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Chronic Pain Management and Its Relationship to Physiological Variables

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Abstract

Chronic pain (CP) is defined as pain lasting more than 3 months. It affects thousands of Canadians daily through biological, psychological and social factors. Not only are physiological factors affected in those who experience chronic pain but also sleep, mood, and general quality of life. We do not yet know the exact biological mechanisms through which acute pain and injury develop into chronic pain, however, in this article; we discuss a dominant hypothesis that might offer an explanation: Central Sensitization. In addition, the purpose of this article is to explore the biological mechanisms of chronic pain and the importance of using physiological measures to assess the outcomes of pain management programs. This paper draws attention to the importance of having further research conducted in order to understand the underlying biological causes of chronic pain as well as identifying specific biomarkers that can be used to measure treatment outcomes. This will allow us to design effective and innovative pain management programs in order to improve the quality of life for CP patients.

Keywords: Chronic pain; Stress response; Central sensitization; Pain management; Physiological measures

Introduction

Burden of chronic pain in Canada

Chronic pain (CP) is defined as pain lasting ≥3 months and its subjective perception is complex: it is comprised of interacting biological, psychological and social factors [1]. CP continues to be an ongoing challenge in Canada, affecting as many as 20% to 29% individuals nationwide [2]. For those living with a CP condition, it can provoke significant long-term debilitation and suffering [3]. In particular, CP can negatively affect many domains of a patient's health including sleep, cardiovascular fitness, mood, sexual functioning and overall quality of life [1]. Among Canadians waiting for effective intervention to relieve their CP, over two thirds reported 'severe pain' (i.e., ≥7 out of 10 on a Likert scale) that considerably impacted their quality of life and daily functioning [4]. CP also poses enormous economic burden on individual and societal levels. For example, Canadians with CP awaiting treatment reported an average median monthly cost of $1,462 (CDN) for care [5]. In a newly publicized population-based study [6], they found that the incremental healthcare costs amounted to 50% higher in patients managing CP than their healthy control counterparts. From a broader perspective, Canada spends approximately $6 billion annually on direct CP expenditure, and $37 billion annually on indirect costs (i.e., loss of job productivity, loss of jobs, employee sick days etc.) [7]. Evidently, more resources and research should be directed at combatting this pressing health concern.

The stress response

It has been established that CP may develop as a result of a dysfunctional stress response [1]. Normal functioning, interdependent systems (i.e., nervous, endocrine and immune) interact to adaptively respond to an acute stressor or injury. This bodily response is known as allostasis and is necessary to maintain homeostasis, thereby protecting vital internal processes. When presented with a stressor, allostatic systems such as the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS) promote a 'fight or flight' response so that individuals can effectively respond to the homeostatic imbalance. In many cases, the HPA axis facilitates the release of cortisol into the blood stream, which is a glucocorticoid that can be metabolized to provide one with sufficient energy to combat the stressor [8]. Concurrently, the sympathetic nervous system of the ANS elevates heart rate and blood pressure, respiration rate, muscle tension and other sympathetic responses to achieve the same goal of recovery. In his original General Adaptation Syndrome theory, Selye [9] postulated that people are in the 'alarm stage' when initially reacting to a stressor. In the second phase, the 'resistance stage', an individual maintains their arousal to overcome the stress.

When allostatic systems, like the HPA axis and ANS, are not able to return body processes to equilibrium, allostatic load can develop [10]. Allostatic load is a condition that results from the overstimulation, ineffectiveness, or failure to turn off allostatic systems. For example, if a stressor persists for an extended period of time, the HPA axis may continually release cortisol, which can exceed an adaptive amount [11]. Excessive cortisol release, or hypercortisolemia, can have harmful effects contributing to altered mood states, fatigue and headache. Moreover, prolonged release of cortisol can increase one's susceptibility to illness and infection due to its effect of supressing the immune system [12]. Alternatively, when exposed to great psychological or physical stress, the HPA axis can be under-functioning, and therefore unable to adapt to stressors [8]. This adverse reaction parallels Selye's [9] third Exhaustion stage of the General Adaptation theory, whereby the body can no longer cope with the stressor, as a result of depleted metabolic resources.

Stress systems and chronic pain

CP has been theorized to persist as a result of this faulty stress response. In particular, CP continues *via* bio psychosocial factors even after the original painful stimulus is removed [13]. This effect has been extensively studied in individuals living with fibromyalgia (FM) [8,14,15]. FM is characterized by widespread pain throughout the body, disordered sleep, fatigue and depressed affect [16]. Adverse ANS and HPA axis functioning have been theorized to contribute greatly to the pathogenesis of FM in that it disrupts, or is a consequence of, the normal functioning stress response [17]. Studies have frequently reported that individuals with FM demonstrate hypocortisolemia, an important marker for HPA dysfunction, compared to those living without CP [8]. As well, individuals with FM have abnormal circadian rhythms and consistent sympathetic hyperactivity during night-time hours, compared to a healthy population [18]. It is reasonable that this dysfunction in stress systems may be present in a variety of CP conditions due to CP being labelled as a global condition for its similarities in response to treatment [19].

Literature Review

Chronic pain and the intersecting nervous, endocrine and immune systems

The nervous system is involved in the stress and/or injury response by transduction: peripheral afferent nociceptors distinguish tissue injury from innocuous stimuli and transmit pain signals to the dorsal root of the spinal cord [20]. The noxious signals then transmit *via* the neocorticospinal thalamic tract to the contralateral thalamus and secondary somatosensory cortices for processing. Noxious transmission also stimulates the release of peptides (e.g., Substance P) that contributes to increased inflammation [12]. This heightened immune response increases one's vulnerability to successive stimuli, strengthening the painful response. As well the continuous inflammation has been shown to be damaging to the dorsal horn of the spinal cord, a prominent neural pathway that transmits pain signals to the brain for perception [12]. In particular, if the dorsal horn is subject to continuous painful stimuli, nociceptive facilitation might be favoured over nociceptive inhibition, a consequence of its plasticity [21]. This is damaging and may lead to CP, as the pathway's increased sensitivity to painful inputs enhances responses to injury [22].

The neural system also interacts with the endocrine system to produce a stress response through frontal-amygdalar circuits and the aforementioned HPA axis [23]. The amygdala is involved in one's conditioned fear response and cognitive factors (e.g., anticipation, interpretation and memory) and can thus stimulate neural circuits initiating a stress response without physical tissue damage. The endocrine stress response is facilitated primarily through three systems: the locus coeruleus (LC) noradrenergic system, the HPA axis and the sympathetic-adrenomedullary (SAM) system [24]. During a stress response, catecholamines (i.e., norepinephrine and epinephrine) are released from the adrenal medulla [25]. These hormones are the primary effectors of the SAM system, and once released, increase sympathetic activity and a heightened stress response (e.g., increased heart rate, blood pressure, respiration rate, etc.). Additionally, stressful stimuli increase the production of corticotropin-releasing hormone (CRH) in the hypothalamus [26]. Once released, CRH then stimulates the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH exerts its effects when it binds to surface receptors on the adrenal cortex, facilitating the release of glucocorticoids (e.g., cortisol) into the blood stream. In a typical stress response, recovery is achieved through negative feedback loop mechanisms. If the recovery state is not attained, dysfunction can occur particularly long-term endocrine deregulation in the HPA pathway. In fact, ACTH serum abnormalities have been documented as a biomarker for uncontrolled CP [27].

Central sensitization in chronic pain

The exact biological mechanism by which acute pain/injury persists into CP is not wholly elucidated. However, a dominant hypothesis is that the development and maintenance of CP may be associated with a condition of the nervous system known as central sensitization. According to Pergolizzi [28], central sensitization can be defined as, "pain hypersensitivity that may arise from a reduced threshold for activation and an abnormal amplification of sensory signalling within the central nervous system" (p. 1129). Central sensitization is often characterized by widespread long-term pain, reduced pain threshold (i.e., allodynia) and amplification of pain responses (i.e., hyperalgesia). In general, repeated noxious stimulation in the periphery can lead to excitatory facilitation and reduced inhibition of noxious processing, due to the plasticity of the central nervous system [13,29].

The precise mechanism of this process involves a host of different intercellular signalling pathways, namely the up-regulation of noxious receptors and neuromodulators [13]. When input or injury from periphery synapses reach the dorsal horn of the spinal cord, substances such as substance P and glutamate are released. This creates an environment where somatosensory neurons are more susceptible to depolarization, thereby lowering the threshold for neuronal excitability [30]. These compounds, in combination with post-synaptic ion channels such as N-methyl D- aspartate (NMDA) receptors, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic aid (AMPA) receptors allow previously innocuous pain signals to reach the thalamus for processing. If the pain input from the periphery persists, there can also be an increase in the number of post-synaptic NDMA receptors, leading to enhanced pain [28]. Central sensitisation has been shown to have a key role in patients with osteoarthritis, rheumatoid arthritis, and related musculoskeletal conditions [31].

Chronic pain and its relationship to physiological variables

As mentioned, individuals living with CP may have a heightened and altered stress response, which can be indicated by a number of biological markers [8,32]. For example, CP patients are documented to have abnormal serum cortisol levels, elevated levels of lipopolysaccharide stimulated inflammatory markers, lowered levels of dehydroepiandrosterone, serotonin, and growth hormones, as well as deficient oestrogen, among others [8]. However, it is still uncertain whether dysfunctional stress systems (i.e., HPA axis, ANS, and immune system) precede and/or predict the development of CP [33]. For example, in a recent 6-year longitudinal cohort study, stress system functioning (as informed by physiological indicators) was not associated with the onset of CP, either independently or through its interaction with adverse life events [8].

CP patients may show further physiological signs of ANS dysfunction. For this reason, indicators of sympathetic activity can be used as surrogate outcomes in studies evaluating changes in CP states over time. In one study, Olsen et al. demonstrated that compared to a pain-free group, chronic pain patient displayed higher baseline heart rate and greater systolic blood pressure reactivity during a cold pressor

test, and a higher mean arterial pressure ratio [34]. In addition, there is current evidence suggesting that CP patients may exhibit further dysfunction of the ANS, particularly that of parasympathetic dysregulation [35]. HRV can be used as a measure of autonomic functioning, and recent meta-analytic evidence by Koenig et al., [35], has reported that chronic pain patients experience decreased heart-rate functioning of moderate-to-large effect size. This is significant, as decreased HRV may be associated in the pathogenesis of many CP disorders [36]. It has been hypothesized that CP patients may experience continual arousal from sympathetic influences, overriding typical variability from parasympathetic factors. This association between decreased HRV has been established in the literature, especially for those affected by FM [37].

Multidisciplinary interventions and the importance of the biological perspective

There is currently an abundance of research examining the efficacy of multidisciplinary CP interventions predominantly on psychosocial outcomes [1]. One such study compared the outcomes of multidisciplinary chronic pain programs to usual care provided by independent physicians over the span of 6 months [38]. The multidisciplinary rehabilitation program (MRP) involved restorative exercise therapy, physiotherapy, cognitive behavioral therapy, progressive muscle relaxation and education about chronic pain [38]. Compared to usual care, the MRP was found to be significantly better for improving the mental and physical health of patients. As well, the MRP had positive psychosocial impacts on participants: those undergoing the program took less days off work and had a higher overall outlook for a successful outcome [38]. Measures that were used to assess the effect of the program were patients' responses in self-report questionnaires [38]; there is a plethora of studies of this nature that utilize subjective, self-report measures. However, there have been limited attempts that focus on using physiological measures that are performance based and objective as a way to assess the effects of pain management programs [39]. A recent systematic review that focused on mindfulness skills training (MST) illustrates this very point. Out of 15 studies that focused on the effects of pain management programs on physical functioning, only two were identified as using performance-based measures to assess outcomes [39]. The significance of using more objective measures to assess physical functioning in order to illustrate effects of MRP cannot be overstated. Subjective measures such as self-reports are subject to recall and response bias due to social desirability and inaccurate memory of participants further compromising their reliability and validity [39]. It has been suggested that, "subjective assessments are almost always biased, sometimes completely misleading" [40]. Using objective measures like biomarkers is a more accurate way to depict outcomes of pain management programs on physical performance; it can diminish issues of recall and response bias and improve accuracy [41]. Adding on to this, recent systematic reviews of MRP have found conflicting results. Out of the most recent systematic reviews, one reported no clinical significance on physical quality of life, one reported time-limited clinical significance while another reported a significant effect on physical health [39]. A potential explanation for such inconsistent findings could be the fact that outcomes of such programs are measured with such a wide variety of assessment tools. This illustrates the importance of having objective methods of measuring MRP outcomes; identifying potential biomarkers of chronic pain and standardizing measurement tools might hold the key to consistent findings. Furthermore, in one of his papers, Stephen Morley discusses the importance of giving patients tangible takeaways to the effects of pain management programs [40]. Although it is widely accepted that treatments are more effective than no treatments at all, Morley examines how the way outcomes of such treatments are measured can make it difficult to conceptualize and communicate exactly what benefits patients will experience [40].

Discussion

Morley [40] discusses how simply telling patients certain treatments "work" is not enough, patients deserve to know how and what objective changes can occur with treatment. Although it is important to note self-report measures have their own benefits, (e.g how participants feel about their chronic pain after treatment), objective measures such as biomarkers hold the promise of diminishing inconsistent results that are associated with subjective scoring. Thus patients will be able to better understand and conceptualize the benefits of chronic pain programs. Therefore, it is imperative that research continues to evaluate the underlying biological mechanisms of CP conditions, especially in large, population-based studies [33]. This will allow us to explore and utilize standardized biomarkers that will in turn allow us to identify MRP benefits more effectively and accurately. As it stands, there is still a degree of uncertainty in the extent to which biological dysfunction precedes or proceeds a CP condition and exactly what physiological factors are the most principal to CP. Recently, a study was conducted to explore how mindfulness meditation can impact physiological neural mechanisms associated with CP [42]. The investigators were able to successfully display, for the first time, that meditation involved endogenous opioid pathways, and that it had beneficial analgesic effects on pain [42].

Conclusion

As there is paucity of research focusing on the physiological mechanisms underlying the beneficial effects of interdisciplinary treatments, studies such as these [42] are hopefully the first of many that explore more objective measures of chronic pain. Since biological pathways are inextricably linked to the persistence of CP conditions, more research examining the physiological response to current accepted interdisciplinary treatments, such as meditation and relaxation interventions, will aid in the development of smarter and more effective therapies.

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