Focus Article

Steroid Dysregulation and Stomatodynia (Burning Mouth Syndrome)

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Stomatodynia (burning mouth syndrome) is characterized by a spontaneous, continuous burning pain felt in the oral mucosa typically of anxiodepressive menopausal women. Because there is no obvious organic cause, it is considered a nonspecific pain. This Focus Article proposes a hypothesis based on the following pathophysiological cascade: chronic anxiety or posttraumatic stress leads to a dysregulation of the adrenal production of steroids. One consequence is a decreased or a modified production of some major precursors for the neuroactive steroid synthesis occurring in the skin, mucosa, and nervous system. At menopause, the drastic fall of the other main precursor supply, the gonadal steroids, leads to a brisk alteration of the production of neuroactive steroids. This results in neurodegenerative alterations of small nerve fibers of the oral mucosa and/or some brain areas involved in oral somatic sensations. These neuropathic changes become irreversible and precipitate the burning pain, dysgeusia, and xerostomia associated with stomatodynia, which all involve thin nerve fibers. J OROFAC PAIN 2009;23:202–210

Key words: adrenal steroid, burning mouth syndrome, functional pain, gonadal steroid, idiopathic orofacial pain, neuroactive steroids, neuropathic pain, stomatodynia

Several chronic pain conditions are labeled "functional" or "nonspecific" syndromes. These include chronic fatigue syndrome, tension-type headache, irritable bowel syndrome, fibromyalgia, temporomandibular disorders, atypical facial pain, and stomatodynia (burning mouth syndrome). They share several characteristics: they have no identifiable lesion; their etiology is unknown; they often coexist in the same individual[1–4]; their prevalence is higher in females; and patients often present with psychological distress. In this Focus Article, stomatodynia is used as a model to propose a hypothesis for the pathophysiology of functional pain conditions.

Stomatodynia is characterized by a spontaneous, continuous burning pain that is felt in the oral mucosa. The burning sensation is often accompanied by oral dysesthesia, decreased or impaired taste (dysgeusia), along with a feeling of abnormal saliva often identified as xerostomia. The prevalence in the general population is about 0.7%, with a large majority of peri- or postmenopausal women.[4–8]

Stomatodynia is of Neuropathic Origin

In the past, there were debates as to whether stomatodynia is of somatic or psychological origin. There is at present histological, pharmacological, psychophysical, electrophysiological, and imaging evidence that suggests that a neuropathic mechanism underlies stomatodynia.

Changes in the Peripheral Nervous System

In a controlled histological study performed with immunohistochemical and confocal microscopic techniques, tongue biopsies from stomatodynia patients revealed diffuse morphological and density changes reflecting axonal degeneration in the epithelial and subpapillary nerve fibers, with a trend toward a correlation with the duration of symptoms.[9] Neuropathy affecting the fine fibers of the oral mucosa has also been recently confirmed in stomatodynia patients.[10]

The involvement of the peripheral nervous system has also been shown in clinical studies. For instance, topical application of neuroactive drugs relieved the symptoms in many patients.[11,12] The neuropathic nature of stomatodynia is also supported by psychophysical studies that have shown changes in somatic sensations in the tongue. The initial report of a decreased heat pain tolerance of the tongue tip[13] has been later substantiated by other psychophysical studies. Using argon laser stimulation, Svensson et al found an increase in orofacial pain thresholds in patients with stomatodynia.[14] Similarly, Forssell et al found that sensory thresholds at the lingual mucosa were abnormal in 76% of the 46 patients in the study.[15] An increase in cold and warm thresholds on the tip of the tongue was also reported by Granot and Nagler.[7] Interestingly, there have been reports that in stomatodynia patients, both the threshold and duration of the burning sensation were increased in response to nociceptive heat stimulation in the oral mucosa, but not at the thumb.[16] In addition, altered taste sensitivity was reported to be present in patients with stomatodynia[17,18] whether dysgeusia was present or not.[19] Changes in taste may be signs of deafferentation, since there are reports that taste threshold increased following tooth extraction or tooth pulp removal.[20,21] This is in line with evidence showing the interaction between gustatory and somatic receptors in the lingual mucosa in both animals[22] and humans.[23]

Changes in electrophysiological recordings have also been reported. Stomatodynia is associated with modifications of the threshold for the tactile and nociceptive components of the blink reflex.[15,24] Abnormality in trigeminal somatosensory-evoked potentials has also been described.[25]

There is also evidence that stomatodynia patients suffer from visceral disturbances that are generally mediated by oral thin fibers. These include dysfunction of the neurovascular control of oral mucosa blood flow[26] and modification of the composition of saliva.[7,27]

Taken together, the above data suggest a dysfunction of the thin afferent fibers in stomatodynia patients. It is important to note that the relationship between chronic pain of a burning type and thin fiber neuropathies is not unique since it has also been observed in microneurographic recordings in the leg.[28]

Involvement of the Central Nervous System

Imaging studies suggest that stomatodynia may also be associated with central changes. Photon emission tomography studies showed nigrostriatal or putamen neurons dopamine hypofunction in a group of 10 patients with stomatodynia.[29,30] A recent functional magnetic resonance imaging (MRI) study reported that patients with stomatodynia showed less volumetric activation of the entire brain as compared to the control group.[31] The involvement of the central nervous system is also supported by clinical studies which showed that not all patients responded to topical treatment with clonazepam[12] or local anesthesia.[11]

Recently, lingual nerve anesthesia was shown to totally block the spontaneous pain of stomatodynia in a subset of patients but had no effect on pain in another subset.[32] These results suggest that the pathophysiological mechanisms underlying stomatodynia may be predominantly peripheral, central, or mixed, depending on the individual.

In summary, there is convincing evidence that stomatodynia is a neuropathic disorder. However, the cause of the neuropathic changes is unknown, and a hypothesis linking stomatodynia with alterations in steroids levels is proposed below.

Stomatodynia Neuropathy is Associated with Steroid Dysregulation

Any hypothesis about the causes of neuropathic changes in stomatodynia should take into account three key features: *(1)* the over-representation of peri- and postmenopausal women; *(2)* the high prevalence of anxiety/depressive disorders among stomatodynia patients; and *(3)* the strictly oral

location of the symptoms. It is proposed that these three features are associated, respectively, with alteration of gonadal, adrenal, and neuroactive steroids levels.

The Over-representation of Postmenopausal Women May Be Related to Gonadal Steroid Alterations

Several lines of evidence suggest that altered levels of female sex steroid hormones may predispose women to stomatodynia. The disorder is much more prevalent in women than it is in men: from 3 to 20 women for 1 man, depending on the study, the most commonly accepted ratio being between 7 and 10 women for 1 man.[5,6,8,17,33] Female patients have an average age of approximately 60 years and 90% are postmenopausal or perimenopausal.[4,6,34] There is also a positive correlation between stomatodynia and the presence of marked menopausal symptoms.[17] Although not sufficiently documented, it seems that some subjects with hormonal unbalance, either men or young women, are also at risk for stomatodynia. For example, an over-representation of oophorectomized and/or hysterectomized women have been reported in two consecutive studies: 18% of oophorectomized women had burning oral sensations[35] and 71% of stomatodynia women had hysterectomies.[32] In addition, male patients with stomatodynia are, on average, older than female ones and may be supposed to have low gonadal hormone levels.[17,36] The above data suggest that, in many patients, stomatodynia may be associated with changes in sex steroid levels.

The High Prevalence of Anxiety/Depressive Disorders May Be Associated with Adrenal Steroid Alterations

Although stomatodynia is no longer considered a psychological disorder in light of evidence supporting its neuropathic origin, patients often present with high scores in psychometric scales, depression, and anxiety.[17,32,36–44] However, anxiety is now considered as a more important contributing factor than depression to the pathophysiology of the disorder.[32] Likewise, chronic stress and posttraumatic stress disorders seem to play a more important role than recent and acute adverse life events[39] unless these were perceived as severe ones.[38] For instance, there have been reports that early stressful family or social life events of long duration, or chronic life difficulties, are particularly correlated with stomatodynia.[32,45] As stated by Zakrzewska[4]: "Patients may have had a difficult childhood, inadequate parenting, poor adaptation to school and work, marital and financial strife and other adverse life events. In some patients it is a manifestation of cancerophobia, many give a history of familial cancer." Also there are reports that patients who either had mothers who were depressed or had recent bereavement or experienced more difficult confinement and deliveries of their children, were more prone to develop stomatodynia.[32] Later in life, these patients with early or/and chronic life difficulties may display exaggerated behavioral responses and pain to ordinary late-life stressful events.[46]

Recently, it has become clear that chronic stress and posttraumatic stress disorders, anxiety, and major depression can induce dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid dysregulation.[47–51] In a study comparing stomatodynia patients to controls, Amenábar et al found both an increase in anxiety score and in basic salivary cortisol level.[52] A sustained increase of cortisol level is also observed in patients with chronic stress.[53–55] Exaggerated cortisol concentration,[56–60] hyperactivity of the HPA axis,[61,62] and impaired feedback control of HPA activity have also been reported for patients with major depression. These dysfunctions result in a hypothalamic hyperdrive[63] or adrenal hypertrophy.[64]

Although not investigated in stomatodynia patients, low cortisol levels have also been reported in patients with other chronic conditions including fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, irritable bowel syndrome, low back pain, burnout, and atypical depression.[65–67] Hypocortisolism has also been observed in posttraumatic stress disorder.[48,66–68] It is thought that hypocortisolism follows a period of repetitive overstimulation of the HPA axis with excessive release of cortisol. This would imply that stress-induced excessive cortisol happens first, followed by hypocortisolism. This sequence would parallel the clinical history of some patients with stomatodynia who experience prolonged periods of stress before the onset of their symptoms.[45,69,70]

Taken together, the above data suggest that severe or chronic stress and anxiety are associated with HPA dysfunction, which may underlie the pathophysiology of stomatodynia.

The Strictly Oral Location of the Symptoms May Be Related to Neuroactive Steroids

One of the most striking features of stomatodynia is the very restricted location of the burning sensation within the mouth,[1–4,17,31] even if comorbid

pain conditions are present. This suggests that an exclusive mediation of hormonal steroids through the bloodstream is unlikely.

Neuroactive steroids may explain the restricted location of the symptoms: they are synthesized by nearby cells and are active through paracrine, autocrine, or intracrine activities either peripherally or in the brain. This has the advantage of limiting the steroid activity to the restricted body regions where the synthesizing cells are located and points to the site-specific feature of neuroactive steroid action.[71–75]

Detailed descriptions of the neuroactive steroids can be found in many reviews.[76–81] Briefly, neuroactive steroids are synthesized by cutaneous cells and some neurons, glial, and Schwann cells in the peripheral and central nervous systems.[75,80,82–85] Their precursors can come from endocrine glands, or be synthesized in several kinds of peripheral tissues. For instance, estrogens and androgens are neuroactive steroids when they are synthesized outside endocrine glands, and their precursors include dehydroepiandrosterone (DHEA), an androgenic steroid that can be synthesized in both adrenal and peripheral tissues. Progesterone can also be converted into another important group of neuroactive steroids collectively called the 3α-reduced neuroactive steroids. This group includes 3α-5α tetrahydroprogesterone (allopregnanolone or THPROG) and 3α-5α tetrahydrodeoxycortico-sterone (THDOC).[80,86] It is important to note that neuroactive steroid levels are not static, but change dynamically in a variety of physiological and pathological conditions including stress, depression, aging, and treatments with antidepressants and antipsychotics.[80] Finally, there are interactions between intracrine, autocrine, paracrine, and endocrine modes of activation of the steroid receptors.[71] The complex interactions and complementary activities of systemic and local steroids may induce peripheral and/or central neuropathy observed in stomatodynia, as discussed below.

Effects of Steroid Dysfunctions on Neural Tissues

Several lines of evidence support the role of steroids in neuroregeneration and protection, both in the peripheral and central nervous systems, although corticosteroids may also have a deleterious effect on the nervous system.

Gonadal steroids may protect neural tissue against acute nerve or brain injuries or neurological diseases, as suggested by epidemiological and clinical studies (see Schumacher et al).[87] In vivo and in vitro animal experiments have also shown that estradiol or other gonadal steroids such as progesterone, allopregnanolone, and testosterone facilitate nerve regeneration and offer protection against injuries or degenerative changes induced by excitotoxic conditions.[87–89]

Several neuroactive steroids have been shown to have a role in neuroregeneration and protection both in the peripheral and central nervous systems. After injury, locally synthesized pregnenolone metabolites (progesterone, dihydroprogesterone [DHPROG], and THPROG) reduce damage and promote peripheral and central neurological recovery in rats.[90–92] The myelin sheath and Schwann cells seem to be special targets for these progesterone derivatives, since treatment with progesterone, DHPROG, and THPROG influences the proliferation of Schwann cells and increases the number of small myelinated fibers in the peripheral nervous system. This is compensated for by a decrease in a similar number of unmyelinated axons.[85,87,93] It is suggested that neuroactive steroids themselves, or their synthetic receptor modulators, might represent a therapeutic approach aimed to counteract neurodegenerative events in peripheral nerves.[85] DHEA and DHEA sulphate have also been shown to be major neuroprotective agents.[90,94] In fact, low DHEA sulphate levels seem to contribute to worsening of neurodegenerative diseases in humans.[95] More importantly, the local production in neural tissues of the active metabolites of DHEA may oppose, via a paracrine mechanism, a deleterious effect induced by glucocorticoids.[96]

While adrenal cortisol normally has a positive role on neural tissues,[97] both low and high levels of cortisol have been reported to be damaging to these tissues.[98] For example, both high and low cortisol levels have been shown to predict mortality after a stroke,[96] and a steady increase in glucocorticoid levels causes degenerative loss or morphological changes of neurones in the hippocampus, the amygdala, and the prefrontal brain.[99,100]

In addition to the long-term dysfunction of the HPA axis and its effects on the neural tissues, a dysregulation of the sympathetic nervous system can also occur in the presence of chronic stress. For instance, hypocortisolism in patients with stress-related chronic disorders is associated with a hyperactive sympathetic nervous system producing increased catecholamine levels.[1] Such a HPA-sympathetic nervous system dysregulation may underlie the disturbed vasoreactivity seen in stomatodynia patients.[26]

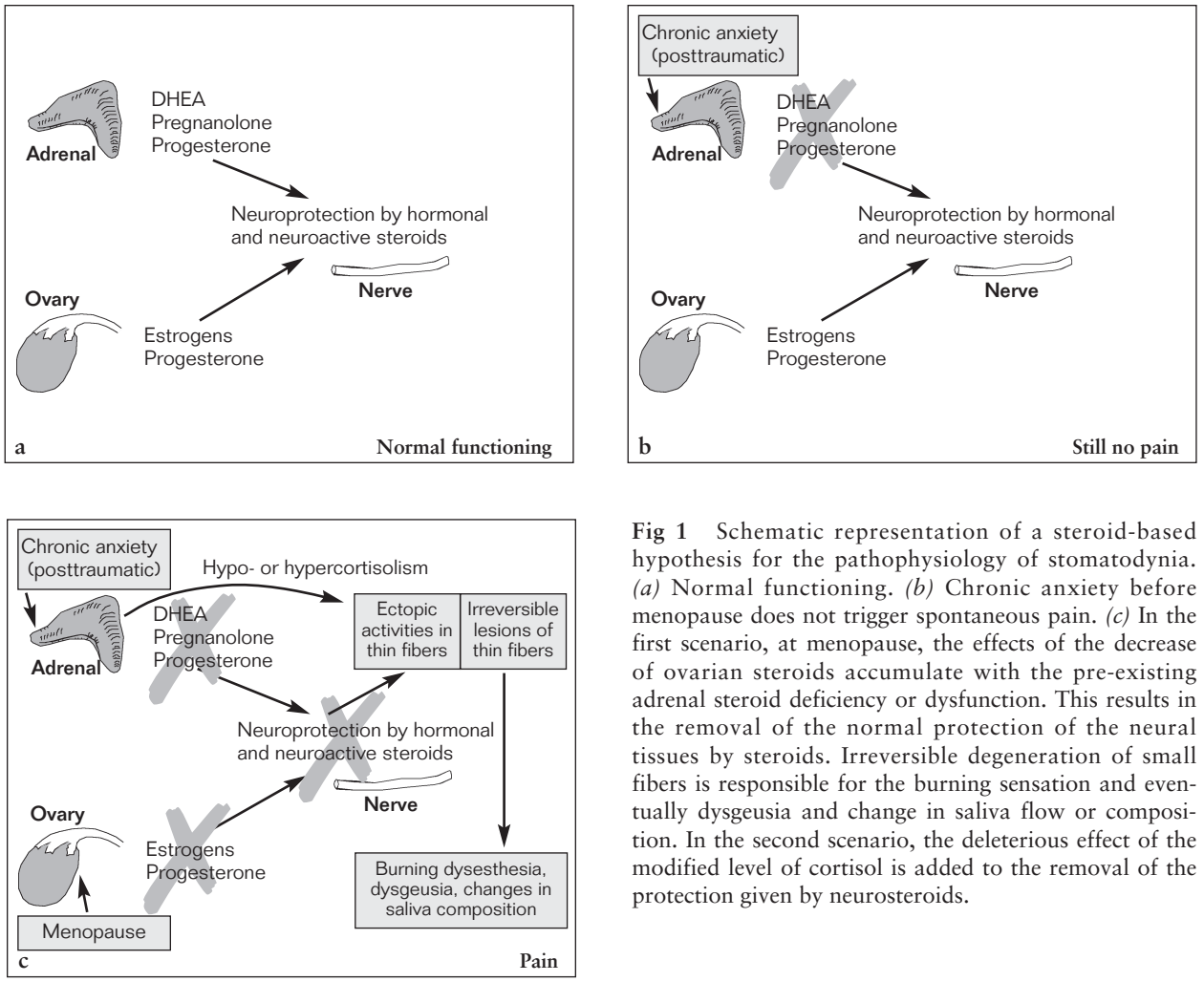

Fig 1 Schematic representation of a steroid-based hypothesis for the pathophysiology of stomatodynia. *(a)* Normal functioning. *(b)* Chronic anxiety before menopause does not trigger spontaneous pain. *(c)* In the first scenario, at menopause, the effects of the decrease of ovarian steroids accumulate with the pre-existing adrenal steroid deficiency or dysfunction. This results in the removal of the normal protection of the neural tissues by steroids. Irreversible degeneration of small fibers is responsible for the burning sensation and eventually dysgeusia and change in saliva flow or composition. In the second scenario, the deleterious effect of the modified level of cortisol is added to the removal of the protection given by neurosteroids.

Taken together, the above data suggest a role for steroids in neuroprotection and link persistent changes in their level to neurodegeneration. This leads to the hypothesis that neurodegeneration changes observed in stomatodynia patients may be due to the drastic and concomitant changes in several sources of steroids.

Additional Considerations

Although the individual concepts described above are well founded, the link between them remains hypothetical. Two possible scenarios are proposed (Fig 1). In the first possible scenario, the occurrence of stomatodynia mainly at the time of menopause in women with chronic stress/anxiety disorders is due to a fall in gonadal steroids levels concomitantly with a change in adrenal steroid regulation. The presence of chronic anxiety or posttraumatic stress provokes a functional impairment of the HPA axis, leading to a dysregulation of the adrenal production of steroids. Since some of these steroids such as DHEA or progesterone are major precursors for neuroactive steroids, a decrease or a change of their blood concentration will translate into a decreased production of neuroactive steroids in the oral mucosa (and/or from some brain areas involved in somatic sensations from the mouth). This local decrease in the production of neuroactive steroids may be asymptomatic at first. It is, however, more likely to induce clinical symptoms when the decreased concentration of neuroactive steroid precursors is aggravated by a drastic fall in the systemic supply from the gonadal steroids, which occurs at the time of menopause or at the end of the progressive and late fall in the secretion of androgens in aging individuals of both sexes. This

results in a drastic alteration of the production of neuroactive steroids in the mouth or special brain areas associated with somatic sensations, which, in turn, triggers neurodegeneration and the symptoms associated with stomatodynia.

In the second scenario, the collapse in gonadal steroids and corresponding neuroactive steroids and their neuroprotective effects, and the increase in adrenal steroid levels and their deleterious neuronal effects, at least in the peripheral nervous system, result in neurodegenerative changes that have been reported in histological studies of biopsies obtained in stomatodynia subjects.

Steroid-induced neuropathic changes that occur in both scenarios may provoke the symptoms associated with stomatodynia, since it is well documented that somatic sensations in the mouth, such as burning pain, dysgeusia, and xerostomia, all involve thin nerve fibers. In fact, the interaction between salivary efferents, gustatory, and thin somatic afferents have been described in stomatodynia.[7,19,21,27] Furthermore, the degeneration of thin gustatory primary afferent fibers, and the removal of their inhibitory control on small somatic afferents from the mouth,[21] has been suggested as the cause of the burning sensation.[101]

The above hypothesis does not provide explanations as to why the burning sensation is not experienced in areas other than the mouth, although the question regarding the restriction of signs and symptoms in some body areas and not others can also be raised for other pain conditions and diseases. For instance, it is unclear why myofascial pain of the masticatory muscles and herpes zoster are mainly unilateral, and why herpes zoster affects only a few dermatomes. However, the biologic role of steroid hormones at the mucosal level is supported by experimental data. In a study using formalin tests, pain levels increased after gonadectomy in the perioral areas but not in the hindpaws of female rats; the reverse was observed in male rats.[102] Ovariectomy in the rat provoked significant changes in the oral mucosa, ie, a decrease in the thickness of the keratinized epithelial oral mucosa. These alterations were most significant at the tongue tip, the site most frequently affected by stomatodynia, and were partially reversed with hormone replacement therapy.[103] Testosterone has also been shown to influence deeply the functions of the submandibular gland in both male and female mice.[104] In humans, however, hormone replacement therapy has only offered marginal relief of symptoms associated with stomatodynia in noncontrolled studies.[35,105–108]

The above hypothesis also does not account for the fact that not every postmenopausal woman with major stress disorders develops stomatodynia. As for other pain conditions, it is likely that genetic and environmental factors and their interaction also play important roles in the mechanisms underlying the pathophysiology of stomatodynia.

In conclusion, this Focus Article has reviewed a body of literature pointing to the possible involvement of adrenal, gonadal, and neuroactive steroids in inducing the neuropathic changes and resulting symptoms that are observed in stomatodynia. While large-scale studies are needed to compare the reactivity of the HPA axis and steroid levels in stomatodynia patients and control subjects, future research should also include pharmacological manipulations to elucidate the mechanisms by which steroids influence functional pain disorders.

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