure 11). The reticular formation has two components [100].

The ascending reticular formation is also called the reticular activating system. It is responsible for the sleep-wake cycle, thus mediating various levels of alertness. This part of the reticular system projects to the mid-line group of the thalamus, which also plays a role in wakefulness. From there, information is sent to the cortex [100].

The descending reticular formation is involved in posture and equilibrium as well as autonomic nervous system activity. It receives information from the hypothalamus. The descending reticular formation also plays a role in motor movement. The descending reticular nuclei in the brain are involved in reflexive behavior such as coughing, chewing, swallowing and vomiting [100].

Thus, one role of the reticular formation is to provide activation of the cerebral cortex. The process of arousal is highly important because it serves to change excitability levels (i.e., prime the sensory [and other] neurons) of the cortex so that they will become more receptive to other sensory inputs that reach the cerebral cortex through the classical ascending sensory pathways.

The panel on the right are shown the ascending connections of the reticular formation and inputs into the reticular formation from lower levels of the central nervous system (Figure 11). The reticular formation receives spinoreticular fibers (shown in red). The ascending reticular fibers project either directly to the intralaminar nuclei (shown in red) or indirectly through an interneuron from the solitary nucleus to the dorsolateral pons first (shown in blue); neurons from intralaminar nuclei then project directly to the cortex (shown in red) or to specific thalamic nuclei, which then project to the cerebral cortex (not shown in this diagram). By either direct or indirect routes, inputs from the reticular formation can influence cortical activity and the transmission of sensory signals to the cortex. CN = cranial nerve [101, 102].

Figures 11 and 12 show the projections of stimulations from the spinal cord ariving through the reticular formation and being distributed appropriately to the varrious other parts of the limbic and cortical systems according to the nature of the stimulation [104]. After evaluation of the stimulation (comparing the stimulation to previous memories) appropriate responses are generated and distributed by the descending pathways. This would include responses to nociceptive stimulation or psychological stimulation [77].

From PET scan data, we have learned that pain: 1) is mediated by a distributed cerebral network; 2) there are network elements that are common among studies; 3) differences in the activation patterns in these different studies may reflect differences in the perception of different intensities and types of pain; 4) the pain-associated network develops sequentially over time [105]. So it is clear that the perception of tissue injury or potential tissue injury is perceived in the periphery, the noxious signal is transduced by nociceptors, and transmitted to the spinal cord. The initial segregation of the signal occurs at the level of the peripheral nociceptors and at the spinal cord.

Figure 13 shows that primary sensory neurons (Aβ, Aδ, and C fibers) have specific termination patterns in the spinal cord. Aβ fibers enter the spinal cord primarily penetrating to lamina IV and sending collaterals to the dorsal column. Aδ fibers terminate in laminas I and V. C fibers normally terminate in lamina II. Since Aβ fibers are large and myelinated, they transmit signals rapidly. Aβ fibers are partially myelinated and transmit signals at intermediate speed. C fibers are small, unmyelinated and therefore transmit signals slowly. Thus, the signals delivered by these fibers are separated by time and space, and thus allow the brain to distinguish different types of stimuli. (See Figure 12 modified from Woolf et al.) [106].

But Mannion et al, have shown that in neuropathic conditions C fibers may die out and the Aβ fibers sprout back to lamina II. Now the brain, receiving signals from Aβ fibers, which normally synapse with spinal cord interneurons that

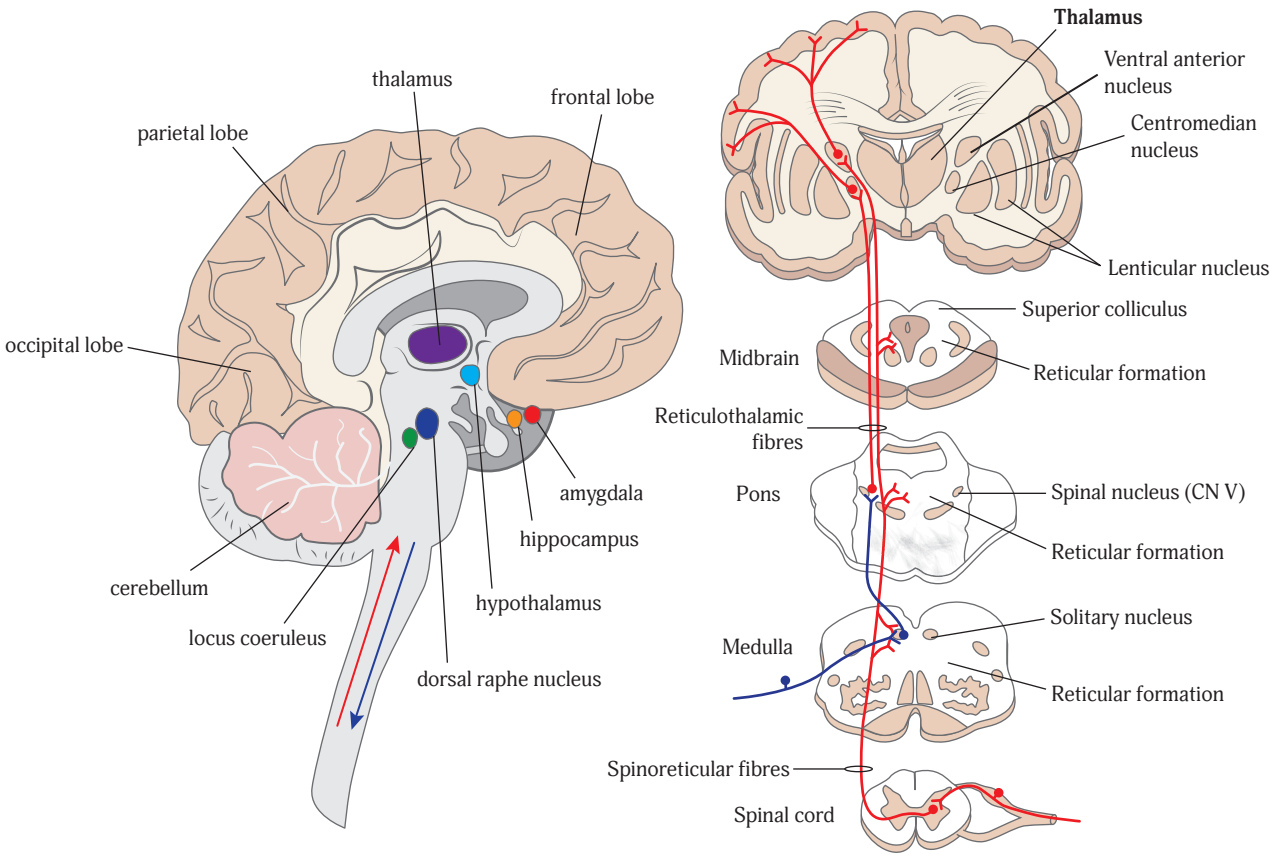


Figure 11. The relationship of the thalamus to the reticular activating system (small red and black arrows) and the other areas of the brain important to memory and pain are shown. *Editorial comment: redesigned for publishing purposes*

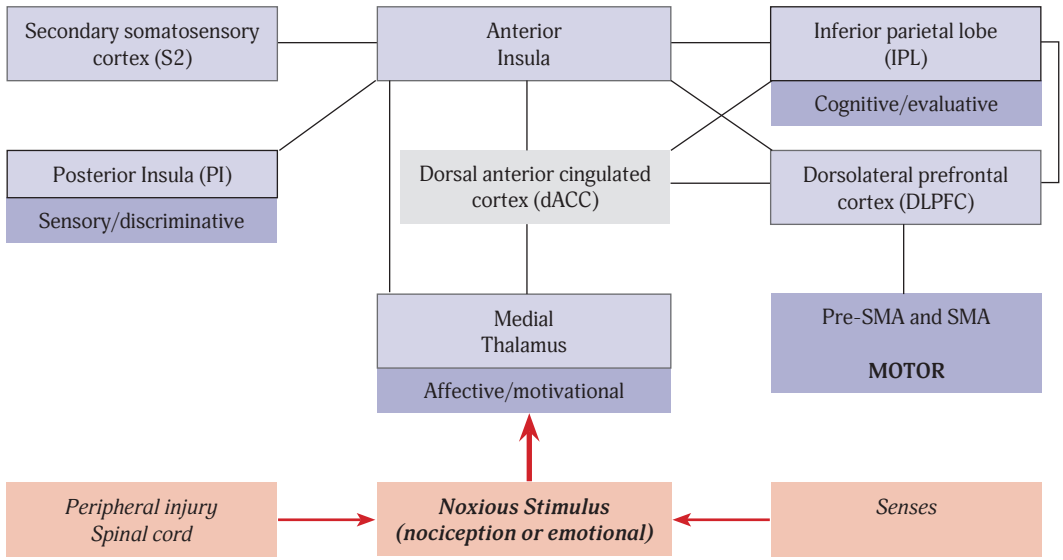


Figure 12. The figure demonstrates the relationship of the thalamus to other areas of the brain that are involved in assessing the significance of a sensory input from the periphery of the body and formulating a response to that stimulus. (Modified from Wilcox CE [103] et al.)

transmit non-nociceptive touch sensations; interprets the signals as if they were generated by Aδ or C fiber synapses, primary and secondary nociception in response to tissue injury and inflammation [107, 108].

On the other hand, Hughes et al did not corroborate sprouting of Aβ fibers into the superficial lamina II and I, [109] and opined that the enhancement of tactile inputs to neurons in the superficial laminas after nerve injury could

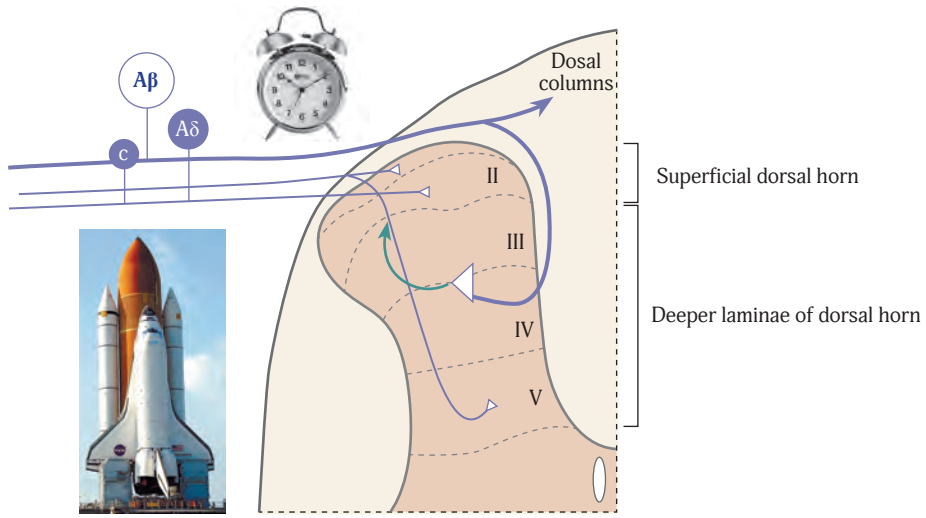


Figure 13. Nociceptive signals to the spinal cord are separated in time and space. *(Mannion R.J., Woolf C.J., Clin J Pain 2000; 16:S144-S156 (Modified)) [107] Editorial comment: redesigned for publishing purposes*

result from increased efficacy of glutamatergic transmission as proposed by Harris et al. [110] or a reduction of GABAergic inhibition in these pathways as surmised by Moore et al. [111]. In any event it is clear that once a change occurs at the spinal cord level, the information being transmitted to the brain is now incorrect.

Shin and Eisenach opined that injury of nerves innervating somatic structures enhances nociception from stimulation of viscera with convergent input from nearby dermatomes. This suggests that somatic neuropathic pain could be accompanied by an increased likelihood of visceral pain [112]. These findings mandate a review of peripheral mechanisms leading to states of peripheral and central sensitization.

Mechanisms of allodynia and hyperalgesia in neuropathic pain

Allodynia and Hyperalgesia are the two most constant features of neuropathic pain and often associated with apparent opioid tolerance. Very intensive research has taken place since the 1970s in order to elucidate the anatomical and molecular pathophysiological changes that occur in the spinal cord. These changes lead to the conditions of increased pain to a normally noxious stimulus (hyperalgesia) and pain to a normally innocuous stimulus (allodynia), which frequently accompany spontaneous pain in patients with injury to the peripheral nervous system, whether the injury stems from a traumatic, a metabolic, or a chemotherapeutic cause [112].

Enormous strides have been made in our understanding of the biochemistry and even genetics of pain transmission and neuronal processing of information. The following will of course be incomplete, since there are still gaps in our knowledge. Nevertheless, this review intends to be comprehensive enough for clinical relevancy and academic study.

As already discussed, synaptic plasticity is fundamental to many neurobiological functions, including memory and pain. Central sensitization refers to the increased synaptic efficacy established in somatosensory neurons in the dorsal horn of the spinal cord following intense peripheral noxious stimuli, tissue injury or nerve damage. This heightened synaptic transmission leads to a reduction in pain threshold, an amplification of pain responses and a spread of pain sensitivity to non-injured areas [113].

In the cortex, long term potentiation (LTP) – a long-lasting highly localized increase in synaptic strength – is a synaptic substrate for memory and learning. Analysis of the molecular mechanisms underlying the generation and maintenance of central sensitization and LTP indicates that, although there are differences between the synaptic plasticity contributing to memory and pain, there are also striking similarities [114].

Recently it has been discovered that, by means of up-regulating the function of N-Methyl-D-aspartate *(*NMDA) receptors, the Src kinases mediate the induction of long-term potentiation (LTP) in the CA1 region of the hippocampus, or long-term depression (LTD) which is also NMDA receptor activation dependant [115]. This enhanced NMDA receptor function boosts the entry of Ca^{2+}, which may thereby trigger the downstream signaling cascade, ending in potentiation of non-NMDA receptors. This functional role for Src may be important in physiological and pathophysiological processes in the central nervous system including the perpetuation of chronic pain and cytotoxicity of brain cells [115].

Rivat et al have shown that even non-nociceptive environmental stress (NNES) can induce analgesia (SIA) through endogenous opioid release [116]. Unfortunately, the animals exposed to non-nociceptive stress in early life also may become hypersensitive to nociception in later life. Previous studies reported that a single opioid exposure activates NMDA receptor dependent pro-nociceptive systems leading to long-term pain vulnerability after analgesia. 116 Rivat, et al., confirmed that prior inflammatory pain or exposure to opioids favor the development of pain vulnerability after non-nociceptive environmental stress (NNES). This indicates that low levels of opioids induce opposite effects, which are analgesia vs hyperalgesia; depending on prior life events (Epigenetic Memories) [116].

Two main experimental models can be related to the clinical appearance of physical pain perception observed in patients. One is the model of inflammation, and the other is the model of nerve injury. As mentioned earlier, models for visceral pain have also been described [112]. With these models, researchers have been able to formulate a better understanding of the mechanisms by which acute pain may lead to chronic pain.

Sensory information is transmitted from the periphery (skin, muscles, viscera, etc.) via sensory afferent neurons through the dorsal root ganglion (DRG) to the central nervous system (CNS) [108, 113, 117]. Receptors of A-delta fibers are usually one stimulus specific and are most likely responsible for responding to intense mechanical stimulation (1st pain). C-fiber terminal receptors are multi modal and respond to different high threshold stimuli [118]. Some A-delta fibers penetrate the dorsal horn to terminate at deeper layers IV and V which are the normal termination sites of A-beta afferents in the dorsal horn of the spinal cord [118]. The WDR second order neurons can respond to input from A-beta, A-delta, and C-fibers, and show a large degree of neuronal plasticity manifesting as increased firing rate with repetitive C-fiber input (known as wind-up), as well as increased receptor field size with repetitive C-fiber activation [119,120].

Information is passed from one neuron to another by means of neurotransmitters, i.e., chemicals that are released from vesicles at the pre-synaptic terminal by the process of exocitosis, which then diffuse across the synapse, to act in some way upon the membrane of the post-synaptic terminal neuron. This process is calcium dependant [73]. Glutamate is the primary excitatory amino acid (EAA) neurotransmitter responsible for sensory transmission from C-fiber primary afferents to WDR neurons in the dorsal horn [119, 120]. Glutamate can act on several EAA receptor sites on the WDR neuron membrane [121].

Two main subtypes of glutamate receptors have been identified based on their molecular cloning, electrophysiological properties, and pharmacologic antagonists [122]. At least twenty separate genes have been identified in the encoding of these receptors [123]. These two main subtypes are inotropic, which are receptors coupled to G proteins and modulate intracellular second messengers such as inositol triphosphate, calcium, and cyclic nucleotides.122 Considering the inotropic ion channel linked receptors, three additional subtypes have been identified based on response to selective agonists which resemble glutamate or aspartate but do not exist naturally [122]. These are:

1. N-methyl-D-aspartate (NMDA)
2. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)
3. Kainate (NK1, NK 2)

Activation of these receptor sites by glutamate leads to opening of the channels and influx of calcium and sodium into the neuron [108, 124]. The influx of positively charged ions leads to depolarization of the membrane and activation of voltage gated calcium channels [122]. This leads to further calcium influx and if unchecked eventually to wind up, gene expression, phenotypic changes within the spinal cord dorsal horn cells, new protein production, acute opioid tolerance and hyperalgesia, central sensitization and finally at the brain level neurocitotoxicity [113, 122, 125, 126, 127, 128, 128, 130] (Figures 14, 15).

At least four types of voltage-dependant calcium channels have been identified, each with specific properties and antagonists [131]. The influx of calcium by way of activation of the NMDA receptors leads to mobilization of intracellular calcium and to subsequent cascades of intracellular biochemical events and changes in second messenger systems [113, 118, 122, 125].

Stimulating a neuron produces a baseline response [132]. Some neurons such as A-beta fibers have a response that is proportional to the intensity of the stimulus over a very wide range [132]. Other neurons such as some C-fiber neurons will fire with an increasing response to a continued stimulus barrage and at some point; the response will begin to increase out of proportion to the intensity of the stimulus [132]. Further, the response may continue even after the stimulus has been removed [133, 134]. This phenomenon is known as wind-up and has been demonstrated by direct stimulation of neurons in the absence of pathology such as inflammation or nerve injury. [132]. And wind-up can occur while animals are under deep general anesthesia [132]. Basal pain (also known as first pain) is targeted through the AMPA receptor [132]. First pain can also occur in animals under deep general anesthesia [47, 132].

Receptors determine what effect neurotransmitters will have. Glutamate, the primary EAA neurotransmitter for excitation, as well as other peptides such as glycine are released from the primary afferent neuron and activate the AMPA receptor [47, 113, 132]. Primary hyperalgesia or allodynia is therefore a peripheral event [46].

Activation of the AMPA receptor allows its ion channel to open permitting the influx of calcium and sodium ions and depolarize the membrane [122]. The AMPA receptor has a 2,3-benzodiazepine modulator site on the receptor which can modulate the response of this receptor to continued stimulation [122]. Activation of the AMPA receptor is a prerequisite for activation of the NMDA receptor which is responsible for secondary hyperalgesia, wind-up, and other exaggerated neuronal responses [47, 113, 122, 141, 149].

It appears that after AMPA receptor activation and subsequent voltage shift towards depolarization of the neuron membrane as a result of influx of sodium and possibly calcium, the magnesium block of the NMDA receptor channel is removed, allowing glutamate and the co-agonist glycine to activate the NMDA receptor [46, 122, 127, 128, 132].

This process involves the inhibition of Na^+/K^+-ATPase by zinc, causing a coincident increase in $[Na^+]_i$ and activation of "Src kinase" resulting in the potentiation of NMDA receptor activity followed by a lasting up-regulation of NMDA receptor activity. In brain cells cytotoxicity can be mediated by the same signaling cascade involving the Na^+/K^+ ATPase and Src (Figure 16). [135, 136, 137, 138, 139].

The glycine site must be occupied in order to activate the NMDA receptor and glycine site blockade is effective in re-

versing mechanical hyperalgesia in inflammation and neuropathic pain models [138]. Activation of the NMDA receptor results in calcium influx into the cell. Thus in order to activate the NMDA receptor-channel, certain particular conditions must be met; the presence of glycine as co-agonist in addition to glutamate, together with a non-NMDA (e.g., AMPA) induced depolarization (setting in motion the zinc modulated production of Src kinase) to remove the magnesium channel blockade [132, 136].

Continuous or intense C-fiber stimulation occurring at the periphery can lead to NMDA receptor activation by the above mechanism and lead to wind-up [129, 133, 140]. This can be facilitated by peripheral events such as inflammation or peripheral nerve injury. Non-noxious stimulation will not normally lead to wind-up. This phenomenon of wind-up is also known as spinal sensitization [113, 118, 133, 141].

Proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which are released in response to inflammation or tissue injury and trigger activation of other cytokines, are associated with development and maintenance of inflammatory and neuropathic pain [142]. Besides glutamate, C-fibers also release peptides such as substance P; but the release of these is separated in space and time from release of EEA's [133]. Substance P along with glutamate can activate neurokinin receptors and contribute to depolarization unblocking of the voltage-dependant magnesium blockade of NMDA receptor channels.[143, 144, 129] [129, 143, 144].

Ketamine, an NMDA receptor antagonists as well as substance P antagonists can both block C-fiber afferent evoked temporal summation of impulse discharges of the dorsal horn neurons but not Aδ-afferent evoked responses [133, 144, 15, 146]. Since NMDA receptor activation appears necessary for wind-up and hyperalgesia to occur, and since the NMDA receptor remains inactive under physiologic concentrations of magnesium even in the presence of glutamate [144], it appears that modulation of NMDA receptor activation is a neuroprotective mechanism.

Activation of the AMPA receptor channel precedes activation of the NMDA receptor, opening the channel to the influx of calcium into the neuron [144]. The influx of calcium into the neuron has then been shown to be associated with a host of intracellular biochemical events leading to increase activation of NMDA receptors (positive feedback system), increase spontaneous discharge frequency, expanded receptive fields, wind-up and the behavioral manifestations of allodynia and hyperalgesia [46, 118,122, 126, 127, 133, 141, 144, 148, 149, 150, 151].

The initial biochemical event linked to influx of calcium after activation of the NMDA receptor by the EAA glutamate is activation and translocation of protein kinase C (PKC) [113, 122, 141]. As indicated earlier, influx of calcium also leads to increased transcription of immediate early gene (IEG) c-fos, which may regulate the subsequent expression of the endogenous opioid genes preproenkephalin and preprogynorphin [118, 152, 153]. The appearance of another immediate early gene c-jun is also thought to be a marker of neuronal injury. The generation of nitric oxide (NO), also known as endoplasmic relaxing factor, via the induction of the enzyme nitric oxide synthase (NOS) leads to diffusion of NO gas back to the presynaptic membrane and facilitation of the release of additional glutamate [148, 154, 155, 156].

Nitric oxide by diffusing out of the cell has a positive feedback effect on the presynaptic neuron, facilitating further release of glutamate and increasing the efficiency of activation of NMDA-receptors [129, 148, 151, 156]. Substance P stimulated activation of NK1 postsynaptic receptors leads to gene transcription with the appearance of c-fos [129, 157, 158]. New mRNA coding for new protein kinase C (PKC) then appears within thirty minutes of stimulation leading to further NMDA receptor activation [153, 155, 157]. Pre-treatment with morphine can reduce c-fos formation [159, 160, 161]. But once the gene has been activated, the consequences of its expression may be much more difficult to counter. [122] Increases in c-fos and PKC have been correlated with development of opioid tolerance [127, 144].

Opioids, presumably by their ability to reduce the release of presynaptic transmitters or to inhibit interneurons early in nociceptive pathways initially reduce or block the c-fiber inputs into the dorsal horn WDR neurons [127, 159]. But if c-fiber stimulation continues, wind-up breaks through, probably because of the development of opioid tolerance, possibly again through actions of PKC on the mu receptor in the WDR neuron membrane and uncoupling of G proteins from mu receptor activation [126, 127, 129, 160, 161, 162].

Wind-up is thus a phenomenon of both acute and chronic pain [113, 132, 141]. Opioid tolerance can be prevented by administration of CNQX, a non NMDA receptor blocker, which also prevents machano-allodynia and hyperalgesia [144]. Opioid tolerance can also be prevented by administration of NMDA receptor antagonists like Ketamine, MK-801, and dextromethorphan [118, 153]. These mechanisms are extensively reviewed by Manion et al.,Costigan et al., and Latremoliere and Woolf [108, 113, 141]. Brookoff gives us a simplified cartoon of the above events (Figure 14).

Figure 16 shows that when the process of central sensitization results in bombardment of the brain with nociceptive signals (or at least what the brain suspects to be nociceptive stimuli) the same process of activation of NMDA receptors can take place, leading to calcium influx, which in the case of brain cells, can lead to cytotoxicity and cell death [130]. Apkarian et al have shown that patients with chronic low back pain followed with serial MRI scans over long periods of time loose brain mass [163].

There are three main opioid receptor types. The Mu opioid receptor is the most ubiquitous and most well studied. It is active in antinociception and analgesia, in the brain, the spinal cord, and in the periphery. It is also active with respect to the side effects of opioids such as sedation, respiratory depression, pruritis, nausea, and urinary retention. Mu opioid tolerance develops in chronic neuropathic pain because of uncoupling of the G-protein from the Mu receptor inactivating the function of control of the K^+ channel [126, 127, 129, 136, 138].

More recently, interest is gaining in the development of Kappa specific opioids that would function primarily in the

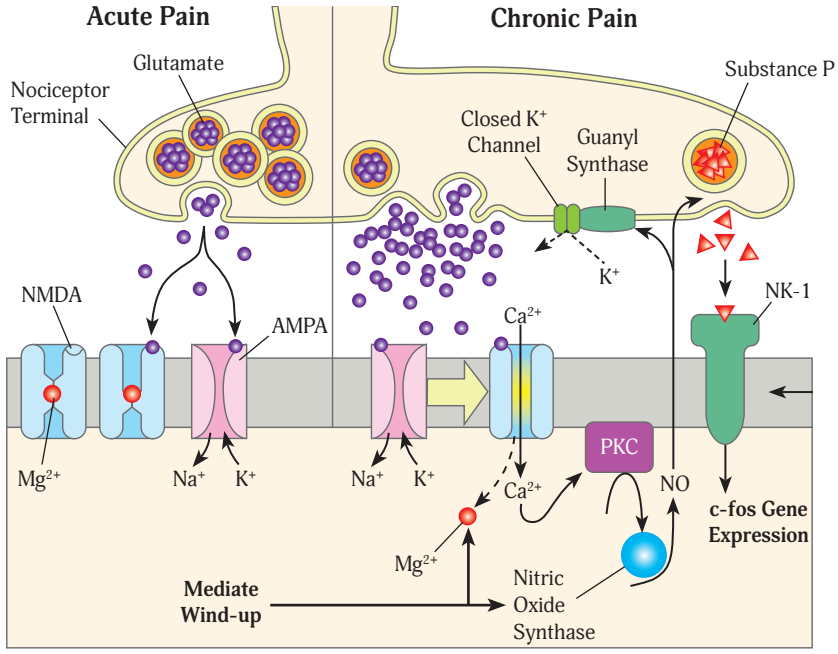


Figure 14. Protein Tyrosine Kinase – opens NMDA channel of the wide dynamic range (WDR) post synaptic membrane (Src kinases which are Zinc dependant). Protein Tyrosine Phosphatase – closes NMDA channel, Striatal Enhanced Phosphatase (STEP) – closes NMDA channel.
(Brookoff D. Chronic Pain: 1. A New Disease? Hospital Practice 2000;35 No 7:45-59) [129]. *Editorial comment: redesigned for publishing purposes*

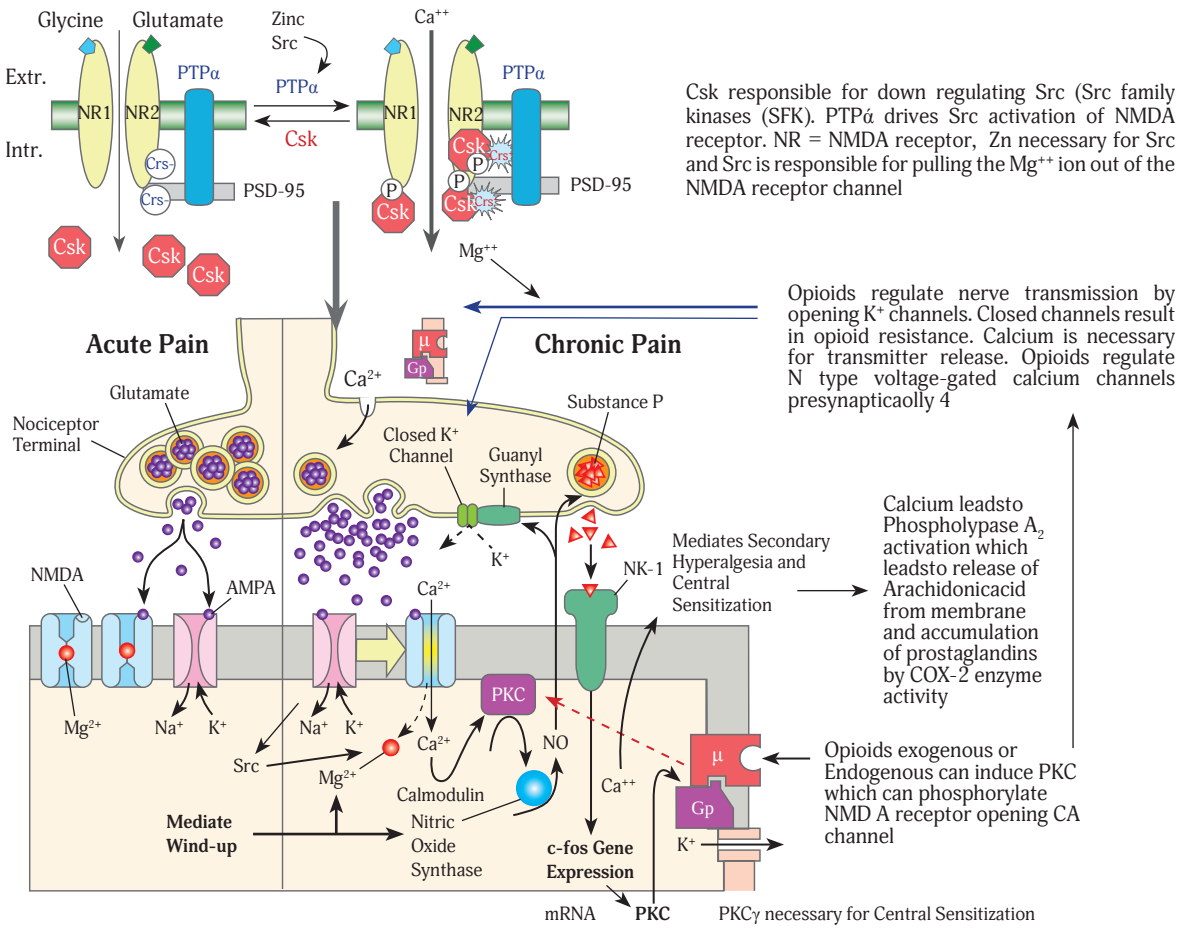


Figure 15. The figure depicts a more complex summary of the events leading to wind-up and central sensitization. *(See text for explanation)*
Modified from Mayer et al, Mao et al, Brookoff, Groveman, and Manzerra et al. [126, 127, 129, 156, 158]. *Editorial comment: redesigned for publishing purposes*

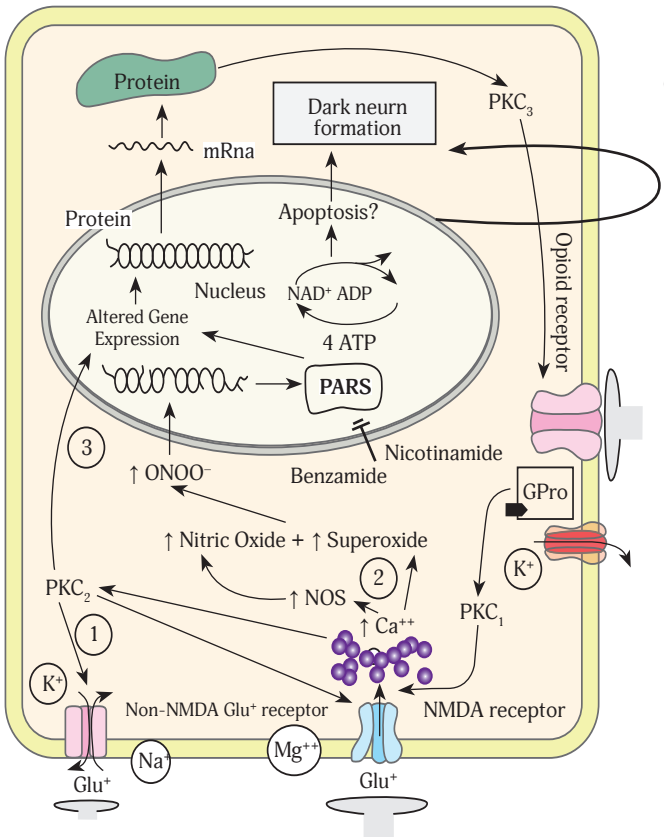


Figure 16. 1) AMPA receptor activation leads to 2) NMDA receptor channel opening with influx of Ca^{++}, as well as, 3) nuclear gene expression, and eventually 4) apoptosis (cell death) modified [130]
Editorial comment: redesigned for publishing purposes

periphery to reduce acute nociception from tissue injury and inflammation. Intra-articular injection of non-systemically active doses of morphine into joints has been shown to be effective in acute post operative pain and in chronic pain of osteoarthritis [16, 165, 166].

Delta opioid receptors are also attracting interest in that they may play a role in modulating opioid tolerance, dependency and addiction. There are other mechanisms of modulation within the nervous system other than from opioids, which act to reduce or prevent wind-up or second pain. The GABA system for example which probably acts by preventing or reducing access of A-beta afferent stimulation into a sensitized dorsal horn, an important component of the gate control system [167]. Once wind-up occurs and receptor fields have been expanded, allodynia and hyperalgesia may be stimulated even by light touch or thermal stimulation of A-beta or A-delta and C-nociceptors [141, 144].

Of course, all peripheral stimuli that reach the dorsal horn neurons are eventually transmitted to higher centers in the brain for processing where nociception is perceived as pain. Besides local modulating systems, the brain has multiple descending modulating systems which can be incorporated into a defense against wind-up and the production of allodynia and hyperalgesia of chronic pain states (refer back to figures 5 and 6 [53, 68, 168].

Central sensitization leading to cell death in the brain

Kapitzke et al present a complete review of the role of immune cells attracted to inflammation and the role of endogenous release of opioids that suppress nociception in the periphery [168].

Cytotoxicity produced by wind-up and transmission of excessive stimulation to the brain leading to excessive glutamate release and intracellular calcium buildup can lead to failure of central modulation (Figure 15) [122, 169]And this may well result in chronic pain. Phase three pain could then be considered the state of chronic pain when there is a complete dissociation between stimulus and pain experience, pain as the disease, "Maldynea." [17].

Lesions in the dorsal funiculus will knock out three descending pathways. In this model inflammation will lead to rapid production of hyperexcitability. Blocking brain serotonergic descending pathways leads to an increase in spinal dorsal horn c-fos levels and increased hyperalgesia in inflammation. Enhancement of serotonergic descending pathways inhibits c-fos appearance and hyperalgesic behavior in animal inflammatory models [53, 56]. Small sensory neurons like c-nociceptors are dependent on Nerve Growth Factor (NGF) for survival. Endogenous NGF is increased in the presence of inflammation, but is also associated with the development of hyperalgesia [170].

Therefore signal transduction through NGF appears to be a necessary component of at least some inflammatory pain states [171]. Selective antagonists to NGF like trkA-IgG can both block the development of hyperalgesia to inflammation but also reverse established hyperalgesia [172]. But trkA-IgG does not block first pain. It would however, be most useful for chronic inflammatory pain, but requires inflammation to be present for systemically administered drug to reach its necessary peripheral site of action [173]. It is abundant in the CNS and found in 70% of sensory c-fibers. It acts on NKI (NK2) receptors in the dorsal horn [173].

Substance P is released both antidromically in the periphery as well as presynaptically from c-fibers in the dorsal horn spinal cord [141]. Pre-protachkinin and NK1 receptors are upregulated by peripheral tissue damage. Substance P injected intrathecally produces hyperalgesia, and dorsal horn spinal cord neurons are excited by substance P. NK1 receptor antagonists block the windup and facilitation of intense nociceptive input (second pain) but do not block acute nociception (first pain) [174]. They may be effective in both nerve injury nociception and inflammatory nociception. NK1 antagonists also appear to have the effect of reducing the nausea from morphine [175].

Summary

As Daniel Brookoff aptly stated, chronic pain continues to be perceived as a characterologic disorder rather than a serious, potentially fatal, medical disease. The general lack of understanding of how persistent pain becomes magnified and ingrained prevents many patients from receiving the level of

care that they need to regain control of their lives and resume normal activities [129].

Heisenberg's Principle states that it is theoretically impossible to simultaneously measure both the position and the velocity of an electron, as measuring either one disturbs the other. In studying the nervous system, increasing the precision of the measurement decreases the connectivity of the neurons under observation and vice versa [176]. Fromm implies that in order to study the connectivity of the central nervous system to its neurons, that it is therefore necessary to integrate data obtained from all investigative techniques and synthesize a comprehensive theory of memory, reaction, modulation, failure of modulation, suffering, and pain; as well as response to therapy [176].

Noxious stimulation in the periphery leads to activation of nociceptors and the transmission of signals to the central nervous system which will lead to the perception of acute pain (First Pain). If tissue injury occurs, a host of secondary events take place both in the periphery and centrally which if not modulated or moderated, will lead to a facilitated state of hyper-sensitization, wind-up, allodynea and hyperalgesia (Second Pain). This is true for visceral pain as well. If this does not resolve, a state of chronicity will be established that can remain as perceived pain in spite of resolution of the original injury in which there is dissociation between the pain experience and the inciting stimulus (Phase Three Pain). Likewise, peripheral or central nerve injury leads to abnormal neuronal processing of non noxious stimulation, again leading to a facilitated hypersensitized state, with wind-up, allodynia, hyperalgesia, opioid tolerance, and chronic pain.

But as has been discussed and first proposed by Engel, what appears to be the initiating event that started the patient towards chronic pain, e.g. surgery, or a whiplash, is actually the culmination of a series of events (Hits) that have taken place over the lifetime of the individual, resulting in establishing the chronic pain prone personality which is a function of the mind [127, 177].

Buchheit et al describe how identical twins, with identical genetic makeup and presumed identical histones at birth, have different outcomes following total knee arthroplasty surgeries in later life [150]. They opined that environment pressures, physical and psychological pressures on one twin may differ from the experiences of the other twin. One twin develops chronic pain and the other has a successful surgical outcome. The chronic pain twin had already undergone changes within the central nervous system and synaptic development of pain related memories, enhanced by the multiple hits resulting in the poor outcome to the final hit [23]. This is not unlike the results that Schofferman and his associates reported for lumbar spine surgery [3].

The chronic pain can now present as psychological trauma that remains as enigmatic pain long after the initiating events. And this may also explain the enigmatic pain of FM which is without a doubt a manifestation of central sensitization [177].

The problem however as Grzesiak postulated, is that vulnerability to chronic pain is the result of a complex interaction of conscious and unconscious memories that promote suffering [27, 77]. Often the actual memories have remained dormant until some current life event brings forward the expression of the long hidden suffering. Grzesiak also reminds us that "trauma" is not processed by linguistic encoding, but rather by implicit sensory storage that is not accessible to verbal psychotherapeutic inquiry [77]. So the true dilemma becomes apparent that if we cannot illicit the history of traumatic events, we can't prepare the patient for the trauma of surgery, or understand the reason behind the suffering of chronic pain for which no physical sign is apparent. However, age regression hypnosis may provide an avenue to those repressed memories.

Grzesiak rightly states that trauma does not lead to psychogenic pain [77]. The human body is well equipped to deal with the stress of trauma (physical or emotional). Trauma instead causes a neurobiological vulnerability in various neuroregulatory systems that enhances or sensitizes the psychological processing of sensory information so that perception of pain becomes a "synergistically-elaborated aggregate of peripheral neural transmissions and idiosyncratic, psychodynamic meanings." [77]

Research into the mechanisms of chronic pain have centered on the identification of the target receptors which could be blocked or activated selectively to prevent sensitization and wind-up. Identification of those at risk through genetic testing, identification of phenotypic protein markers, better complete medical and psychosocial history taking, and early intervention to prevent wind-up may lead to the prevention of chronic pain. This requires a paradigm change away from treatment of chronic pain to prevention of chronic pain by aggressive management of acute pain states and emotional traumas, most likely through a genetically guided, polypharmacy, multi-modality delivery approach.

The capacity of the brain to process, store, and use information subserves such a considerable number of functions that it is generally believed that there is no cognition without memory. [178, 179, 180]. The process of memory formation in the brain does involve NMDA receptor activation, yet at the same, activation of NMDA receptor activation in the brain can be cytotoxic to brain cells. If one were to propose that the Off Cells of the RVM undergo apoptosis as a result of NMDA receptor activation, a major opioid related endogenous modulating pain system would become non functional. The patient would remain with only active On Cells and could result in the total body pain syndrome observed in many sufferers of chronic pain.

The Pain Experience belongs to the patient. Ultimately pain is always in the patient's head. But we are rapidly learning that recognition of the alterations in the phenotypic expression of the patient's genetic makeup ultimately will help us understand why the patient is experiencing chronic pain…why the patient continues to Hurt. In Figure 17 is a schematic representation of how various "hits" can lead to memories of "painful events." If in the future physicians can diagnose protein changes within the brain that represent these "painful memories," it may be possible to change protein synthesis within the brain through such mechanisms as the use of viral vectors to deliver mRNAs to the affected cell types [179].

Memory formation, consolidation and transformation
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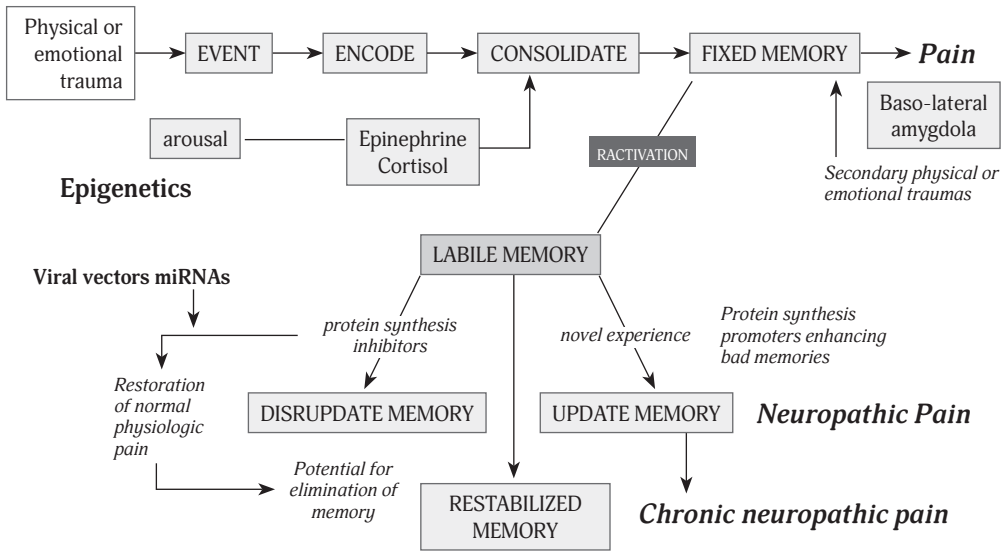

Figure 17. Schematic representation of how various "hits" can lead to memories of "painful events."
(Modified from Nadel et al and Chavez et al.) [92, 180]

"Absence of evidence is not evidence of absence!" Carl Sagan, Astronomer.

"The ancestor of every action is thought." Ralph Waldo Emerson.

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Патофізіологія хронічного болю

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Резюме: *Гострий біль завдає шкоди і найчастіше є результатом тканинного ураження. Дія хронічного болю така сама. Хоча ті, хто страждає від хронічного болю, також схильні пов'язувати ці напади з пораненням, хворобою або хірургічним втручанням, першопричина є значно складнішою. Хронічний біль найчастіше не супроводжується жодним шкірним проявом, пов'язаним з ушкодженням, хворобою або хірургічною маніпуляцією. І майже завжди ті, хто страждає від хронічного болю, також мають різні форми депресії та/або тривоги. Було з'ясовано, що процес центральної сенситизації, який є результатом травмування тканини, полягає у множинних молекулярних змінах у мозку, що закріплює хронічний біль. Генетичні, епігенетичні, стресові чинники навколишнього середовища та емоційні фактори – усі вони відіграють роль у зміні ступеня розвитку стану хронічного болю. Дана стаття з'ясовує, як формується у мозку синаптична пам'ять внаслідок і фізичних, і емоційних травм (мультимодальні чинники ураження), що призводять до прогресування хронічного болю, у зв'язку з порушенням у мозку низхідних модуляторних механізмів, які контролюють «біль» або запобігають його появі.*

Ключові слова: *епігенетичні чинники, пам'ять, центральна сенситизація, хронічний біль.*

Патофизиология хронической боли

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Резюме: *Острая боль вредит и чаще всего является результатом повреждения ткани. Хроническая боль также вредит. Несмотря на то, что страдающие от хронической боли также склонны связывать ее атаки с ранением, болезнью или хирургическим вмешательством, первопричина намного сложнее. Чаще всего хроническая боль не сопровождается кожным проявлением, связанным с повреждением, болезнью или хирургической процедурой. И почти всегда страдающие от хронической боли имеют также различные формы депрессии и/или тревоги. Было определено, что процесс центральной сенситизации, являющийся результатом повреждения ткани, заключается во множественных молекулярных изменениях в мозгу, что закрепляет хроническую боль. Генетические, эпигенетические, эмоциональные и стрессовые факторы окружающей среды – все они участвуют в смене стадии развития состояния хронической боли. Статья определяет, как в мозгу формируется синаптическая память в результате и физических, и эмоциональных травм (мультимодальные факторы повреждения), что приводит к прогрессированию хронической боли, в связи с нарушением мозговых нисходящих модуляторных механизмов, контролирующих или предупреждающих «боль».*

Ключевые слова: *эпигенетические факторы, память, центральная сенситизация, хроническая боль.*