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REVIEW

How may stressful experiences contribute to the development of temporomandibular disorders?

Gustavo Hauber Gameiro · Annicele da Silva Andrade · Darcy Flávio Nouer · Maria Cecília Ferraz de Arruda Veiga

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Abstract Temporomandibular disorders (TMD) comprise the most common cause of chronic facial pain conditions, and they are often associated with somatic and psychological complaints including fatigue, sleep disturbances, anxiety, and depression. For many health professionals, the subjectivity of pain experience is frequently neglected even when the clinic does not find any plausible biologic explanation for the pain. This strictly biomedical vision of pain cannot be justified scientifically. The purpose of this study is to demonstrate, by original articles from the literature and recent studies conducted in our own laboratory, the biological processes by which psychological stress can be translated into the sensation of pain and contribute to the development of TMD. The role of the hypothalamic–pituitary–adrenal axis, the serotoninergic and opioid systems in the pathogenesis of facial pain is exposed, including possible future therapeutic approaches. It is hoped that knowledge from apparently disparate fields of dentistry, integrated into a multidisciplinary clinical approach to TMD, will improve diagnosis and treatment for this condition through a clinical practice supported by scientific knowledge.

Keywords Stress · Pain · Temporomandibular disorders · Nociception · Temporomandibular joint

G. H. Gameiro (✉) · D. F. Nouer
Department of Orthodontics, Piracicaba Dental School,
University of Campinas—Unicamp,
Av. Limeira 901 C.P. 52,
CEP 13414-900 Piracicaba, São Paulo, Brazil
e-mail: ggameiro@fop.unicamp.br

A. da Silva Andrade · M. C. Ferraz de Arruda Veiga
Laboratory of Orofacial Pain, Department of Physiology,
Piracicaba Dental School, University of Campinas—Unicamp,
Piracicaba, Brazil

Introduction

Temporomandibular disorders (TMD) are musculoskeletal pain conditions characterized by pain in the temporomandibular joint (TMJ) and/or the masticatory muscles [51]. The clinical condition of TMD can also involve sounds during mandibular movement and limited mandibular movement [63]. TMD pain is the commonest symptom that compels patients to seek therapy. The prevalence of the signs and symptoms of TMD has been reported to vary from 6 to 93%, while only 3.6 to 7% of the general populations have been estimated to be in need of treatment [8, 18, 51, 52, 67]. These wide ranges of prevalence may be probably due to different criteria and methodologies used. Although the underlying cause of TMD remains poorly understood, it is widely recognized to be multifactorial, involving physiological, behavioral, and environmental factors. In dental research, dental occlusion and parafunctional activities were the two etiologic factors that have received the most attention in epidemiological studies [53, 79]. The etiologic role of malocclusion, jaw position, and biomechanical factors has been questioned. For example, various studies did not find association between occlusion and TMD (for a review, see [13, 43, 76]). When such association was present, some studies revealed that occlusal factors were only weakly associated with TMD signs and symptoms [54, 64]. A prospective investigation over two decades into signs and symptoms of TMD indicates that a lateral forced bite between the retruded contact position and the intercuspal contact position and a unilateral crossbite deserve further consideration as possible local risk factors for development of TMD [54]. In relation to oral parafunctions, some experimentally induced habits can cause pain, similar to that related by patients with TMD [9, 66]. Although parafunctional clenching involves in-

creased masticatory muscle activation [29], which can sometimes evoke pain [2], bruxism activity was not always correlated with TMD pain [71]. Moreover, there are people classified as bruxers, who did not present history of pain in masticatory muscles [23, 50]. Therefore, it is difficult to establish any direct relation to prove that parafunctional activities can really cause TMD.

On the other hand, Laskin [49] was the first to suggest that the main factor responsible for TMD is the emotional instead of the physical aspect. During the last decade, numerous investigations have been devoted to understand the relationship between psychological stress and TMD [33, 80, 85]. Patients suffering from this condition report that their symptoms increase during stressful situations [78]. De Leeuw et al. [15] consider that muscle dysfunction and accompanying pain are very often the result of stress-induced muscular hyperactivity [15]. Stress-induced muscular dysfunction may induce secondary changes in the TMJ. Raised elevator tonus leads to increased intraarticular pressure in TMJ and alteration in the normal biomechanics, resulting in microtraumatic damage to the joint capsules and disk attachment. However, the studies that investigate psychological factors present mixed results. Some investigators related electromyographic changes in masticatory muscle baseline values between patients with TMD and control individuals [38, 61, 73], while others did not find significant differences in electromyographic activity baseline values between patients and controls [65, 88]. These inconsistencies may be probably due to different methodologies used.

The authors believe that both physical and psychological factors contribute to the onset and maintenance of TMD. The balance of these factors produces many individual differences in the perception of pain. More important than to argue in support of the supremacy of some etiologic factor (physical or psychological) is to understand to what extent some factors are responsible, how they are involved, and what can be done to alleviate the suffering of TMD patients.

The purpose of this article is to demonstrate the biologic process by which stressful experiences can influence pain perception and, thus, the development of TMD. The notion of the physiological and pathophysiological manifestations of stress system is described, including possible future therapeutic approaches.

Stress system—physiology

Life, as a high-order dynamic equilibrium, is constantly in a state of threatened homeostasis, or stress. Thus, the forces that disturb homeostasis, the stressors, are counterbalanced by adaptive forces generated by the organism [10]. Both physical and emotional stressors set into motion central and peripheral responses, designed to preserve homeostasis [31]. Centrally, neural pathways are facilitated, which, among other functions, mediate arousal, vigilance, cognition, as well as appropriate aggression, with concurrent inhibition of pathways that subserve vegetative functions, such as feeding and reproduction. Peripheral changes occur principally to promote an adaptive redirection of energy. Thus, oxygen and nutrients are directed to the central nervous system (CNS) and the stressed body site [34].

It has to be borne in mind that not all states of stress are noxious. Selye [77] made it clear when he coined the terms “eustress” and “distress”. Hence, he believed that mild, brief, and controllable states of challenged homeostasis could actually be perceived as pleasant or exciting and could be positive stimuli to emotional and intellectual growth and development [77]—it is notable that stress system activation occurs during both feeding and sexual activity, for example. Selye [77] believed that it was the more severe and uncontrollable situations of psychological and physical distress that led to frank disease states.

The central components of the stress system are located in the hypothalamus and the brainstem and include the corticotropin-releasing hormone (CRH) and the locus ceruleus–norepinephrine/autonomic sympathetic nervous systems [11]. The peripheral limbs of the stress system are the hypothalamic–pituitary–adrenal (HPA) axis, together with the efferent sympathetic/adrenomedullary system, and the components of the parasympathetic system [10]. Central CRH and norepinephrine systems, together with peripheral secretion of large amounts of glucocorticoids and catecholamines, affect virtually every cell in the body [12]. Moreover, the stress system also interacts with other major CNS elements, including the mesocorticolimbic dopaminergic system, the amygdala, the hippocampus, and the arcuate nucleus proopiomelanocortin neuronal system [12]. The orchestrated interplay of several neurotransmitter systems in the brain underlies the characteristic phenomenology of behavioral, endocrine, visceral, autonomic, and immune responses to stress. These neurotransmitters include CRH, arginine vasopressin (AVP), opioid peptides, substance P, dopamine, serotonin, and norepinephrine. Therefore, an explanation about the functions of the neurotransmitters and hormones involved in the stress response is outside the scope of this article (for a review, see the work of Herman and Cullinan [36]). It is important to emphasize that most of the molecules mediating stress effects are the same as those associated with pain modulation (for a review, see the paper of Millan [62]) so that the ability of stressful experiences to alter pain transmission and perception is obvious. Melzack [60] postulated the existence of a pain neuromatrix in which the experience of pain is produced by multiple influences

and comprises a widely distributed neural network with input from the body's stress regulation systems, including the HPA axis.

HPA axis—pathology

Dysregulation of the HPA has been demonstrated in several psychiatric stress-related disorders, such as depression [21] and posttraumatic stress disorder [87], which have a significantly higher prevalence among patients with TMD [44]. Stress system dysregulation can be expressed either as hyperfunction or as hypofunction. HPA axis hyperactivity occurs, for example, in melancholic depression [5], anorexia nervosa [40], obsessive–compulsive disorder [37], panic anxiety [31], and chronic active alcoholism [82]. On the other hand, stress system hypoactivation, rather than sustained activation, in which chronically reduced CRH secretion may result in pathologic hypoarousal, characterizes conditions such as fibromyalgia [32], seasonal depression [81], atypical depression [30], some forms of obesity [5], and the chronic fatigue syndrome [16]. In relation to TMD, it would appear that most TMD patients show HPA axis hyperactivity. Geissler [27] used biochemical evidence (urinary cortisol:creatinine ratios) to show that patients with TMD have higher urinary cortisol than normal individuals and therefore are under greater emotional stress. This study was carried out in patients who had been rendered free of pain or had only residual discomfort, so the stress factor would thus be emotional rather than pain-induced. Another recent study [45] indicated very high daytime cortisol levels in patients with facial pain, surprisingly much higher than those seen in depression or in fibromyalgia patients with generalized muscle pain [42]. It remains possible that facial region pain represents a greater stimulus to HPA axis activation than pain elsewhere in the body.

Considering that pain itself acts as a strong activation of the HPA axis [68], it is possible that high levels of cortisol in TMD patients represent a physiological response to chronic stress, with pain as a potential stressor, associated with chronically increased CRH or other HPA axis central mediators. Increased activation of the stress axis central components may result in hyperalgesia [48].

The study of the mechanisms involved in the relationship between stress and pain modulation in humans becomes more difficult because of methodological, psychological, and ethical problems. On the other hand, animal models of nociception are very useful to understand the neural basis of the mechanisms involved in pain perception. The authors' laboratory is using an animal model of nociception, the TMJ formalin test [72], to evaluate the influence of stress on nociception induced by TMJ injury. The authors observed that rats submitted to chronic restraint stress (2 months) showed an increase in nociceptive responses, indicating that chronic stress could induce hyperalgesia [25]. The mechanism by which chronic stress produces hyperalgesia is not clear. In fact, more than one mechanism could be involved. The HPA axis is just one of the stress system biological mediators. Next, the role of the serotoninergic and opioid systems in stress-induced hyperalgesia will be emphasized.

The role of serotoninergic system

Neurons that contribute to ascending nociceptive pathways involved in pain sensation are inhibited by descending serotoninergic and noradrenergic fibers [83, 84]. Changes in the central serotoninergic system activities might, at least partly, explain the bidirectional changes in nociception (analgesia and hyperalgesia) seen after different stress conditions. For example, after acute exposure to different types of adverse psychological or physical stimuli, there is an increase in the extracellular concentrations of serotonin in several brain regions, especially in the raphe magnus [1]. Conversely, prolonged stress diminishes the efflux of serotonin in some brain structures known to be activated by stress, such as the amygdala and the lateral septum [41]. The magnitude of tonic inhibition of pain transmission within the spinal cord horn appears to be dependent on the behavioral state of the organism (depressed mood, anxiety, and fear) [58]. The authors suggested that anxiety and stress can cause a deficit in the central serotoninergic transmission, which produces a sensitization of central pain relay pathways. First, stress was induced in rats by immobilization for 1 h (acute stress) or 2 months (chronic stress). This method is efficient to increase hormonal levels, as was detected by plasma corticosterone and ACTH determination by radioimmunoassay [25]. Next, the authors' test to evaluate nociception in the TMJ was used, as previously described [24]. Briefly, the rats received a 50-μl injection of diluted formalin (1.5%) into the left TMJ region. The injections were given via a 30-gauge needle introduced into the TMJ capsule. After the TMJ injection, the rat was placed in the test chamber, and nociceptive behavioral responses, characterized by rubbing the orofacial region (seconds) and flinching the head (number of times), were quantified for 30 min. A selective reuptake inhibitor, fluoxetine, was used to block the stress-induced hyperalgesia. Actually, fluoxetine administered 30 min before formalin had an analgesic effect analogous to that of morphine, observed in one of the authors' studies [26]. These results are also consistent with correlational studies indicating that anxiety is related to increased pain reports in clinical settings [69, 70].

Schreiber et al. [75] found that fluoxetine relieved low back pain with efficacy similar to that of amitriptyline, and they suggested that fluoxetine could be an alternative for patients who unable to tolerate tricyclic antidepressant side effects. The authors question the possibility of generalizing experimental findings to clinical settings, that is to say, it is too early to affirm that fluoxetine could be effective for treating TMD patients, even though some studies related that 5-HT reuptake inhibitors have been associated with tooth clenching or tooth grinding [28]. Future studies should evaluate the possibility of dentists using fluoxetine to treat TMD patients.

Opioid modulation

A major advance in the conception of the neural pain processing occurred in the past decade. It has become clear that pain is not passively received by the nervous system but is filtered and controlled (modulated) even at the first sensory synapse by complex modulatory systems [62]. The existence of multiple pain-modulatory systems is used to clarify the bewildering profile of clinical observations resulting from various pain treatments. The major components of these systems are the intrinsic opioid systems, which are activated in stress situations and can diminish pain sensation [6]. For example, Maixner et al. [56] have shown that ischemic pain induced in the left arm was able to reduce pain sensation in patients suffering from acute dental pain. One important question is whether these endogenous inhibitory systems are functional in patients suffering from chronic facial pain. It is possible that chronic orofacial pain associated with TMD results from diminished inhibitory systems in the CNS. There is also evidence to support this idea. For example, 70 to 80% of TMD patients suffer from psychosomatic diseases such as ulcers, headache, low back pain, asthma, and dermatitis [49, 74]. The biochemical contents of psychological and physiological stress are elevated in TMD patients when compared with controls [27, 45], suggesting that individuals with TMD are really under greater emotional stress than control individuals.

The authors' data from an experimental TMJ pain model indicate that endogenous inhibitory systems may be less effective under chronic stress conditions. The authors' results demonstrate that repeatedly stressed rats display decreased morphine effects on nociception compared to nonstressed controls in the TMJ formalin test [25]. The tolerance of response to morphine observed in the authors' study agrees with the hypothesis suggested by previous studies that chronic stress could modify opioid system activities (for a review, see the results of the study of Drolet et al. [17]).

Stress as risk factor of TMD

There is currently considerable evidence that psychological factors are of importance in the understanding of TMD, but there is less evidence that these factors are etiologic. The issue of whether psychological factors cause TMD or reflect the impact of TMD on the person remains unknown, although there is strong evidence that some patients with TMD are more anxious and/or depressed compared with asymptomatic controls. Research findings have supported a relationship between anxiety, muscular tension, and TMD symptoms [22, 61]. In a sample of adolescents with signs and symptoms of TMD, anxiety and depression were present in 16.58 and 26.71% of subjects, respectively [7]. In another study, the psychological status assessment showed that 39.8% of patients with TMD experienced moderate to severe depression, and 47.6% had moderate to severe nonspecific physical symptom scores (somatization) [86].

To associate treatment need for TMD and age, gender, and stress, Kuttilla et al. [47] found that women showed more signs and symptoms of TMD, and it seems to be explainable by their higher stress. The higher prevalence of TMD in women than in men has been attributed to an interaction of a variety of factors ranging from biological and hormonal factors to psychological and social ones. An explanation about sexual dimorphism in TMD pain is beyond the scope of this review (for this topic, see the works of Beireter [4] and Karibe et al. [39] for reviews).

The recent theoretical approaches to explain the relationship between the physical and psychological dimensions of pain include psychodynamic, cognitive, behavioral, and biologic models. Psychodynamic theories refer to the inability to modulate and express emotional conflicts, e.g., fear and guilt, and may underlie this relationship. In cognitive terms, helplessness and lack of control, and in behavioral terms, severe reduction in activity due to escape from stressful work or monetary compensation. Biologic theories refer to key transmitters that have been shown to mediate neuroanatomic pathways in control of both pain and psychological stress [25, 26]. We emphasize the relevance of biologic theories because they provide solid evidence to understand the integrated biopsychosocial concept of the etiology of TMD.

The scientific methods available to study the relation between stress and TMJ pain include animal and human studies. To date, only the two authors' studies cited in this article have examined the possible mechanisms involved in the link between stress and TMJ pain using an experimental animal model [25, 26]. In the clinical field, studies in psychoneuroimmunology have implied the relevance of emotional stress and its effect on neuroendocrine function and TMD [3, 55, 57]. While evidence for the role of

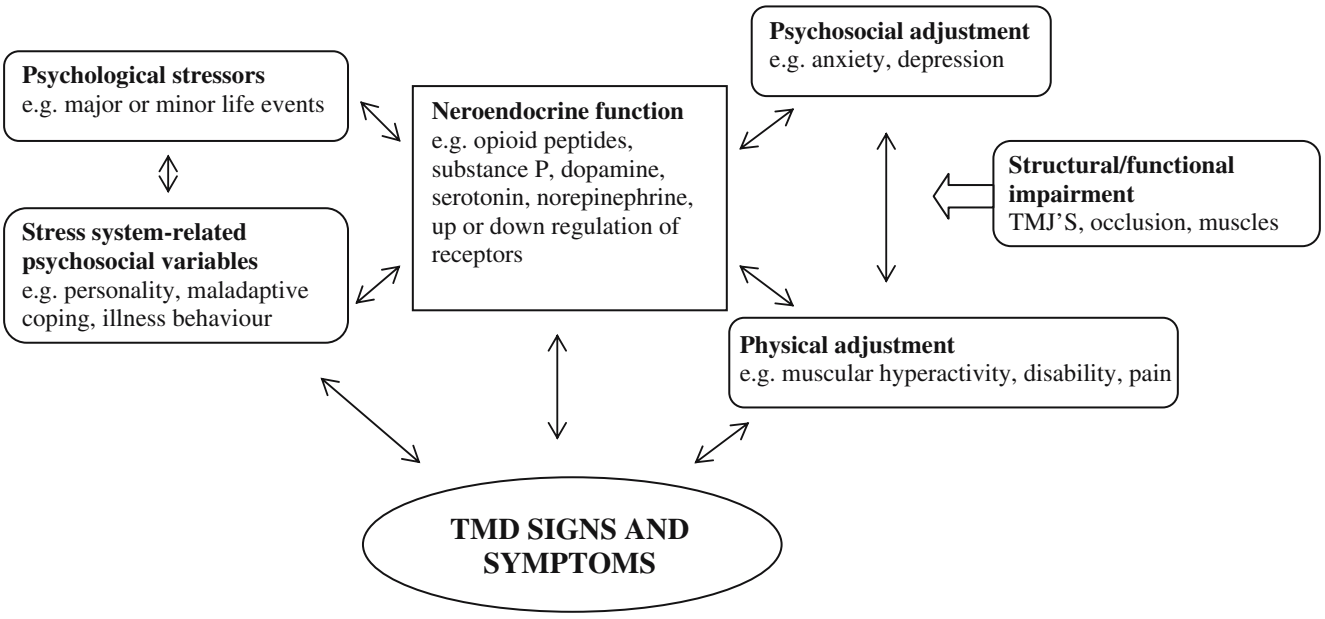

Fig. 1 A range of psychosocial (central event) and physical variables (peripheral events) may modify or exacerbate the effects of stressors on disease-related outcomes

psychological stressors in stress system relationships with regard to TMD is not yet fully confirmed, a proposed integrated biopsychosocial model of how stress may impact on TMD can be drawn (Fig. 1).

The importance of the psychological factor in this integrated model is emphasized by the neuromatrix theory proposed by Melzack [60], in which pain is produced by the output of a widely distributed neural network in the brain (central event) rather than directly by sensory input evoked by injury, inflammation, or other pathology (peripheral event). Thus, the diagnosis, assessment, and management of TMD must include both physical (e.g., TMJ, occlusion, and muscles) and psychological (e.g., personality, affective states, and distress) factors.

Conclusions and future therapeutic directions

Many patients with chronic facial pain improve with antidepressants whether or not they have a comorbid depressive disorder [19, 20]. Antidepressants have the ability to modulate HPA axis activity and increase glucocorticoid receptors, though the mechanism by which this occurs is still unknown [59]. In view of the involvement of the HPA axis in depression and the deleterious effects of prolonged high cortisol levels, research into the potential treatments of mood and pain disorders has focused on modulating the effects of hypercortisolemia. A promising approach is the use of CRH antagonists, and there are several trials testing these agents in a variety of psychiatric disorders including depression [35, 46]. Another possibility is the use of glucocorticoid receptor antagonists to block any detrimental effects of the raised levels of circulating cortisol and also cause a compensatory upregulation of glucocorticoid receptor number [14].

The authors concluded that the influence of stress on TMD is not as simple as suggested according to Laskin's theory, in which the stress evokes chronic recurrent muscular hyperactivity that progressively damages the joint, which in time becomes symptomatic [49]. The authors propose that stress can profoundly affect the biological processes of pain transmission and perception. Thus, inappropriate adaptational responses could be maladaptive and act as stressors themselves (orofacial pain is a strong stressor), feeding into a sustained vicious cycle (Fig. 2).

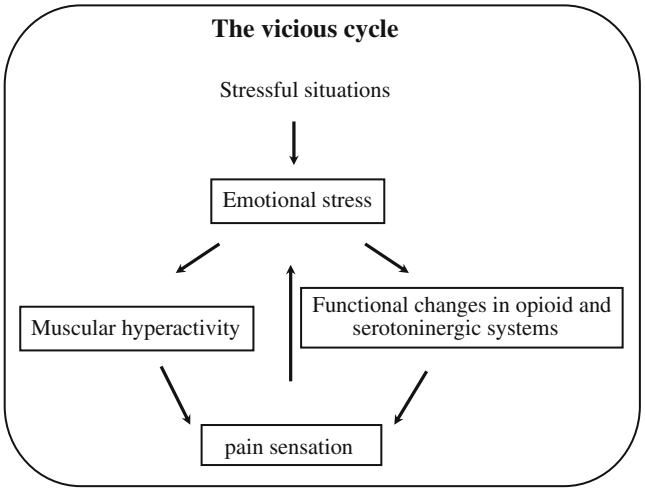

Fig. 2 Diagram illustrating the cycle stress–pain–stress that can occur in TMD patients

In the authors' opinion, nociceptive controls exist not only for very stressful and/or nociceptive stimuli but also for very mild stress that occurs constantly, i.e., situations occurring daily. This might explain why patients with TMD often have onset of their symptoms during periods of psychological stress (i.e., anxiety) and exacerbation of symptoms during periods of stressful situations [78].

Future research on stress-induced pain modulation should consider the multidimensionality of stress (physiological and subjective experience) and its impact on the development of TMD. In addition, to provide a more complete understanding of the centrifugal control of pain, it is hoped that such information might suggest ways of relieving pain by less invasive means. The theoretical framework for testing the hypothesis that a dysregulation in the stress system can lead to TMD has been set in place, with the potential for improved understanding, diagnosis, and treatment of these disorders.

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