Influence of the Hypothalamic-Pituitary-Adrenal Axis on Temporomandibular Disorders. Short Article *

Influencia del eje hipotalámico hipofisiario suprarrenal en los trastornos temporomandibulares. Artículo corto

Influência do eixo hipotálamo-hipófise-adrenal nas disfunções temporomandibulares. Artigo curto

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DOI : https://doi.org/10.11144/Javeriana.uo43.ihpa
Submission Date: 15 August 2023
Acceptance Date: 6 May 2024
Publication Date: 26 December 2024

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ABSTRACT

Background: For some time, the relationship between temporomandibular disorders (TMD) and psychobiological factors has been explored. Psychological stress has been shown to produce chemical changes in the body, one of which is the increase

in cortisol levels regulated by the hypothalamic-pituitary-adrenal (HPA) axis. This triggers physiological and pathological bodily changes, such as TMD. **Purpose**: To analyze current evidence on the influence of the HPA axis on TMD and methods for measuring cortisol levels. **Methods**: A narrative literature review was conducted using a sample of articles from the PubMed, Google Scholar, ScienceDirect, and Cochrane databases, published between 2008 and 2022. Narrative reviews, systematic reviews, meta-analyses, and in vivo and in vitro studies were included. **Results and Conclusions**: Initially, 220 titles were identified, of which 27 articles were selected for full-text reading and analysis. The evidence links altered HPA axis dynamics to the pathophysiological development of TMD as an adaptive response to environmental stress-inducing factors. Activation of this axis stimulates the production of cortisol, neuropeptides, and inflammatory mediators, leading to characteristic signs and symptoms and increasing the likelihood of joint degeneration.
Keywords: cortisol; dentistry; hydrocortisone; hypothalamic-pituitary-adrenal axis; sleep disorders; stress; temporomandibular disorders; temporomandibular joint disorders

RESUMEN

Antecedentes: Durante algún tiempo, se ha tratado de explicar la relación de los trastornos temporomandibulares (TTM) con factores psicobiológicos. Se ha comprobado que el estrés psicológico produce alteraciones químicas en el organismo. Una de ellas es el aumento de los niveles de cortisol regulado por el eje hipotalámico hipofisiario suprarrenal (HPA), el cual desencadena cambios corporales fisiológicos y patológicos como los TTM. **Objetivo:** Analizar evidencia actual sobre la influencia del eje HPA en los TTM y los métodos para medir los niveles de cortisol. **Métodos:** Se realizó una revisión narrativa de la literatura a partir de una muestra de artículos obtenidos en las bases de datos PubMed, Google Scholar, ScienceDirect y Cochrane y publicados entre 2008 y 2022. Se incluyeron revisiones narrativas, sistemáticas y metanálisis, así como estudios *in vivo* e *in vitro*. **Resultados y Conclusiones:** Se identificaron inicialmente 220 títulos de los cuales se seleccionaron 27 artículos para lectura de texto completo y análisis. La evidencia relaciona la dinámica alterada del eje HPA con el desarrollo fisiopatológico de los TTM como respuesta adaptativa frente a factores ambientales que inducen estrés. La activación de este eje estimula la producción de cortisol, neuropéptidos y mediadores inflamatorios, lo que genera signos y síntomas característicos, además de incrementar la probabilidad de degeneración articular.
Palabras clave: cortisol; desórdenes temporomandibulares; eje hipotálamo hipofisario adrenal; estrés; hidrocortisona; odontología; trastornos de la articulación temporomandibular; trastornos del sueño

RESUMO

Antecedentes: Há algum tempo, tentativas têm sido feitas para explicar a relação das disfunções temporomandibulares (DTM) com fatores psicobiológicos. Está comprovado que o estresse psicológico produz alterações químicas no corpo. Um deles é o aumento dos níveis de cortisol regulados pelo eixo hipotálamo-hipófise-adrenal (HPA), o que desencadeia alterações corporais fisiológicas e patológicas, como a DTM. **Objetivo**: Analisar as evidências atuais sobre a influência do eixo HPA na DTM e métodos para medir os níveis de cortisol. **Métodos**: Foi realizada uma revisão narrativa da literatura a partir de uma amostra de artigos obtidos nas bases de dados PubMed, Google Scholar, ScienceDirect e Cochrane e publicados entre 2008 e 2022. Foram incluídas revisões narrativas, sistemáticas e meta-análises, além de estudos in vivo e in vitro. **Resultados e Conclusões**: Foram identificados inicialmente 220 títulos, dos quais 27 artigos foram selecionados para leitura e análise do texto completo. As evidências vinculam a dinâmica alterada do eixo HPA ao desenvolvimento fisiopatológico da DTM como uma resposta adaptativa a fatores indutores de estresse ambiental. A ativação desse eixo estimula a produção de cortisol, neuropeptídeos e mediadores inflamatórios, levando a sinais e sintomas característicos e aumentando a probabilidade de degeneração articular.
Palavras-chave: cortisol; eixo hipotálamo-hipófise-adrenal; estresse; hidrocortisona; odontologia; distúrbios da articulação temporomandibular; distúrbios do sono; distúrbios temporomandibulares

INTRODUCTION

The hypothalamic-pituitary-adrenal (HPA) axis is considered the primary endocrine regulatory axis in response to depression in humans (1). It responds to both physical and psychological stressors by secreting catecholamines (epinephrine and norepinephrine) through the sympathetic nervous system, and glucocorticoids, such as cortisol, via the adrenal gland. Cortisol is identified as the main marker associated with the dysregulation of this axis (2).

Cortisol, a glucocorticoid hormone secreted by the zona fasciculata of the adrenal cortex, plays a role in activating anti-inflammatory processes and is considered a biological marker of stress and anxiety

(3,4). A study evaluated salivary cortisol levels in young adults with temporomandibular joint disorder (TMD) and positive levels of depression (1). The results indicated that salivary cortisol assessment could help identify psychological etiological factors responsible for TMD. While no correlation was found with mild TMD pain, a positive correlation was observed with moderate and severe pain (1,3).

TMD encompasses a group of musculoskeletal conditions that cause pain and dysfunction in the masticatory muscles, temporomandibular joints (TMJ), and associated structures (5). They are the second most common cause of pain in the orofacial region, following dental pain, with an approximate prevalence of 40 % in the general population (6). It has been suggested that research on the etiology of TMD should focus on biological factors, such as its higher prevalence in women (80 %), possibly related to estrogen, and psychosocial factors, such as stress and anxiety (1). Some studies also indicate that patients with TMD exhibit altered HPA axis dynamics (7,8).

Although previous studies have explored the relationship between HPA axis dysregulation and its role in the development of TMD (6,7), its pathophysiology remains incompletely understood. This highlights the need for further research, both descriptive and clinical, to better understand this correlation. The objective of this narrative literature review was to analyze recent evidence on the potential influence of the HPA axis on TMD. The research question guiding the review was: What is the influence of the HPA axis on TMD, and what is its mechanism of action?

MATERIALS AND METHODS

A narrative literature review was conducted based on an exhaustive bibliographic search in the PubMed, Cochrane, Google Scholar, and ScienceDirect databases. The search terms and Boolean connectors used were: *HPA Axis AND TMD*; *(TMD OR Temporomandibular disorders) AND cortisol*; *sleep disorders AND stress*. The inclusion criteria for article selection included narrative reviews, systematic reviews, and meta-analyses, as well as in vivo and in vitro studies analyzing the influence of the HPA axis on TMD. The search was limited to publications between 2008 and 2022 and to articles in English and Spanish. Clinical case reports and articles published before 2008 were excluded.

The collection and selection of studies were carried out in four stages. In the first stage, available publications were gathered from digital databases. In the second stage, five reviewers analyzed the titles and abstracts of the articles following the eligibility criteria, eliminating duplicates. In the third stage, the full texts of relevant publications were evaluated, with the eligibility criteria reapplied. Finally, in the fourth stage, the selected articles underwent a critical appraisal to determine their scientific merit, resulting in the inclusion of a total of 27 publications.

FINDINGS AND DISCUSSION

The evidence identified and analyzed in this review is presented below in four sections: the mechanism of action of the HPA axis, the mechanism of cortisol regulation, the HPA axis and its relationship with TMD, and proposed treatments for regulating the HPA axis.

Mechanism of Action of the HPA Axis

One of the most important physiological responses of the human adaptive system to environmental circumstances or stress situations is the activation of the HPA axis and the synthesis of its main end product: cortisol (9,10). This axis is mediated by neuroendocrine neurons that synthesize corticotropin-releasing hormone (CRH), located in the paraventricular nucleus (PVN) of the hypothalamus. Once synthesized, CRH is released into the bloodstream via the hypophyseal portal system, reaching the

posterior pituitary, where it interacts with corticotropic cells. At this level, CRH acts synergistically with antidiuretic hormone to stimulate the production of adrenocorticotropic hormone (ACTH) (9). ACTH is then released into the bloodstream and reaches the adrenal cortex, where it promotes the synthesis and release of glucocorticoids, primarily cortisol (11).

Cortisol exerts its effects on cellular activity through its interaction with intracellular mineralocorticoid receptors (MR or type I) and glucocorticoid receptors (GR or type II), which are present in most tissues. These receptors form a hormone-receptor complex that can stimulate or inhibit gene expression (11). Cortisol release generates multiple systemic effects, such as increased hepatic gluconeogenesis, lipolysis in adipose tissue, reduced calcium reabsorption in the kidneys, and decreased absorption of calcium, magnesium, and phosphorus in the intestinal tract. It also has cardiovascular, metabolic, and immune effects (9,12). Its role in maintaining homeostasis lies in its potent anti-inflammatory effects. In response to any inflammatory condition, whether acute or chronic, the HPA axis is activated, leading to the synthesis and release of cortisol. For this reason, cortisol is considered the primary biological marker of stress and anxiety (2,3) (Figure 1).

Mechanism of Cortisol Regulation

Cortisol regulates its own synthesis and release through negative feedback mechanisms. This occurs via its binding to glucocorticoid receptors in the limbic system, including the hippocampus, amygdala, and prefrontal cortex. In the hippocampus, this hormone-receptor interaction inhibits the PVN and reduces ACTH expression in pituitary corticotropes, thereby limiting HPA axis activation (11-13). Additionally, glucocorticoids have been shown to regulate the HPA axis through peripheral mechanisms, such as the removal of GR receptors in adipocytes, which inhibits the HPA axis. This could be explained by the effects of end products generated by GR action (13). Moreover, neurotransmitters such as glutamate, serotonin, and norepinephrine also influence these brain structures, stimulating the release of more catecholamines and cortisol (6).

The negative regulation mechanisms of cortisol aim to limit tissue exposure to its catabolic and immunosuppressive effects triggered by stress (14). However, the presence of chronic stressors can override this negative feedback mechanism, leading to persistent HPA axis activation, known as allostatic overload. This condition generates non-beneficial stress responses that can cause tissue damage (10,11,13). Literature indicates that diminished negative feedback, associated with HPA axis hyperactivity, is linked to sleep deprivation, often caused by major depressive disorder (15). On the other hand, increased negative feedback has been associated with cardiovascular diseases and schizophrenia (16). During sleep, cortisol release is typically suppressed. However, exposure to chronic stressors elevates cortisol levels during the initial sleep phases, causing fragmentation and further increasing cortisol levels (7).

Obstructive sleep apnea can trigger various comorbidities and sequelae due to hypoxemia caused by recurrent airway obstruction. This condition increases the expression of proinflammatory cytokines, such as interleukin 6 and tumor necrosis factor-alpha. Additionally, overexpression of opioid receptors has been observed, influencing central and peripheral pain sensitization, as well as pain amplification mechanisms. These effects are particularly associated with musculoskeletal pain disorders. Therefore, proper diagnosis and timely management of this condition are crucial (17-21).

HPA Axis and Its Relationship with TMD

Dysfunction of the HPA axis can be influenced by various stressors that induce its stimulation. These factors include reactive stressors such as pain, bodily injuries, immune alterations, and diseases like obesity, food allergies, or chronic inflammatory conditions, as well as the pharmacological agents used for

their treatment. Anticipatory factors, such as social challenges or unfamiliar situations; physical factors, such as exposure to extreme danger; and psychological factors, such as anxiety, are also considered (12,14). Additionally, factors such as the individual's sex, exposure to light or darkness, and changes in feeding schedules can regulate the metabolic activity of the HPA axis (13) (Figure 1).

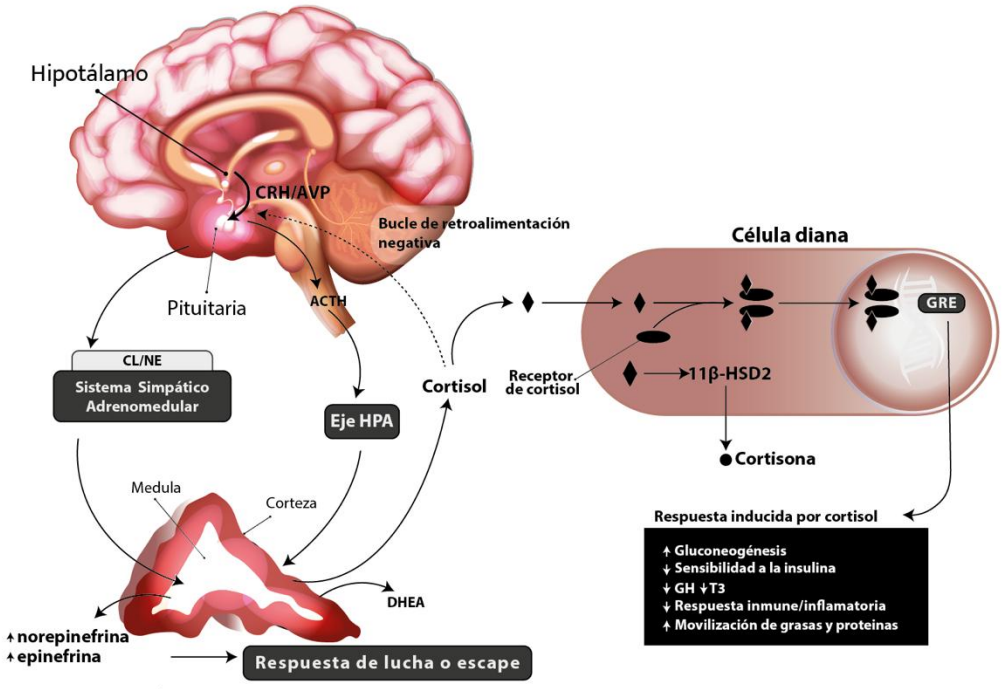

FIGURE 1
El eje HPA y el sistema de respuesta al estrés
Source: Figura modificada de Guilliams & Edwards, 2010 (14).

The key components of the "stress system" are the HPA axis and the sympathetic nervous system. When a stressor activates the hypothalamus, CRH and arginine-vasopressin are released, stimulating ACTH production in the posterior pituitary and activating the noradrenergic neurons of the locus coeruleus/norepinephrine (LC/NE) system in the brain. The LC/NE system is primarily responsible for the immediate "fight or flight" response, mediated by epinephrine and norepinephrine. Meanwhile, ACTH promotes cortisol production in the adrenal cortex. Under normal conditions, CRH and ACTH production follows a predictable circadian cycle and is regulated by a negative feedback mechanism, in which elevated cortisol levels in the blood inhibit their production.

Current evidence highlights the role of the HPA axis in the pathophysiological development of TMD (1,7). A 30 % to 50 % increase in cortisol levels has been observed in stressful situations (6,22). This increase alters pain perception in the CNS, enhances parafunctional habits, and causes tension, stiffness, pain, and hyperactivity in the masticatory muscles. Additionally, it may contribute to TMJ degeneration, such as osteoarthritis or autoimmune arthritis. It has also been associated with chronic conditions like idiopathic fibromyalgia, which can trigger TMJ inflammation and mark the onset of TMD (6,22,23).

To quantify cortisol in the human body, various tests such as ELISA, RIA, HPLC, and LC/MS are used, with samples obtained from saliva, blood, hair, plasma, and urine. Measuring cortisol in blood, saliva, and urine has limitations, as each of these fluids provides a limited temporal window of cortisol activity (10). Therefore, hair analysis is increasingly being used, as it reflects long-term exposure to

certain substances. Analyzing 1 cm to 2 cm of hair can indicate cortisol exposure over several weeks or up to two months (24).

The current gold standard for determining HPA axis activity in humans is the measurement of cortisol upon awakening. This method is based on the characteristic circadian rhythm of the HPA axis (25). Cortisol concentrations gradually increase from 4:00 am to 10:00 am, peaking around 8:00 am. They then decline progressively throughout the day, reaching their lowest levels between 10:00 pm and 4:00 am (9). This circadian increase is associated with the need to mobilize energy in an awake organism to meet its energy demands (13). Additionally, food intake induces small peaks in hormone secretion, suggesting that neither the circadian nor metabolic release of glucocorticoids responds exclusively to stressors (13).

Proposed Treatments to Regulate the HPA Axis

Various therapies and treatments have been proposed to mitigate the symptoms associated with TMD and its relationship with stressors. Badel, *et al.* (26) suggest the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for patients with joint pain and diazepam for those with muscle pain. These medications not only effectively relieve pain but also positively contribute to the psychological state of patients with TMD. Meanwhile, Lazarus and Folkman (27) emphasize psychoeducation as an effective form of psychological support. This approach combines psychotherapy and education through an interactive model that allows individuals, through controlled modifications in their knowledge and skills, to realistically influence their coping capacity in the face of stress.

CONCLUSIONS

The evidence links altered HPA axis dynamics to the pathophysiological development of TMD as an adaptive response to environmental stress-inducing factors. Activation of this axis stimulates the production of cortisol, neuropeptides, and inflammatory mediators, leading to characteristic signs and symptoms and increasing the likelihood of joint degeneration.

RECOMMENDATIONS

It is recommended to include the study of the HPA axis in the dentistry curriculum. This would enhance both clinical and laboratory diagnosis in patients with TMD, contributing to a more comprehensive and effective approach to this pathology.

It is suggested that healthcare professionals incorporate complementary tests during the diagnostic phase of TMD to identify potential HPA axis alterations. This would enable a more comprehensive and appropriate treatment for the patient, contributing to an improved quality of life.

Due to the limited information available on the topic, it is suggested to conduct more prospective studies and randomized clinical trials to expand knowledge and strengthen scientific evidence.

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*Original research.

How to cite this article: Durán Urdiales DB, Cárdenas Gómez EP, Benalcázar Arias MV, Armijos Freire SD, Astudillo Uchupaille AM, Bravo Torres WD. Influence of the Hypothalamic-Pituitary-Adrenal Axis on Temporomandibular Disorders. Short Article. Univ Odontol. 2024; 43. https://doi.org/10.11144/Javeriana.uo43.ihpa