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'Pain Memory': A Brief Review

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Abstract

In neurobiology, a changed response to the same stimulus means "learning", whereas the retention of these changes is called "memory". These terms encompass a variety of neuronal and behavioral processes, including chronic pain.

It is not uncommon many of our patients ask us questions such as "similar pain experience", or "reminds me of a previous pain I had". We unfortunately come short in interpreting their statements. It behooves us to familiarize ourselves with these terms, including "memory pain", "recalled pain", and similar pain memory experiences.

Accumulating evidence suggests chronic pain is a type of nociceptive memory. Evidence from recent studies further supports the idea pain is a network phenomenon not mediated by single proteins or a single brain region, but by multiple pathways at different levels: cortical, subcortical, spinal, and peripheral levels.

At a cellular level, severe pain or trauma leads to long-lasting changes in the CNS making the brain "hypersensitive" to future pain. Specifically, the enzyme PKM-zeta is believed to play a key role in building and maintaining these memories.

If we divided the pain memory into subheadings, we would possibly have a more organized way of describing pain memory and memory cells into hormonal level, neurochemical, brain level, and brain matrix level.

At a hormonal level: During a stressful or traumatic event, the body releases hormones like only part of the puzzle. At a neurochemical level and brain-based memory: cortisol and adrenaline, which encode emotional memories more robustly. At a brain matrix level, the brain's memory and emotional centers encode trauma as if it were "still happening," maintaining a state of high alert to protect the body from "threats".

Conclusion: Implications of cellular mechanisms, particularly neurons and immune cells, that can "remember" an injury or a pain, is becoming a plausible theory of pain memory cells.

Evidence points that chronic pain is a type of nociceptive memory. It is stored through epigenetic modifications, changes in gene expression, and cellular communication, affecting future pain experiences. Alterations in immune cells, such as macrophages, leads to a lasting "memory" that worsens the pain and plasticity and makes the pain persist.

At a cellular and molecular level, pain memory involves alterations in gene expression, how cells transcribe/translate proteins, and the physical structure of DNA.

Chronic pain changes structures of neurons, such as the dendritic spines, affecting connections between cells and the ability to recall pain memory.

Pain memories are stored in neurons, including those in prefrontal cortex, involved in emotion and learning. Immune cells, like macrophages, can also carry a long-lasting pain memory. More research is needed to study pathways at cortical, subcortical, spinal, peripheral levels.

Keywords: Plasticity, memory cells, memory pain, nociception, chronic pain, BDNF, PKC, LTP, DNA methylation, epigenetics, plasticity

Introduction

It is estimated that 20% of the world population suffers from chronic pain. This poses a huge economic burden on any country's health system. In addition, it is associated psychosocial interruptions, emotional dilemma, work and income issues, and lack of sleep related consequences. Despite the substantial advances in our understanding of how pain mechanisms work, there remains a significant puzzle as relates to pain memory, recalled pain, and what causes the pain experience and its memory.

For pain memory, the in-depth understanding of the pathways involved, the role of hippocampus, cell signaling, gene transcription, epigenetics, the concepts of plasticity, synaptic connections, LTP, memory consolidation, cell signaling, and transmission, all allowed us better explanation of how pain has its own memory. Yet, all these discoveries do not explain the cascades that take place. These remain theoretical interpretations in an ocean of neuroscience.

In this manuscript, we will review the most recent plausible theories related to the memory of pain. We will divide these theories into a) psychological and neurocognitive approach, and b) neuro-molecular and neuro-biological approach.

Psychological and Neurocognitive Theories Behind Pain Memory:

1- Brief Review of "Founding Theories" related to Pain Memory:

The year of 1957 witnessed the earliest theoretical talk about pain, and its memory came from Ernest Jones, a Welsh psychoanalyst[1]. He postulated that the inability to vividly remember past pain is a result of intense 'repression'. He called it a 'defense mechanism' that pushes the painful experience out of conscious, imaginative memory to protect the ego from distress and threat [1].

In 1972, in a book chapter, Endel Tulving, theorized there were 2 types of memories of pain [2]: episodic and sematic as two parallel and partially overlapping processing systems. He elaborated the differences between the two reside in the: a) nature of stored information, b) denotative reference of input events, c) conditions and circumstances of retrieval, and d) the susceptibility to interference and erasure of input events [2].

In 1979, the pain pioneers, Dennis and Melzack [3], conducted studies on rats after dorsal rhizotomy. They found that painful "irritation triggers central neural activity" characteristic of normal pain processing, and that the "pain memory" continued "unchecked, thereby accelerating the onset of the abnormal central neural activity which triggers biting or chewing responses" [3].

In 1990, in humans, Katz and Melzack, studied amputation pain in 60 amputees[4]. They concluded that "somatosensory inputs of sufficient intensity and duration, produces lasting changes in central neural structures which combine with cognitive-evaluative memories of the pre-amputation pain to give rise to the unified experience of a past pain referred to the phantom limb"[4]. In this study, for the first time, there was a clear differentiation of 2 major components of pain memory: a somatosensory and a cognitive aspect [4].

We will not explicitly delve in the advances past the early 1990s, but we will address the most important ones as we cover the topic of pain memory. In the authors' opinion, after the pioneering work of Dennis and Melzack, on pain memory, this area of neurobiology amassed huge interest that exploded with heavy interest in bench lab work and clinical research. The advances in the field of medicine and surgery, with more procedures and post-operative challenges taking place, posed more challenges on this field. More attention was paid to fighting pain, being a human right, and more efforts were placed to the change of acute pain to chronic. The fields of pain memory, pain neurobiology, and translational pain, amassed massive interest in the decades to follow, especially with the discoveries of new pathways, neurotransmitters, and relationship of neurons with glial cells, immune cells, growth factors, and much more. New concepts in pain emerged, such has plasticity, hyperalgesia, centralized pain, resistant neuropathic pain, and the roles of nociceptors, brain derived neurotrophic factor (BDNF), early and late Long-Term Potentiation (LTP), Protein Kinase C (PKC) particularly PKC zeta, Zeta Inhibitory Peptides (ZIP), role of spinal dorsal horn, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPARs), and much more.

2- The Concept of Autobiographical in Pain Memory:

While Francis Galton is credited with being the "founding father" of the psychology of autobiographical memory for his early experimental work in the 1870s, the specific term "autobiographical memory" was more widely adopted and popularized later, particularly through the work of researchers like Ulric Neisser in the late 20th century[5].

Autobiographical memory refers to a memory consisting of episodic memories (memory of events) for specific previous experiences, and semantic general knowledge about oneself and the world [6,7]. The episodic memory is a neurocognitive system, different from other memory systems, that allows humans to remember previous experiences [6]. Episodic and semantic type memory are interconnected together and are interdependent and affect one another throughout the stages of memory processing [8].

3- Hippocampus as a Locus of Autobiographical Memory:

The site of pain memories and experiences point to the Hippocampus as the area of pain memory[9]. Research showed that parahippocampal cortex, specifically in the posterior parahippocampal gyrus is responsible for recollection (encoding and retrieving)

information, whereas the perirhinal cortex, located in the anterior parahippocampal gyrus, is responsible for familiar information, (encoding and retrieving) and specific item information[9]. To confirm the hippocampus as the site for pain memory, researcher used neuroimaging studies and confirmed, the right anterior hippocampus has abnormally lower activity and reduced connectivity to the medial prefrontal cortex in chronic low back pain patients [10].

The right hippocampus is "integral to the recollection of perceptual memory content, a defining feature of episodic memory" [7,11]. Research showed the right hippocampal activity is important for the retrieval of "perceptual episodic memory content". If damaged, the right hippocampal negatively interferes with activation of the areas that are responsible to process perceptual memory content. This study conformed the hippocampus contributes to recollection by "retrieving and integrating perceptual details into vivid memory constructs" [11].

4- Interconnection of Hippocampus to the Cortex:

Ayoub et al, demonstrated an interconnection between the right anterior hippocampal regions and the medial prefrontal cortex[10]. She demonstrated chronic pain can occur when there is abnormality in the functional connectivity between these regions[10]. Mutso at al, using functional MRIs, to identify intrinsic and extrinsic hippocampal functional connectivity, also concluded the reorganization of processing within the hippocampus and between the hippocampus and the cortex was found as a culprit in the transition of pain from subacute to chronic pain, and underlined the learning and emotional abnormalities associated with chronic pain [12].

It is worth mentioning that this section is much more elaborate in details than it is. In normal physiological cases, the connectivity of hippocampus to the cerebral cortex is very complex. In pathology, it is even more intricate and complicated, and it is not the goal of this manuscript to delve in those details.

Neurobiological and Molecular Basis Behind Pain Memory:

1– **Pain Plasticity and Pain Memory:**

Simply put, the brain's ability and capacity to change and adapt is plasticity. Pain memory is the persistence of pain signals within the brain, even after the original insult has passed and healed. The brain is unable to extinguish the pain signaling.

For the brain to change and adapt, neuroplasticity includes structural and functional changes for the brain to undergo to enable it to adapt to environmental changes, to learning, memory, and even rehabilitation after the brain is injured[13]. That fact is the neurochemical foundation for memory formation [14].

2– **Initial Nociceptive Stimulation and Transmission of Pain Signals**

Pain perception is a very complex and intricate cascade of events. It involves the peripheral and central nervous systems. Multiple nerve components, cells, and molecules work in sync to underlie the transduction, transmission, modulation and perception of pain signals [15]. This mechanism begins with 'tissue damage' and ends with perception of pain. The pain receptors, the "nociceptors", are peripheral transducers of pain signals. These are distributed in the skin, mucosal lining, muscles, tendons, bone layers and periosteum, blood vessels, and internal organs [15]. Nociceptors are regarded as the gatekeepers and initiators of pain sensation [15] and are considered the "locus" of pain memory [16].

The terminals of the nociceptors are supplied with ion channels that generate electrical signals via regulation of the ion current across membranes[15]. Without going into many details, there are multiple types of ion channels that are activated depending on the outcome of pain. The electrical signals produced by nociceptors are subsequently transmitted to spinal cord via nerve afferent axonal sensory neurons, that include 3 types of primary afferent fibers depending on the anatomical characteristics and functions, including Aβ, Aδ and C fibers[15].

Past the nociceptive stimulation, a single painful insult can trigger multiple neurons in the dorsal root ganglion (DRG). Spinal projection neurons collect, activate, and convey the intricate signals into ascending pathways, thereby completing the conversion from the peripheral to central nervous systems [15].

Once at the level of ascending tracts, action potentials trigger the release of different excitatory neurotransmitters and neuromodulators. These bind to postsynaptic receptors, activating the excitability of "next level" neurons [15]. Depending on the level and type of stimulation, multiple neuropeptides can be released with each corresponding to each neuromodulating function[15]. Excitatory neurotransmitters include Glutamate, Aspartate, Histamine, CGRP, and Substance P. Inhibitory neurotransmitters include GABA, Glycine, Endogenous Opioids, and Cannabinoids. Additionally, 5-HT function depends on the receptors activated. Norepinephrine can be excitatory (alpha1, beta), inhibitory (alpha2), and Nitric Oxide (excitatory or inhibitory)[15].

At this stage, inflammatory cells, such as mastocytes, neutrophils, microglia, and mediators such as TNF-α, interleukins, prostaglandin E2, work on neurons and associated cells within the nervous system[15]. Activation of the inflammatory cells sensitize nociceptors and decrease pain threshold, bridging responses to innocuous insults and pain sensations caused by stimuli[15], whereas long-term inflammation modulates the nervous system plasticity and causes pain chronicity[15, 17].

3– **Higher Cortical Processing of Pain Signals:**

In addition to the ascending spinothalamic transduction tracts, multiple areas of the brain are involved in the descending pain modulation pathways, such as the periaqueductal gray (PAG) (considered a hub of descending inhibitory apparatus), rostral ventromedial medulla (RVM), lateral reticular nucleus, locus coeruleus, nucleus reticularis paragiagantocellularis, nucleus raphes magnus[15]. These pathways maintain an intricate balance, under normal conditions, but when pain hypersensitivity occurs, it can interfere with this homeostasis [15].

In the brain, there is no one region responsible for pain memory. There are multiple regions that are in constant "talk". Areas responsible for pain perception include: the primary somatosensory cortex, secondary somatosensory cortex, anterior cingulate cortex (ACC), prefrontal cortex (PFC), insular cortex, amygdala, thalamus, cerebellum, and PAG [18].

The areas associated with affective aspects of pain and regulate emotional and motivational responses prefrontal region and limbic system (ACC, amygdala, Ventral Tegmental Area (VTA), and the Nucleus Accumbens (NAc))[18,19,20].

In an elaborate study that demonstrated structural and biochemical plasticity in the role of hippocampal extracellular matrix (ECM) in regulating pain and memory, Tajerian et al reported deficits with decreased hippocampal dendritic function, altered ECM microarchitecture, decreased ECM rigidity, and changes in the levels of key ECM components and enzymes, including increased levels of MMP8, an enzyme involved in breaking down the extracellular matrix,

particularly collagen [21]. She also reported abnormalities in long-term potentiation (LTP) and a loss of inhibitory interneuron perineuronal ECM nets, potentially accounting for the abnormalities in LTP [21]. She also showed MMP8 is upregulated after the injury while its genetic downregulation normalizes the behavioral, electrophysiological, and extracellular alterations [21].

In a study addressing the epigenetic hypothesis of the genome of pain memory, Alvarado et al. stated there were chronic pain changes in rodents' brain anatomy and function, in areas including the hippocampus, amygdala, perirhinal cortex, and PFC [22]. He added that in humans, multiple studies pointed to a "decrease in gray matter, decreased cortical thickness, abnormal cortical function, and altered connectivity in various brain regions in a wide range of chronic pain conditions" [22].

Interestingly, researcher showed that addressing chronic pain with treatment can restore a normal brain function in the adult human PFC [23]. This raises the likelihood that therapies geared towards pathological changes in the PFC have potential therapeutic roles [23].

4– **Pain-Related Gene Expression & Epigenetic Mechanisms in the Frontal Cortex:**

Pain, particularly chronic pain, can lead to significant changes in gene expression within the adult prefrontal cortex (PFC) through epigenetic mechanisms, such as DNA methylation [22]. These changes affect genes related to immune function, synaptic activity, and cognitive processes, and can last long after the initial insult, contributing to chronic pain and its associated cognitive and emotional ramifications [22]. These epigenetic changes in the PFC, alter gene expression without affecting the DNA sequence itself [22]. These gene expression changes can contribute to the "genomic memory of pain," causing long-term structural and functional abnormalities in the PFC [22].

Epigenetic mechanisms are important for long-term synaptic plasticity and modulation of gene expression. These mechanisms regulate gene transcription by helping with physical relaxation or condensation of chromatin. They act as regulators of the molecular changes underlying pain [24]. Epigenetic mechanisms also were epigenetic mechanisms implicated in the development of acute and chronic pain and possibly contribute to the transition from acute to chronic pain states by supporting maladaptive molecular changes [24].

5– **DNA Methylation in the Brain: Its role in Pain Memory:**

DNA methylation is a dynamic process involved in memory and synaptic plasticity[25].

DNA methylation is a mechanism that can "remember" pain experiences by altering gene expression in the brain. As we know, chronic pain can lead to widespread alterations in DNA methylation, particularly in the prefrontal cortex and amygdala, contributing to the persistence of pain and its associated emotional components. These changes can involve both global methylation alterations and specific changes in genes related to pain sensitivity and neuronal function [26]. These researchers showed behavioral interventions that reverse chronic pain also remove differences in DNA methylation in the brain [26].

DNA methylation pertains to forms of DNA chemical modifications. Most DNA methylation sites exhibit aggregated distributions, known as CpG islands. It changes chromatin structure, DNA conformation, DNA stability, and interactions with proteins, precisely regulating gene expression without editing base sequences [15].

Alvarado et al hypothesized a prediction that changes in DNA methylation in promoters and enhancers of individual genes will result in alterations in gene expression contributing to pain-related changes in brain structure and function [22].

It is now well-known DNA methylation contributes to the chronic changes in behavior and gene expression [22]. It provides proof and evidence of linking peripheral injury-triggered central changes in DNA methylation and transcriptional regulation [22]. In addition, long-term alterations in DNA methylation can provide a molecular substrate for chronic pain-related changes in the brain, forming a ''memory trace'' for pain [22].

Conclusion

In reviewing this manuscript, we noticed a scarce data related to pain memory and its genesis. Despite that, the last three decades exhibited a much better understanding of pain mechanisms but also presented with significant challenges in neuroscience to identify the cellular and molecular processes that underlie pain memory.

Our expectations are high since pain is of the most common symptom that brings patients to clinicians. But we still don't have a therapeutic solution of pain memory. A thorough understanding of the mechanisms involved in this cascade will hopefully help us find a myriad of therapeutics that potentially address each step of the pain pathways.

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