The genesis of chronic pain

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Abstract

The theories behind the evolution of the genesis of chronic pain are explored from a historical perspective. The major focus of the article explores the biomedical and the psychosocial factors that contribute to the genesis of chronic pain in particular how the physical and psychological interact together. Risk factors and pre-existing determinants are discussed.

Keywords Biomedical; chronic; genesis; pain; psychosocial; risk factors; theories

Royal College of Anaesthetists CPD Matrix: 2E03

Learning objectives

After reading this article, you should understand:

- the history of the theories of pain medicine
- the current definition of pain
- the concept of the biopsychosocial model of pain
- the biopsychosocial contributors linked to the genesis of pain

The International Association for the Study of Pain (IASP)[1] in 1986 defined pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of tissue damage or both'.

A brief history of pain

Pain has been described since time immemorial. In the book of Genesis in the Bible, we read that Eve was told: '*I will make your pains in childbearing very severe; with painful labour you will give birth to children*'. Few of us, if any, will escape without some experience of intense pain during our lifetimes. For some people, however, pain becomes a chronic, intractable state that has a significant impact on their quality of life.

The word pain itself derives from the Latin poena, meaning 'penalty.[2] This reflects the tradition of pain being seen as a kind of punishment or test of faith inflicted upon mankind. In Ancient Greece, Plato and Aristotle both looked upon pain as being an emotional rather than a sensory experience, something that was experienced by the human heart. Aristotle believed it to be like a spirit that entered the body through an injury. The Intensity Theory of Pain[2] was first described by Plato in the fourth century BC where he described how pain occurred as an emotion when there was a stronger stimulus than normal.

In 1664 Rene Descartes[2] wrote the Treatise of Man wherein he discussed pain. He depicts a young man holding his foot close to a fire explaining that pain travels in a specific pathway connected from the periphery to the brain. His belief was that cutting this specific pathway should alleviate all pain. In 1794 Darwin went one step further in '*Zoonomia*', only to be followed 100 years later by Erb, describing that pain occurred when a sensory stimulus reached a specific intensity rather than being secondary to a specific pain stimulus.

In 1811, Charles Bell put forward the *Specificity Theory*:[2] he proposed that nerves had different functions and that the brain was not a homogenous structure as had been proposed by Descartes. The implication was that pain messages travelled via a specific pathway, whereas other sensations travelled by other pathways unique to each sensation. Francois Magendie[2] in 1856 went on to describe the specific organization of nerves within the spinal cord. This theory was challenged initially as it went against the teachings of Aristotle that pain was an emotion and a quality of all senses. In 1894 von Frey postulated that there were four sensory modalities one of which was pain, a theory further reinforced by Goldsheider and Blix[2] who described specific skin spots which if stimulated would cause pain.

In 1906, Sherrington[2] described the term *nociceptor* and further endorsed the Theory of Specificity of pain. In 1929, Nafe postulated the Pattern Theory of pain, proposing that it was the pattern in which way a stimulus occurred that led to pain. In 1965, Melzack and Wall,[3] the fathers of modern pain medicine, proposed the Gate Theory of pain – a theory that linked the Specificity and Pattern theories. They described the presence of nociceptors as well as touch receptors. These led to nerve fibres which synapsed within the dorsal horn of the spinal cord and in the substantia gelatinosa, the latter acting as a gate in the spinal cord. Thus, when the painful signal reached a specific intensity, the gate opened and activated pathways which led to pain being experienced. They also proposed that fibres coming down from the brain could also determine when this 'gate' opened. In 1968, Melzack and Casey[3] went one step further to describe pain in a multidimensional way, describing sensory–discriminative, affective–motivational and cognitive–evaluative components. This ethos is encompassed in the IASP modern definition of pain and is the cornerstone of the biopsychosocial model of pain.

The *biomedical* model of pain

The conventional biomedical model narrowed pain to the dichotomy of physiological or psychological in origin. Any pain response that did not correlate with the degree of tissue damage was considered 'unreal' or psychological. It was too rigid to explain the complexities of chronic pain. George Engel[4] is credited with the introduction of the biopsychosocial model of

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illness. In contrast to the biomedical model, he put forward the theory that illness results from a complex interaction between various biological, psychological and social factors. Subsequently, Loeser[4] applied this model to pain.

The *biopsychosocial* model of pain

To understand the biopsychosocial model in pain it is imperative to appreciate the difference between nociception and pain. *Nociception* is defined[1] as the stimulation of nerves conveying information about tissue damage to the brain, while *pain* refers to the subjective experience resulting from transduction, transmission and modulation of nociception and its complex interactions with genetics, previous history of pain, current mood state and surrounding socio-cultural environment. There is significant evidence that demonstrates that nociception is neither sufficient nor necessary for pain.

It is also essential to underline the difference in the presentation and characteristic features of acute and chronic pain.

Acute pain has a recent onset and usually has a variable but short duration. As a response to injury or tissue damage, it decreases in intensity as the healing process sets in. It can also be present without injury or tissue damage as in exercising skeletal muscle. The time course of pain and healing can, in most cases, be reasonably predicted based on the site, cause and nature of injury or disease. Tachycardia, increased peripheral blood flow and blood pressure, increased muscle tension and sweating secondary to autonomic hyperactivity accompany acute pain states in a similar fashion to that seen in anxiety states.

Chronic pain is the occurrence of persistent pain over a period of time that goes beyond time associated with natural healing. It is arbitrarily defined by some authors as pain lasting longer than 3–6 months. It is less amenable to alleviation by conventional medical treatment. Anatomical, physiological and biochemical pathology identified by physical examination and diagnostic tests do not always adequately explain the persistence of pain. Unlike the autonomic hyperactivity seen in acute pain states, patients with chronic pain tend to exhibit neurovegetative symptoms including altered appetite and weight, disrupted sleep, decreased energy and libido, diminished concentration and increased irritability. The characteristic feature of chronic pain is that non-noxious stimuli such as normal day-to-day activity become painful.

Perception of pain whether acute or chronic, is modified by the patient's emotional status - depression, anxiety and anger can all impact on this perception. It can be modified by higher cognitive functions including previous experiences, beliefs and expectations. A woman facing labour pain for the second child is more likely to be anxious and have a heightened response to pain, if she had faced a complicated labour the first time round. A footballer who fractures a foot with potentially life-changing career implications is more likely to have a heightened response to pain, than another person in a routine job where such a fracture may be perceived more as a temporary nuisance rather than a life changing disaster.

Patients who have chronic pain usually have tried and failed various medical and surgical treatments targeted towards relief of their pain symptoms. The ensuing emotional distress, impact on family and socioeconomic status become significant problems in their own right. Fordyce's work on behavioural pain management interventions cemented the role of psychosocial and physical therapy interventions for chronic pain management. All of this, culminated in a biopsychosocial model of interdisciplinary care, incorporating physical treatment with cognitive, behavioural, environmental, and emotional interventions. From this emerged four dimensions related to the idea of pain: nociception, pain, suffering, and pain behaviour.

The Neuromatrix Model of Pain, proposed by Melzack[3] in 1999, carried this forward by introducing the stress component into the pain equation. According to this, each individual's unique neuromatrix comprised from genetics, sensory modalities and memory determines the overall interpretation of the experience of pain.

Biological factors implicated in the genesis of pain

Biological factors may be responsible for initiating nociception as well as maintaining and modulating the pathophysiological changes in the genesis of pain.

Gender

Despite the fact that women are more likely to lead healthier lifestyles and to seek medical help earlier, several acute pain states such as post-surgical and procedural pain as well as chronic pain conditions such as back pain are more common in women than in men. Although psychosocial factors are implicated, there is also evidence[5] to suggest that there is a gender difference in the response to painful stimuli. Sex hormones also affect pain perception, with evidence showing that women have different pain thresholds and sensitivity during different parts of the menstrual cycle. There is also evidence to support a difference in mu receptor activity in the two genders.

Genetic factors

The genome of each individual influences the basal sensitivity of pain, the likelihood of developing chronic pain conditions and also the response of the body to pharmacological analgesic agents. Various genes[5] have been mooted including those coding for opioid receptor mu 1 receptors, the catechol-O-methyl transferase enzyme, multidrug resistance gene (MDR1) transporter proteins, the melanonocortin-1 receptors, guanosine triphosphate (GTP) cyclohydrolase, enzymes that metabolize analgesics, and various genes encoding substances involved in the immune system. Various studies[5] indicate that chronic pain has heritability ranging from 30% to 70% (median ~45%). Moreover genes have been shown[5] to explain approximately 40% of the variance in pain catastrophizing. Catastrophizing about pain has been clearly linked to an increased incidence of chronic widespread pain. There are also links mooted to the heritability[6] of persistent post-surgical pain and understanding these could lead to perioperative pain management based on algorithms structured on individual risk factors.[10]

Disease processes: nociceptive and neuropathic pain

Malignancy, trauma, auto-immune disorders, infection and ageing all share some common features in terms of generation and exacerbation of nociceptive pain. Traditionally, **nociceptive** pain has been defined[1] as: '*Pain elicited by the injury of body*

tissues and activation of nociceptive transducers at the site of local tissue damage …'.

Another source of pain may come from a direct effect on the nerves themselves — **neuropathic** pain[1] is defined as *'pain initiated by or caused by a primary lesion of the nervous system or dysfunction in the nervous system'.*

Inflammation leads to the release of chemical mediators including prostaglandins, leukotrienes, proteinases, neuropeptides and cytokines into tissues which in turn stimulate primary afferent nerves such that activities which can normally be done without pain, become painful. This is the underlying neurophysiological basis of **allodynia** defined[1] as *'the triggering of pain by stimuli that would normally not cause pain'* and **hyperalgesia** defined[1] as *'an increased sensitivity to pain'*. Thus when a painful stimulus induces active inflammation, the sensitized area spreads and with this additional neurons are also activated. This leads to a lower pain threshold and a further increase in the sensitivity of adjacent neurons.

Thus in a third-degree burn, the nerves can re-innervate healing scar tissue leading to an overabundance of neurotransmitters such as substance P and calcitonin gene-related peptide (CGRP). Similar changes can be seen in malignancy where there is infiltration of such nerves by tumour. An increase in the level of endoneurial tumour necrosis factor-alpha (TNF-alpha) released by mast cells also contributes to neuropathic pain following nerve injury.

Mixed nociceptive and neuropathic pain states also occur in osteoarthritis where inflammatory mediators including prostaglandins, vasoactive intestinal peptide and CGRP are released into the joint. These reduce the threshold at which nociceptors are triggered and lead to spontaneous pain and mechanical hypersensitivity. A-b, A-d, and C fibres have glutamate as their primary excitatory neurotransmitter. A painful stimulus leads to glutamate activating N-methyl-D-aspartate in the spinal cord. Other mediators are also involved including neurotrophin, prostaglandins, substance P, CGRP.[11,12]

A-d fibres transmit impulses from peripheral nerves into the dorsal root to lamina I and V of the dorsal horn of the spinal cord. C fibres also transmit impulses albeit at a slower rate to lamina II of the dorsal horn. From there on, signals travel via the ascending pain pathways to the brain stem, hypothalamus, thalamus and cerebral cortex. In turn, descending pathways arise from the somatosensory and limbic cortex and descend down to the dorsal horn to modify activity in the spinal cord.

Pain reaches our consciousness via transmission between the thalamus and cortex.[7] Two systems are thought to be involved: the lateral system and the medial system of the lateral spinothalamic tract. The lateral system is thought to be responsible for analysing pain location, duration, intensity and quality whereas the medial system is thought to be responsible for perception of pain and also other functions including attention, learning and affective responses. Pain pathways are not hardwired but exhibit marked plasticity.

Sensitization at peripheral, spinal and cortical levels accounts for many of the clinical features associated with chronic pain. Plasticity leads to nerve endings sprouting into tissues that are usually deficient of such nerve endings, for instance cartilage. This in turn perpetuates the pain problem. In addition, other nerve fibres — so-called silent nociceptors — that are normally not activated by noxious stimuli become activated in the presence of inflammatory mediators. As time progresses, this increased activity can lead to changes further downstream within the spinal cord: a domino effect ensues in that the second-order neurons in the spinal cord in turn become more active, leading to enhanced transmission of neuronal activity transmitting pain to the somatosensory cortex in the brain. Termed **'wind up',** this can also occur as a result of calcium channels opening up when the presynaptic membrane is depolarized. This results in calcium triggering the release of transmitters. Thus when a peripheral nerve is repeatedly stimulated it produces a response in a spinal neuron that grows with each stimulus. This intensifies the pain sensation and classically leads to **'referred pain'** where pain is experienced in areas of the body away from the original source of pain. An example of this is anterior thigh pain referred from painful lumbar facet joints.

The sympathetic nervous system is also involved in the genesis of pain. A noxious stimulus leads to release of norepinephrine into peripheral tissues. As a result the activation threshold of peripheral nerves lessens and they become more sensitive to stimulation. Resulting vasoconstriction may also lead to more tissue hypoxaemia which in turn can contribute to pain.[8]

Centrally, glia including microglia and astrocytes in the brain and satellite glial cells in the dorsal root and trigeminal ganglia are now known to be key players in pathological and chronic pain mechanisms.[9] Chronic pain is believed to result in phenotypic changes which lead to structural alterations, cell proliferation, loss of neurotransmitter or ion buffering capacities, release of proinflammatory or proalgesic mediators and neurotoxicity. The vanilloid receptor transient receptor potential cation channel V1 (TRPV1), a non-selective cation channel in nociceptive sensory afferents, mediates the release of neurotransmitters, such as glutamate and CGRP in the dorsal horn, which can subsequently activate glia. Other up regulators of glial activity include ionized calcium-binding acid protein[9] and glial fibrillary acidic protein. Indeed it has been suggested that chronic pain could be a result of 'gliopathy,' that is, dysregulation of glial functions in the central and peripheral nervous system.

Iatrogenic

Acute postoperative pain is followed by chronic post-surgical pain in 10—50% of patients depending on type of surgery.[6] Thoracotomy, sternotomy, mastectomy and herniorrhaphy surgery commonly lead to persistent pain Amputation leading to stump pain and phantom pain is also a cause of persistent pain. Peripheral and central neuroplastic changes occur secondary to inflammation and nerve damage during surgery. Apart from the type of surgery, predisposing factors common to other chronic pain states lead to an increased incidence of post-surgical pain. Meticulous attention to perioperative pain relief is essential and herein lays the responsibility of each anaesthetist to use multimodal techniques to provide optimum analgesia.[10] The current trend towards enhanced recovery and fast discharge post-surgery poses an additional challenge. Attention to surgical technique can also have an impact on the incidence of post-surgical pain.

Psychosocial factors implicated in the genesis of pain

Psychological variables influence the patient's assessment and perception of the pain experience while the social factors shape the patient's behavioural responses to the pain process. The

interplay between the biopsychosocial factors is bidirectional.[11] Psychological factors can influence biology by affecting hormone production, structure and function of the brain and autonomic nervous system. The patient's behaviour and beliefs can also alter biology. For example, fear avoidance keeps a person from engaging in certain activities in order to avoid triggering pain symptoms. Though useful in the short term, over time this leads to physical deconditioning that in turn exacerbates nociceptive stimulation.

Moseley and Vlaeyen[12] propose an *Imprecision Hypothesis* — pain occurs as a conditioned response to the multisensory and meaningful events that routinely coincide with, or pre-empt, nociceptive input. Imprecise encoding of those multisensory and meaningful events leads to overgeneralization of the response, such that an adaptive and protective process becomes maladaptive, distressing, and disabling chronic pain.

Adding to this conundrum is the effect of disease itself and the treatments employed including drugs such as opioids and gabapentinoids upon cognitive and behavioural factors. Such drugs can affect the ability to concentrate, cause fatigue and alter a person's perception of their illness as well as their ability to cope with its effects.

Mental health

A substantial proportion of patients with chronic pain also present with frank symptoms of depression.[11] Sleep disturbance and a high level of anxiety fuelled by concern about possible underlying pathology, financial concerns and worries about an uncertain future are common.

A review of the dynamics between the neuroendocrine system and the generation of chronic pain conditions has revealed that in addition to the impact of general emotional distress, stress hormone elevation produced by the hypothalamic—pituitary—adrenocortical (HPA) system, such as cortisol, has been found to aggravate pain conditions. These differences related to the HPA axis may help to explain individual differences across the spectrum of stress and pain. Several studies[8] have associated HPA dysfunction with chronic pain conditions, such as fibromyalgia, chronic fatigue syndrome, temporomandibular pain disorder (TMD), chronic pelvic pain syndrome, chronic abdominal pain syndrome, multiple sclerosis and rheumatoid arthritis.

In addition, clinical reports indicate that depressed patients who suffer from chronic pain, exhibit alterations in their perception of pain and in their threshold and tolerance to pain. Does chronic pain lead to depression or does a negative mood increase the risk of developing chronic pain? Studies[11] show a consistent relationship between depression and chronic pain with the balance of evidence suggesting that depression stems as a consequence rather than an antecedent of chronic pain. It is often under recognized and subsequently under treated in this group of patients.

Anxiety disorders[11] are also commonly seen leading to catastrophization about the current symptoms and the future which then further compounds the distress associated with pain. Anxiety also leads to fear avoidance behaviour further enhancing physical deconditioning perpetuating the pain cycle. Exposure to stress beyond what normal human beings go through on a normal basis, for instance being involved in a major accident or exposure to warfare can lead to post-traumatic stress disorder: a syndrome of nightmares, flashbacks and emotional distress. This has been shown to be associated with an increased incidence of somatoform distress leading to cortical sensitization and complex chronic pain disorders.

Sexual or physical abuse

Various studies[13] have shown a correlation between the incidence of physical and/or sexual abuse in childhood and the development of chronic pain states. Perhaps not surprisingly there is a link between chronic pelvic pain and abdominal pain and previous history of abuse. However there is also an increased incidence of other chronic pain states in such patients.

Culture

Differences in attitudes, beliefs and emotional and psychological states have been associated within different ethnic groups.[5]

Back pain has in particular been studied across different ethnic groups across the world and there are significant variations across ethnic groups[14] both in terms of incidence, effect on function and sourcing of medical treatment. Possible explanations include cross-cultural differences in social expectations, awareness, legal implications, financial gains, attitudes towards and availability of healthcare combined with individual self-perceived ability and willingness to cope.

Occupation

There is evidence that chronic pain has a detrimental effect on occupation.[14] On the other hand, job dissatisfaction and low level of support in any occupation is also known to lead to higher incidence of sickness and absence from work due to chronic pain. Purely from a physical point of view, jobs that entail heavy physical work, in particular, heavy lifting, or repetitive strain to joints are more likely to lead to chronic musculoskeletal pain. However it is also true that many people in such occupations have other risk factors such as poor housing, low socioeconomic background and low level of education which in their own right also lead to an increased incidence of chronic pain.

Litigation

A history of compensation for a spinal condition, receipt of work-related sickness payments, or personal injury ligitation,[15] are all associated with an increased risk of chronic pain. Litigation and the stress associated with going through this legal process act as a disruptive element to the diagnosis and management of pain. These patients face scrutiny of their symptoms and level of activity to such an extent that they believe that their integrity is being questioned, thus adding further insult to injury. This perpetuates the cycle of frustration, depression and despair. In some patients, there may be an unconscious or conscious behaviour aimed at perpetuating the chronic pain cycle as they believe they have no alternative way to safeguard financial security for their future.

Alcohol and drug misuse

Alcohol and drug misuse in their own right can lead to chronic pain — chronic pancreatitis and neuropathy to name but a few. Increasing use of opiates[11] in the pharmaceutical management of chronic pain has also seen an increase in drug dependency.

Benzodiazepines and gabapentinoids also pose a significant problem, with a risk of diversion. Reliance on alcohol and street drugs is a problem that chronic pain can compound in vulnerable patients.

The present and the future

Functional MRI and positron emission tomography have helped and continue to allow us to understand the role of biological and psychological factors in the genesis of pain. It is of interest that the impact of a chronic pain condition alters through different periods of time and only a longitudinal perspective applied holistically across all aspects of pain illness allows for an evolution of the management along with the disease. At its best the biopsychosocial approach is holistic. It argues that our physiological systems, including genes, are not closed systems but open and flexible according to the demands placed on them. This forms the basis of our genotype-phenotype functioning.

Each patient has a unique genetic footprint albeit sharing similar biopsychosocial dimensions leading to the genesis of chronic pain. By taking this multidimensional view, the biopsychosocial framework leads not only to a better understanding of the patient's pain condition but also to a comprehensive management protocol tailored to suit the individual patient's needs. ◆

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