Chronic pain, stress and their psychoneuroimmunologic implications: A literature review

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Abstract: Clinically, patients often report depressive symptoms, stress and disruptive social lives. The association of these symptoms with pain has been leading researchers in Health Psychology to investigate the possible psychoneuroimmunologic mechanisms underpinning such interaction. This work reviews the concept of chronic pain and its physiological alterations due to the long term exposure to pain stressors, such as the compromising of the Hypothalamic-Pituitary-Adrenal Axis (HPAA), the role of cortisol and the concept of allostatic load. Conclusion: There is a current demand for a larger number of studies involving etiological aspects of the distinct mechanisms involving chronic pain and to support possible new interventions.
Keywords: chronic pain; stress; cortisol.

Dor crônica e as implicações psiconueroimunológicas decorrentes do estresse: uma revisão teórica

Resumo: Clinicamente, as implicações da dor crônica manifestam-se em forma de estados depressivos, estresse e comprometimento da vida social. Esta alta associação tem levado pesquisadores em Psicologia da Saúde a estudarem os possíveis mecanismos psiconeuroimunólogicos implicados nessa relação. Este trabalho revisa o conceito de Dor Crônica e os comprometimentos fisiológicos decorrentes da longa exposição a esta condição, como a alteração funcional do eixo Hipotálamo-Pituitária-Adrenal (HPA), o papel do hormônio cortisol e o conceito de carga alostática. Conclusão: Faz-se necessário um maior número de estudos em psiconeuroimunologia para melhor definir a etiologia dos distintos mecanismos da dor crônica e para delinear possíveis intervenções clínicas.
Palavras-chave: dor; estresse; cortisol.

Chronic pain: An overview

Chronic Pain is defined by the International Association for The Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (www.iasp-pain.org/terms). In medical settings, pain is considered chronic when it persists beyond the healing time needed for the recovery of the injury and lasts for a minimum of six months (Marks & cols., 2005).

The reduced ability to perform daily activities and work often incurs long-term disability. As the majority of chronic pain patients endure their conditions without been successfully treated, a heavy burden in the healthcare system has been increasing. In the UK, work loss caused by back pain alone cost to the NHS £481 million in 1993

(Macrae, 2005). Considering the impact of pain in palliative care, another study revealed that 70% of patients with cancer experience severe pain in the course of their illness, and between 40-60% of patients with AIDS, with increasing pain as the disease progresses (Breitbart & Payne, 2004). Other issue often referred in the medical literature involves chronic pain and work, litigation procedures such as compensations and injuries. An estimated US$ 20 billion is spent yearly in worker's compensation in the U.S alone, not to mention the much higher costs with lost work. It is assumed that such culture has created a state of mind where chronic pain patients are often victim of stereotype caused by the disparity between expressed symptoms and levels of perceived disability (Tait, 2004). Expenditure with common types of pain like lower back pain represent more than 1.7% of Netherlands gross national product and in the US accounts for an estimated cost of US$ 50 billion a year for the health system (Staal & cols., 2002). In a recent review, it has been reported that costs for medical treatment for chronic pain were estimated at the equivalent of £5,000 to £10,000 a year per patient in the U.S (Straus, 2002).

What is known about pain nowadays is increasingly complex. It involves complicated neural interactions, where impulses generated by the tissue damage by ascending and descending systems activated by psychological factors. Melzack and Wall, in 1965, have proposed what is considered today on of the most influential theory to explain the pain experience: the Gate Control Theory (GCT). It was a consistentan innovative concept for pain: the multidimensional aspect of both ascending and descending stimuli. For the first time the direct line of transmission of pain to the nervous system was contested by an elaborated theory whereby psychological aspects play an important role. According to the theory, the dorsal horn of the spinal cord serves as a 'gate': it receives the stimuli (from nociceptors) and transmits to the brain, and receives from the brain information about the emotional and psychological state of the individual. These segments in the spinal cord, which modulated the competing impulses, controlled the ascending physiological and descending psychological information (Dickenson, 2002; Main & Spanswick, 2000). Despite its relative simplicity (the model did not specify peripheral processes), it is still the most comprehensive overall theory of pain modulation and continues to influence the main discoveries of today (Sufka & Price, 2002). Later on, following the critics of a non-existence of a physical 'gate', the authors suggested the neuromatrix theory of pain: the multidimensional experience of pain is produced by 'neurosignature' patterns of nerve impulses generated by a neural network – the body self-neuromatrix. Pain is then produced by the output of a widely distributed neural network in the brain rather than directly by sensory input (e.g. injury). The neuromatrix, which is modified by sensory experience, is the primary mechanism that generates neural patterns that produce pain (Melzack, 1999).

GCT and neuromatrix provided an important attribution to the 'descending' impulses, opening the doors for a more psychological nature for pain. Pain experience varies significantly from individual to individual, drugs also seem to have different effect depending on individual variables; the same pathology can be experienced in terms of pain very differently and not uncommonly there are no physical explanations

to account for report of symptoms, emphasizing the multi-dimensional process involving emotional, physical and perceptual integration of noxious information (Blackburn-Munro & Blackburn-Munro, 2003).

The psychological stages of pain processing explained by Price and Bushnell (2004) is said to involve sensory and emotional dimensions. Sensory qualities are associated with the unpleasantness, just like another symptom such as nausea, which causes discomfort. However, the meaning of the unpleasant is shaped by the person's context, ongoing anticipations and attitudes, and is also associated with the situation that is threatening, such as physical trauma. Part of pain dimensions involves the emotional present feelings or the short-term future, such as fear or distress, and this is considered to be closely linked to both intensity and unique quality of painful sensation. The *extended pain effect* comprises of feelings toward the long-term implications of having pain, such as suffering and psychological stress (Price & Bushnell, 2004). Turk and Flor (1999) consider this last stage as being influenced by the meanings and perceived interference of pain in one's life and it is closely related to the operational conditioning. Contingencies of reinforcement may serve to maintain behaviours, which would explain the presence of pain even though the original nociception is healed.

Negative moods and depression are the most frequent symptoms reported in the literature in association with chronic pain (Blackburn-Munro, 2004; Young & cols., 2004; Graab & cols., 2005; McEwen 2003; Weissbecker & cols., 2006). For such psychological states, it is debateable whether depressive symptoms are a consequence of a demoralised feeling from coping with pain or if the depressive illness share similar physiological mechanisms with chronic pain (Main & Booker, 2000). In one study performed by Gureje and cols. (2001), anxiety and depressive disorder predicted the onset of persisted pain. In fact, pain is the one of the most common symptoms of depression, with the prevalence of depression increasing as the number of sites of pain in the body increases (Kroenke & Price, 1993). On the other hand, studies show that depression often follows chronic pain (Atkinson & cols.,, 1991; Banks and Kerns, 1996), and pain symptoms usually decrease when depression is treated (Detke & cols., 2002). The main supportive hypothesis for pain and depression to be intrinsically linked comes from the fact that many antidepressants have been used successfully in the treatment of chronic pain, which could indicate they share the same mechanistic bases (Blackburn-Munro, 2004). Recent extensive review of depression and pain by Williams & cols. (2006) reflect their mutual interaction and the implications for treatment.

According to Evans and cols. (2000), studies in psychoneuroimmunology revealed that depression is linked to behaviour, immune system or hipothalamic-pituitary-adrenal axis (HPAA), but it is not clear whether the depression might have originated in the brain (through mood change), prolonged activation of HPAA or immune system (linked to inflammatory conditions). What is known is that melancholic mood either accelerates disease progression or is a symptom of immune activation and illness.

The possible neuroendocrine interactions between pain and depression in the HPAA reveal the importance of either symptom to be considered as part the stress response mechanism. Blackburn-Munro (2004) postulates that chronic pain conditions develop primarily as a consequence of long-term maladaptive changes in sensory

processing within pain-signalling pathways. But the limited success of analgesic treatment and consequent success of anti-depressants indicates pain systems to be closely linked to mood regulation in different areas of the brain. Studies performed in rats involving early maternal separation and pinprick stimulation in premature infants revealed lower thresholds for pain during adulthood. The use of anti-depressant treatment helped reducing the symptoms in adult age and has also demonstrated to alleviate nociceptive responses in neuropathic rats and to attenuate HPAA activation (Blackburn-Munro, 2004).

Physiological aspects of pain, stress and the hypothalamic-pituitary-adrenal axis

The understanding of pathways through which brain and neuroendocrine system communicate is essential for the concept of stress and how the body reacts face any stressors. According to Evans & cols. (2000), there are two main ways of communication for the brain to direct physiological responses: the neural (involving efferent neurones) and endocrine (where brain communicates targeted cells to produce hormones). The Automatic Nervous System (ANS), which runs itself without cognition (i.e., cardiac muscle), is divided in sympathetic nervous system (SNS) and parasympathetic (PNS) nervous system. SNS is involved with preparing the body to respond in emergency situations and challenges, whereas PNS mediates rest and energy conservation. The adrenal glands play an important role on the SNS by producing, in its outer layers (adrenal cortex), the hormones called glucocorticoids (GC). The body under stress usually see an increase of GC, making it an important tool for health professionals to use it as a parameter for stress.

Emotional challenge is known to activate the sympathetic adrenomedullary system (SAM), which was first described by Walter Canon (on his fight-or-flight experiments) and extensively reported in Hans Selye's experiments in acute stress (Kemeny, 2003). This system comes into play in threatening situations and results in an increase in involuntary processes that are required to respond to physical threats. Fibres of the SNS release the neurotransmitter norepinephrine at various organs sites (including adrenal medulla), causing the release of adrenaline in the bloodstream. This extremely rapid response can be activated within seconds, producing the "adrenaline boost" after an encounter with unexpected situation. As the stress response continues, the immune system is suppressed and portions of the limbic system are activated (amygdala, hippocampus).

Exposure to a variety of psychological stressors for relatively longer durations (e.g., giving a public speech, seating for an examination) also increases the level of cortisol in the body. This suggests the activation of another system already mentioned previously, the HPAA. In general, neural pathways link stressful stimuli to the hypothalamus, which results in the release of corticotropin-releasing hormone (CRH), which in turn promote secretion of adrenocorticotrophin (ACTH) from the pituitary. ACTH acts in the adrenal cortex to enhance the synthesis and release of GC. The activation of this system occurs within minutes rather than seconds (as in the case of ANS) (Kemeney, 2003). Both systems, however, are known to be activated when facing

stress. The concept of stressor is more likely to involve the stimulation of the HPAA, making it almost a definitional requirement for stress (Evans & cols.,, 2000). This author explains that SAM axis is easily activated in laboratory experiments of acute stress, as opposed to HPAA, which requires a more elaborated and controllable conditions. In fact, time is essential to differentiate acute from chronic stress, and also emphasizes the role of HPAA in the long-term activation of psychological stressors.

The main challenge of the body in chronic stress is to maintain sensitivity to new stressors in a system already chronically over stimulated. Two ways of dealing with this situation is to increase the hormone production and release, or it becomes resistant to the effects of the already circulating GC. In either scenario the negative feedback is lost, causing either hypo or hyper function of the HPA system (Evans & cols., 2000; Melzak 1999).

Understanding the role of the stress system in chronic pain processes significantly broadens the concept of pain and our ability to understand it (Melzack, 1999). If chronic pain is considered as a stressor, it will affect the stress systems. In a prolonged activation of the stress-regulation system, some parts of the body are likely to be damaged (muscle, bones and neural tissue), which, in turn, will cause more pain and initiate a vicious cycle. The emotional aspect is encoded within the limbic system, where the hypothalamus undertakes separated and interrelated functions. Dysfunction of the HPAA has been associated with a variety of chronic pain conditions (Blackburn-Munro & Blackburn-Munro, 2003; Chapman & cols., 2008; Fries & cols., 2005; Hellhammer & cols., 2004) and might be associated with the increased risk of developing mood disorders (Eccleston, 2001; McBeth & cols., 2005; Raison & Miller, 2003).

Blackburn-Munro and Blackburn-Munro (2003) defend the argument of three major overlap points to aetiologically link HPAA and chronic pain. First is the fact that both neuroendocrine and immune systems play a crucial role of adaptation of an organism to stress; secondly, HPAA can be activated by a variety of stressors, including nociceptive stimuli (pain); and thirdly, various components of HPAA cascade have been implicated in the pain response.

The role of cortisol and allostasis

The disruptive nature of pain has been recently linked to affect body's regulation systems, producing physiological stress and initiating complex programmes to restore homeostasis. Due to the complexity of the HPAA and considering its crucial role in the response to stressors, understanding specific alterations in cortisol levels help to establish the connexions between deregulation of neuroendocrinal systems and its recuperation.

Cortisol is part of a group of hormones produced by the adrenal glands: the glucocorticoids (GC). Landys and cols. (2006) explains that GCs have a rapid increase from baseline to maximal levels within minutes of perturbation, suggesting the importance of these hormones in the immediate adjustment of physiological state. In particular, GCs seem to have a central role in suppressing non-essential life processes when in high levels and redirect effort towards survival and recovery. In animals, they

can also stimulate conservation of energy when escape is not possible and also protect organisms against the immediate defence reactions that accompany stress.

The exposure to stressors promotes immunological suppression by cortisol. It inhibits the production of certain cytokines (chemical mediators released by immune cells to regulate activities of other immune cells) and suppresses a variety of immune functions. In the other hand, other immune processes linked to inflammation may be enhanced by its secretion, perhaps to compensate the inhibition of other immune cells (Kemeny, 2003). The long-term effects of a high cortisol levels are explained by Melzack (1999). It plays a central role because it is responsible for producing and maintaining high levels of glucose for the response. At the same time, cortisol is potentially a highly destructive substance because, to ensure a high level of glucose, it breaks down the protein in muscle and inhibits the ongoing replacement of calcium in the bone.

Any site of increased inflammation in the body, including spasm of muscles and tendons, sites of strain, etc, could become the focus of cortisol action and muscle destruction. The breakdown of muscle proteins could be an explanation to fibromyalgia, a musculoeskeletal type of chronic pain. It could also enhance fractures and be the basis of osteoporosis (Melzack, 1999). In other words, cortisol may not be the direct cause of chronic pain, but it may set the background, serving as contributing factor that, together with others, initiates chronic pain.

Recent studies in PNI have suggested two possible dysfunctions of cortisol due to the constant activation of the HPAA: the hypocortisolism and hypercortisolism. Hypercortisolism is well known to be associated with severe health problems, such as hypertension, abdominal obesity, diabetes II and osteoporosis, while hypocortisolism is instead associated with pain disorders, fatigue and enhanced stress sensitivity (Hellhammer & cols., 2004; Fries & cols., 2005, Anderson & cols., 2008). In a study performed by Chiodini and cols. (2006) with asymptomatic diabetes mellitus type 2 patients, basal cortisol levels were found to be over-activated by the HPAA, even though there was no direct stress associated symptom. Fries and cols. (2005) and Meeus and cols. (2008) bring hypocortisolism as preponderant in a series of conditions characterized by the triad of enhanced stress sensitivity, pain and fatigue. Another study performed by Ehlert and cols. (2005) with patients diagnosed with functional gastrointestinal disorder revealed two distinguished subgroups having different alterations in the HPAA. Patients showed both hyper and hypocortisolism depending on psychological variables, such as levels of somatization and depressive mood.

Despite the rapid expansion of plasma and salivary cortisol in the last decade in the stress research, cortisol can be considered one indicator between nine others (e.g. epinephrine, norepinephrine, systolic and diastolic blood pressure, waist-to-hip ratio, etc.) implicated in the break of homeostasis caused by psycho-physiological stress (Kinnunen & cols., 2005). The long exposure to stressors and the break of homeostasis in the body is clarified by McEwen and Wingfield (2003) with the concepts of allostasis and allostatic load. The daily routine of humans and animals include homeostatic mechanisms in place to allow individuals to maintain physiological and behavioural stability despite environmental fluctuations. Other physiologic and behavioural facultative responses are linked to unpredictable events, which require an extra energy

(from stores of fat, protein) and have the potential of becoming a stressor. Allostasis enables the body to maintain stability through change of states and is necessary for survival. The cumulative effect of allostasis could have a negative effect: the allostatic load. The pathway from allostasis to allostatic load is a long-term process consisting of individual genetic, developmental and experiential components. Kinnunen and cols. (2005) explain that whereas allostasis makes the body able to achieve stability through changes by activating different physiological regulation systems, allostatic load refers to the altered activity of regulation systems resulting in imbalance in their chemical messengers, which in long-term imbalance causes the allostatic load. Chapman and cols. (2008) review the concept of allostasis and discuss the physiological implications involved in the accumulation of stressors during the individual's lifespan.

Two main types of allostatic load have been defined by McEwen and Wingfield (2003). In the Type I, allostatic overload, energy demands of the body exceeds energy supply, leading to a limited ability to maintain health in emergency situations. Second, in the Type II, energy demands are not exceeded, but the organism continues to store more energy than it needs. Kinnunen and cols. (2005) explains that in modern societies, Type I allostatic load is rare due to excessive energy consumption. Type II, however, could be easily identified as reflecting the excesses of modern living. Despite the great volume of studies using this nomenclature to characterize the brain pathways to psychological and physiological responses to stressful events, Trevor A. Day (2005) suggests the term involving allostasis is not required. As the allostasis in McEwen and Wingfield (2003) terms represent the effort for the organism to maintain homeostasis, the correct nomenclature would involve just homeostasis and homeostatic load. Although the literature brings two different terms for the same definition, the ones utilized in this work will make reference to McEwen's definitions due to its widespread use.

The definitions of stress could be more easily defined in terms of allostasis and allostatic load. Although stress represents only one factor that could activate allostatic responses, it could be considered as events that are threatening to an individual and which elicit physiological and behavioural responses as part of allostasis in their normal life (McEwen & Wingfield, 2003). Repeated allostasis due to stress after 21 days in animal models revealed structural changes in the hippocampus and amygdala, as well as modification in behavioural, such as increased anxiety, impairment in spatial memory and aggression (McEwen, 2003).

Conclusion

Human beings are complex creatures who are capable to adapt and cope with different social and environmental factors. The stressors originated in a chronic pain condition generate an allostatic response that involves an ensemble of interdependent nervous, endocrine and immune systems. As individuals, it also needs to be taken into account a unique interaction of genetic, epigenetic and environmental factors, as well as past experiences which may increase a vulnerability to a specific organ system.

The existence of HPAA dysregulations can help to clarify the nosological status in chronic pain, better understand its etiology and improve its management. Specific clinical and medical variables should be assessed in prospective studies in PNI to help differentiate chronic from musculoeskeletal and inflammatory pain, especially those related to stress and allostatic load. Further researches are necessary to elucidate specific neuroendocrine mechanisms involving pain and to investigate whether these physiological alterations are also associated to other biopsychosocial variables, which are known to elucidate a physiological response. New prospective interventions with immunosupressive medication have already started in some conditions such as terminal cancer and HIV, but for chronic pain it is still necessary to further investigate specific physiological mechanisms which would help clinicians to better manage both analgesia and stress.

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