Stress and Hypothalamic–Pituitary–Adrenal Axis

Effect on Prognosis of Dental Treatment

Veronica Iturriaga, DDS, MSc, PhD[a,*], Nicol Velasquez, DDS[a], Eli Eliav, DMD, PhD[b], Davis C. Thomas, BDS, DDS, MSD, MSc Med, MSc[c]

KEYWORDS

• Stress and dentistry • HPA and dentistry • Stress and dental prognosis
• HPA and dental prognosis

KEY POINTS

- Stress is a process that activates a set of reactions involving behavioral and physiologic responses.
- The stress response involves an efficient and complex system with modulation at different levels of the central nervous system being driven largely by neural mechanisms, including activation of the hypothalamic–pituitary–adrenal (HPA) axis.
- The HPA axis is a neurohormonal system necessary for adaptation, resulting from the interaction among 3 distinct organs, which mediates the secretion of corticotropin-releasing hormone in the hypothalamus, adrenocorticotropic hormone in the pituitary, and glucocorticoid hormone-cortisol in the adrenal cortex.
- Stress and activation of the HPA axis associated with dental care can negatively interfere with the efficacy of dental treatment, affecting adherence and resulting in total treatment interruption or delay of subsequent appointments.

INTRODUCTION

Stress has been a topic of study in various medical specialties for several decades, and to address it, approaches have been made to understand its effects on the different systems of the organism. The response to stressful stimuli is elaborated by a system that integrates a wide diversity of brain structures, which collectively can detect events and interpreting them as real or potential threats.[1,2] The integration of this information

[a] Department of Integral Adult Care Dentistry, Temporomandibular Disorder and Orofacial Pain Program, Sleep & Pain Research Group, Universidad de La Frontera, Temuco, Chile; [b] Eastman Institute for Oral Health, University of Rochester Medical Center, Rochester, NY, USA; [c] Department of Diagnostic Sciences, Center for Temporomandibular Disorders and Orofacial Pain, Rutgers School of Dental Medicine, Newark, NJ, USA
* Corresponding author.
E-mail address: veronica.iturriaga@ufrontera.cl

Dent Clin N Am 68 (2024) 619–626
https://doi.org/10.1016/j.cden.2024.07.003 **dental.theclinics.com**

results in a rapid activation of the hypothalamic–pituitary–adrenal (HPA) axis , being a fundamental component of the stress response.[1,3] On the other hand, people tend to feel stress in association with dental treatment; this can be triggered by restlessness and fear, understanding that this expression is multifactorial and multidimensional, which considers physiologic, behavioral, and cognitive components of the person.[4,5]

Accordingly, the aim of this article is to describe the effect of stress in its interaction with the HPA axis on the prognosis of dental treatment. In the first instance, general aspects related to the stress process and the participation of the HPA axis will be reviewed, to later relate them to the prognosis of dental treatment.

STRESS AS A PROCESS

Understanding the concept of stress and its biologic substrate is fundamental to comprehending its role in different processes. Hans Selye[6] was one of the first to define it from the biologic point of view, considering stress as "a nonspecific response of the body to any demand made on it."[1,2,7] Other definitions consider it as a state of homeostatic alteration, which generates a response in the organism to maintain homeostasis.[2] Stress activates a set of reactions involving behavioral and physiologic responses (neuronal, metabolic, and neuroendocrine) that allow the organism to respond to the stressor in the most adapted way possible.[8] This response ultimately reflects the activation of specific circuits genetically constituted in the individual and constantly modulated by the environment.[2] For this process to be initiated, the organism must perceive a threat, either real or potential, which leads to the release of various types of molecules. The interaction between these molecules with their respective receptors, at the peripheral and central levels, may result in the stress response. This response, through physiologic and behavioral mechanisms, helps restore the body's homeostasis and promote adaptation.[1]

The stress response involves an efficient, evolving, and complex system, with modulation at various levels of the central nervous system (CNS), being driven to a greater extent by neuronal mechanisms, which activate 2 types of circuits in the CNS, and which develop mainly in 2 phases. The first phase begins with the perception of a stressor; when this situation is perceived as a threat, neuronal pathways are recruited in the brain to maintain physiologic integrity, which involves the activation of the first circuit at the level of the spinal cord, particularly the adrenomedullary sympathetic system. In this way, a rapid physiologic adaptation is provided, with a short-duration response, generating a state of alertness, vigilance, and evaluation of the situation to be faced. The second circuit, and with it, the second phase, involves a neurohormonal process, where the interpretation of the information by supraspinal structures is required and refers to the activation of the HPA Axis. This is a slower process, which generates an amplified and prolonged response.[1,2,9]

The neural mechanisms that drive chronic stress responses may be distinct from those that control acute reactions, including the recruitment of new limbic, hypothalamic, and brainstem circuits. It is critical to consider that an individual's response to acute or chronic stress is determined by a variety of factors, including genetics, early life experience, environmental conditions, gender, and age. The context in which the stressors are generated will determine whether the individual's responses are adaptive.[9,10]

Patients in general many a time feel that stress is "bad." However, physiologically speaking, it may not be all that deleterious. Stress is also part of the defensive phenomenon. For example, a mother who loses her toddler child in a crowd does not really sit around waiting for the child just to show up. Her instinctive activation of the acute stress

response brings about the rapid response of vigilance and the innate impulse to actively search for her offspring. In general, when stress is not biologic, chronic stress may become pathologic with deleterious effects on the body and mind.

HYPOTHALAMIC–PITUITARY–ADRENAL AXIS

The HPA axis corresponds to a neurohormonal system that integrates the secretion of corticotropin-releasing hormone (CRH) in the hypothalamus, adrenocorticotropic hormone (ACTH) in the anterior pituitary, and cortisol in the adrenal cortex. The HPA axis is therefore initiated in the hypothalamus, particularly in the hypophysiotropic neurons of the parvocellular nucleus (PVN) of the hypothalamus, since it is in this nucleus where information from various areas of the CNS is integrated. These neurons send projections to the median eminence of the brainstem, and when activated, they discharge CRH and other releasing factors into the pituitary portal capillary system. These releasing factors are directed to the anterior pituitary, where they stimulate corticotropes to release ACTH into the systemic circulation. ACTH acts on cells in the zona fascicularis of the adrenal cortex to stimulate the production and secretion of glucocorticoid hormones (GCs) into the general circulation, particularly cortisol in humans, and to a lesser extent mineralocorticoids. Once released into the bloodstream, 75% to 80% of the GCs bind to plasma proteins, and a low fraction remain free exerting their immediate physiologic effect, thus maintaining a constant blood glucose level to nourish the muscles, heart, and brain.[2,3,7,8,10–12]

Under physiologic conditions, the HPA axis presents a circadian regulation, with a low basal activity level that varies with the time of day, in addition to presenting negative feedback mechanisms mediated by GCs. ACTH and GCs levels are highest near the beginning of the waking period and are lowest near the beginning of the inactive period; this rhythm depends on neuronal circuits sensitive to changes in light, including afferents from the suprachiasmatic nucleus to the PVN, which physiologically promotes PVN activation but in stressful situations acts as an inhibitor.[2,7,10–12]

It is important to consider then that the HPA axis response to stress results from the interaction among these 3 distinct organs, each of which has its own intrinsic checkpoints for the regulation of GCs secretion.[7,9]

STRESS: HYPOTHALAMIC–PITUITARY–ADRENAL AXIS INTERACTION AND DENTAL TREATMENT

The regulation of stress reactivity is a fundamental priority for all organisms. Stress responses are critical for survival, but they can also generate effects at the physical as well as the psychological level.[7] As mentioned earlier, stress responds to a real or perceived threat to the organism's homeostasis or well-being, and the HPA axis is necessary for adaptation. The perception of different stressors involves complex activation networks, being dependent on the type of stressor or stressor involved. Reactive responses to homeostatic disruption often involve direct noradrenergic conduction, whereas anticipatory responses use oligosynaptic pathways originating in limbic structures. These brain networks ultimately evoke physiologic responses to stress, including activation of the HPA axis, with consequent release of GCs-cortisol, which act on multiple organ systems to redirect energy resources to meet actual or anticipated demand.[1,9,11] On the other hand, circulating concentrations of GCs-cortisol are maintained within normal limits through negative feedback on hypothalamic–pituitary release of CRH and ACTH.[2,3,8,10] In the hypothalamus, the increase in GCs-cortisol early generates a decrease in the frequency of PVN release; thus, the stimulatory effect of CRH on ACTH secretion is inhibited by the action of GCs-cortisol. Importantly, CRH

neurotransmission is not limited to the communication between the PVN and the anterior pituitary, as the existence of extra hypothalamic regulatory mechanisms on PVN function has been observed, since CRH is also expressed in other stress-regulating brain regions, including the central amygdala and the bed nucleus of the stria terminalis,[2,3,7,11] which act as relay centers of the HPA axis, modulating its activity in response to stress.

The purpose of the counter-regulatory mechanism described earlier is to maintain stable basal levels of ACTH and GCs-cortisol. However, repeated or sustained activity of stress responses produces a series of long-term adaptations in these systems, generating changes in gene expression and synaptic plasticity in the stress-regulating brain regions. This situation produces habituation and facilitation phenomena, changes in PVN inputs to favor neuronal excitability, elevated CRH expression, and adrenal hypertrophy, resulting in increased HPA axis excitability with chronic exposure to GCs-cortisol.[2,3,11]

In dentistry, practitioners are aware of the variations that exist in the way patients react to treatment. Maybe small number of people are happy to undergo dental treatment; however, most of them can control themselves sufficiently to accept treatment without excessive signs of stress. However, there is a surprisingly large group of patients in whom stress is more obvious, manifesting itself in a variety of ways and may result in a negative response to treatment. It is estimated that between 10% and 15% of the general population suffers some degree of stress in the face of dental treatment, being perceived as an agonizing experience (**Fig. 1**).[13–15] This is triggered on several occasions by anxiety and fear, with special reference to the expectation of pain, this being one of the main reasons for missing dental appointments. According to the study carried out by Rodriguez and colleagues,[16] approximately 97% of the patients manifest some degree of stress during the execution of their dental treatment.[4,5,13,17,18]

Traditionally dental treatment has been related to pain, where the stress response to pain or even the anticipation of it, initiates the activation of the HPA axis, being a physiologic process that can be expressed in all people.[4] However, the stress generated by dental care causes certain effects in the body in response to the real or perceived threat; these effects include tachycardia, increased blood pressure, hyperglycemia, mydriasis, hyperthermia, nausea, sweating, excessive salivation, and secretion of GCS-cortisol generated by the activation of the HPA axis, which can negatively affect important biologic mechanisms and be a risk factor in the development of certain systemic diseases.[15,18–20] In particular, the immediate period waiting for dental treatment is commonly described as an anxiogenic factor, with prevalence rates ranging from approximately 5% to 20%, being an important factor to consider.[18–22] In reference to the triggers of stress/anxiety in dental treatment, Gale and colleagues[23] reported that the situations that originate high levels of stress/anxiety are in order: the extraction of a tooth, the drilling of a tooth, the dentist's bad opinion about the patient's oral health, and lastly, the action of holding the needle in front of the patient.[24]

From the point of view of dental treatment prognosis, stress and activation of the HPA axis because of dental care influence the efficacy of dental treatment, producing interference in it. It can negatively influence the oral health status of the individual, hinder patient management during care, or also affect subsequent adherence to treatment, which usually results in total interruption or delay in requesting the next appointment, ultimately avoiding subsequent consultations.[14,19–21] Eitnet and colleagues[25] found that dental treatment avoidance is highly correlated with stress/anxiety indices and increased caries morbidity. Yet, when patients with high levels of stress/anxiety attend their consultations, they are highly likely to avoid follow-up appointments to complete their dental treatment. This avoidance results in a higher prevalence of oral pathology, leading to a greater need for and complexity of rehabilitative treatment.[22]

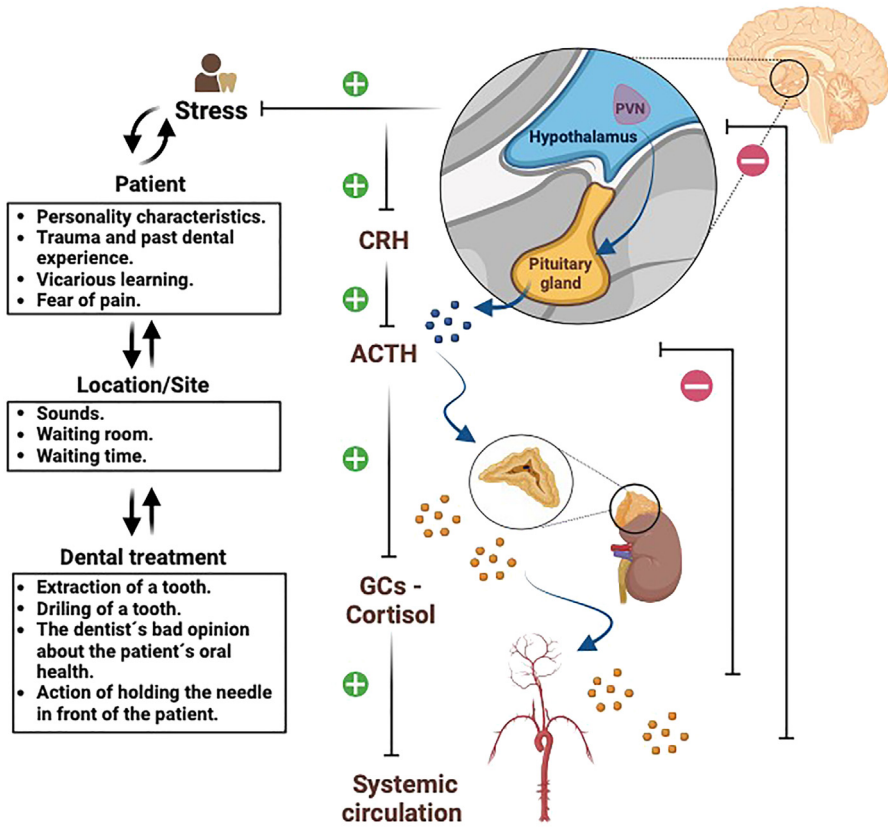

Fig. 1. Schematic representation of HPA axis stimulation. Stress is a complex phenomenon, and its development cannot be due to a single variable. There are a number of factors that have been consistently associated with stress in dentistry, factors that depend on the patient, the site, and the dental treatment. Any one of these factors can initiate the stress response. HPA axis stress responses are initiated by neurons in the PVN, which is the final integrator of the stress response. Neurons in this nucleus produce CRH, which stimulates production in the anterior pituitary of ACTH. ACTH stimulates the production of GCs-cortisol in the adrenal glands. In turn, GCs-cortisol inhibits its own synthesis, inhibiting the synthesis and release of ACTH and CRH, thus self-regulation occurs.

Due to all these factors, there are currently various models of care that seek to help health professionals provide dental care with a view to reducing stress during care and thereby ensure the success of treatment, using affective communication management techniques, relaxation and breathing techniques, music therapy, and even pharmacologic measures such as intravenous sedation, oral sedation, inhalant sedation, and general anesthesia.[13,17,21,24]

CLINICAL IMPLICATIONS IN DENTISTRY

The complexity of the stress response is not limited to neuroanatomy or HPA axis mediators but diverges according to the timing and duration of exposure to the factor, as well as its short-term and/or long-term consequences.[1,2] The stress response, through mediator molecules, promotes alterations in cellular excitability, as well as

in neural and synaptic plasticity, leading to transient and/or permanent changes in physiology and behavior, since HPA axis has the capacity to exert generalized effects through the increase of circulating GCs-cortisol.[1,11]

One of the difficulties frequently reported by dentists during dental treatments and with great impact on oral health is the failure to keep appointments and avoidance of the dentist's intervention, because of stress/anxiety before treatment.[24] Furthermore, it is important to consider that in addition to this, there are certain predisposing factors to this type of situation, where patients with low pain thresholds stand out, which increase sensitivity to dental treatment; those patients who present traits of generalized anxiety should also be considered, and, finally, the transmission of unfavorable attitudes toward dental treatment by other people is also recognized.[17,19,24]

SUMMARY

Considering all of the above, it is essential to understand that the regulation of stress reactivity and HPA axis is a fundamental priority of all organisms, and that this response is controlled by emotional, behavioral, and physiologic components, generating an effect in the short and long term. The knowledge of such organization should allow the dentist a better understanding of the process and the consequences associated with stress and its HPA axis interaction, bearing in mind that one of the main consequences is the interference with dental treatment, which will usually generate the interruption of the treatment and the avoidance of subsequent appointments, negatively affecting the prognosis in these patients. Thus, there is a new challenge for future dentists in the search for new tools and models of care to reduce the levels of stress/anxiety during dental treatment.

CLINICS CARE POINTS

- The response to stressful stimuli is elaborated by a system that integrates a wide diversity of anatomic systems and structures.
- Repeated or sustained activity of stress responses produces a series of long-term adaptations, generating changes in gene expression and synaptic plasticity, with associated habituation and facilitation phenomena in stress-regulating brain regions.
- The interaction between stress and HPA axis in dental treatment can interfere in the prognosis of the treatment, negatively influencing the oral health status of individuals, hindering patient management during care, or affecting subsequent adherence to treatment.

DISCLOSURES

V. Iturriaga and N. Velasquez contributed to the conception and design and wrote the initial draft and figure preparation. D.C. Thomas and E. Eliav contributed to the manuscript by critically revising important intellectual content. All authors gave final approval and agreed to be accountable for all aspects of this work. The study was financed by Project DI20-0018 and the Temporomandibular Disorder and Orofacial Pain Program, Universidad de La Frontera, Chile. The authors declare that they have no conflict of interest.

REFERENCES

1. Godoy LD, Rossignoli MT, Delfino-Pereira P, et al. A Comprehensive Overview on Stress Neurobiology: Basic Concepts and Clinical Implications. Front Behav Neurosci 2018;12:127.

2. Rodríguez-Fernández J, García-Acero M, Franco P. Neurobiología del estrés agudo y crónico: su efecto en el eje hipotálamo-hipófisis-adrenal y la Memoria. Rev Ecuat Neurol 2012;21:1–3.
3. Karaca Z, Grossman A, Kelestimur F. Investigation of the Hypothalamo-pituitary-adrenal (HPA) axis: a contemporary synthesis. Rev Endocr Metab Disord 2021; 22(2):179–204.
4. Dušková M, Vašáková J, Dušková J, et al. The role of stress hormones in dental management behavior problems. Physiol Res 2017;66(3):317–22.
5. Umemori S, Noritake K, Tonami KI, et al. The Effects of Providing Advance Notice and Stress-Coping Traits on Physiological Stress of Patients during Dental Treatment. Int J Environ Res Public Health 2022;19(5):2540.
6. Selye H. The stress concept. Can Med Assoc J 1976;115:718.
7. Herman JP, Nawreen N, Smail MA, et al. Brain mechanisms of HPA axis regulation: neurocircuitry and feedback in context Richard Kvetnansky lecture. Stress 2020;23(6):617–32.
8. Duval F, González F, Rabia H. Neurobiology of stress. Rev Chil Neuro-Psiquiat. 2010;48(4):307–18.
9. Herman JP, McKlveen JM, Ghosal S, et al. Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. Compr Physiol 2016;6(2):603–21.
10. Panagiotakopoulos L, Neigh GN. Development of the HPA axis: where and when do sex differences manifest? Front Neuroendocrinol 2014;35(3):285–302.
11. Packard AE, Egan AE, Ulrich-Lai YM. HPA Axis Interactions with Behavioral Systems. Compr Physiol 2016;6(4):1897–934.
12. Vélez-Palacio A, Balthazar-González V, Campuzano-Maya G. Evaluation of hypothalamic-pituitary-adrenal axis function in children treated with steroids. Med Lab 2013;19:111–25.
13. Bancarali L, Oliva P. Music Therapy Effect on Stress Levels of Internal Users of the Dental clinic of universidad del desarrollo. Int J Odontostomat 2012;6(2): 189–93.
14. Lima M, Casanova Y. Fear, Anxiety and phobia to dentistry treatment. Rev Hum Med 2006;6(1):1–21.
15. Messer JG. Stress in dental patients undergoing routine procedures. J Dent Res 1977;56(4):362–7.
16. Rodríguez O. Prevalencia de ansiedad dental en los estudiantes de la UPAO, Trujillo. 2015. Available at: https://hdl.handle.net/20.500.12759/1055. [Accessed 12 April 2024].
17. Aravena PC, Almonacid C, Mancilla MI. Effect of music at 432 Hz and 440 Hz on dental anxiety and salivary cortisol levels in patients undergoing tooth extraction: a randomized clinical trial. J Appl Oral Sci 2020;28:e20190601.
18. Cohen SM, Fiske J, Newton JT. The impact of dental anxiety on daily living. Br Dent J 2000;189(7):385–90.
19. Mejía-Rubalcava C, Alanís-Tavira J, Mendieta-Zerón H, et al. Changes induced by music therapy to physiologic parameters in patients with dental anxiety. Complement Ther Clin Pract 2015;21(4):282–6.
20. Barreiro-Vera CL, Armijos-Moreta JF, Gavilánez-Villamarín SM. La ansiedad dental en pacientes durante un tratamiento odontológico. Rev Cienc Med (Lourenco Marques) 2023;27:e6010.
21. Ríos M, Herrera A, Rojas G. Dental anxiety: Assessment and treatment. Av Odontoestomatol 2014;30(1):39–46.
22. Hmud R, Walsh LJ. Ansiedad dental: causas, complicaciones y métodos de manejo. J Minim Interv Dent 2009;2(1):237–48.

23. Gale EN. Fears of the dental situation. J Dent Res 1972;51(4):964–6.
24. Caycedo C, Cortés F, Gama R, et al. Ansiedad al tratamiento odontológico: características y diferencias de género. Suma Psicol 2008;15(1):259–78.
25. Eitner S, Wichmann M, Paulsen A, et al. Dental anxiety - an epidemiological study on its clinical correlation and effects on oral health. J Oral Rehabil 2006;33:588–93.