

## MISE AU POINT/IN-DEPTH REVIEW

# CONTRIBUTION OF SYMPATHETIC INNERVATION IN OROFACIAL PAIN

## A Review

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**RÉSUMÉ : Le rôle du système nerveux autonome dans les douleurs orofaciales est actuellement étudié et n'est pas encore entièrement élucidé. Certaines pathologies comme la neuropathie trigéminal ou le *cluster headache* sont difficiles à soigner en partie à cause de la participation du système nerveux autonome. Cette revue de la littérature décrit la contribution du système nerveux sympathique lors des douleurs orofaciales.**

In several clinical painful conditions the autonomic nervous system is activated to further enhance and maintain the nociceptive sensation. Complex regional pain syndrome was first described in 1864 by Mitchell [1] who noticed a persistent burning pain accompanied by local autonomic and trophic changes after a trauma mostly affecting the limbs and named it *causalgia*. In 1946, Evans proposed that this pain had an autonomic component and changed the terminology to *reflex sympathetic dystrophy*. Other terminologies have also been used : Sudeck's atrophy, sympathetically maintained syndrome, shoulder-hand syndrome, atypical post-traumatic syndrome, sympathetic dystrophy, and others [2]. Finally in 1994, the International Association for the Study of Pain (IASP) classified the condition as *complex regional pain syndrome* with two categories : Type I (lack) or type II (presence) of nerve injury with or without an autonomic involvement [3].

In the orofacial area, the trigeminal nervous system provides the main neural substrate of several painful states like migraines, tension type headaches, cluster headaches, chronic paroxysmal hemicrania and temporomandibular disorders. Some of these diseases are accompanied by autonomic dysfunctions. All these entities have been classified by the International Headache Society (IHS) as *primary headaches* group 1 (migraine), group 2 (tension type headache), group 3 (cluster headache, chronic paroxysmal hemicrania) or *secondary headaches* as for the temporomandibular disorders in group 11 [4].

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(In the IASP classification emphasis is given to the pathogenic mechanisms of the disease while the IHS effort is made to give precise and as far as possible, quantitative diagnostic criteria [5].)

These clinical conditions continue to puzzle practitioners. Understanding the different nervous entities and the mechanisms involved will help to find the proper treatment.

The aim of this review is to describe the role of the sympathetic system in those orofacial painful conditions ; a brief pathophysiology of orofacial pain and the role of the sympathetic nervous system in acute pain will be described and two clinical orofacial pain conditions illustrating the role will be detailed.

### PATHOPHYSIOLOGY OF OROFACIAL PAIN

An injury to the head and face elicits pain with no differentiation of its causal agent : biological, chemical, electrical, thermal or traumatic. Under normal circumstances pain is transmitted from the injured site to the brain via the activation of nociceptors which are small-diameter, slowly conducting primary sensory afferents terminating as free nerve endings. Activation of these nociceptors leads to the generation of action potentials in their associated afferent fibers. The signals generated are transmitted to the central nervous system (CNS) and ultimately produce the perceptual and other behavioral responses characterizing pain [6-8]. "*Most of the primary afferents supplying orofacial tissues have their cell bodies principally in the trigeminal ganglion. The central projections of these primary afferent cell bodies enter the brainstem and may ascend or descend in the trigeminal spinal tract from which they give off collaterals that terminate in one or more subdivisions of the fifth nerve brainstem sensory nuclear complex. The collaterals of the fifth nerve's primary afferents fibers activate second-order neurons within the trigeminal brainstem sensory nuclear complex which can be divided into the principal or main sensory nucleus and the spinal tract nucleus which comprises three subnuclei (oralis, interpolaris and caudalis).*" [9, pp 246-7]. The nociceptive afferents will be directed to one of the three subnuclei called caudalis. "*There is a differential contribution to each nucleus/sub-nucleus from each of these projections, e.g. the main sensory nucleus is the principal direct brainstem relay to ventrobasal thalamus of mechanosensitive afferent input from most parts of the orofacial region, whereas most spinal trigeminal neurons directly project to other brainstem structures and to the diencephalon i.e. thalamus and*

hypothalamus. Some of the connections to the reticular formation and other parts of the brainstem are involved in the autonomic reflexes in responses to orofacial stimuli. There are also intrinsic connections between neurons in different components of the complex that underlie the modulatory influences between rostral and caudal trigeminal brainstem neurons. Some trigeminal nociceptive cutaneous and intra oral afferents, including dental pulp afferents, terminate in the more rostral components of the trigeminal brainstem complex and in laminae III-IV of subnucleus caudalis. Most of the small diameter trigeminal nociceptive afferents terminate in subnucleus caudalis, in its laminae I, II, V and VI. In addition this brainstem area also receives input from other cranial nerves such as VII, IX, X and XII and from upper cervical nerves" [9, p. 247].

Substance P, a sensory peptide secreted by nociceptive fibers, is an important factor in inflammation and healing where synchronization between the time when pain starts and the time when healing starts occurs. It has been recently shown that substance P accelerates the healing phase after an injury. In diabetic patients healing is impaired probably due to the fact that in certain neuropathic conditions, damaged nerves secrete less substance P than normally [10-13].

In a recent review by Knight [14], the importance and role of the brainstem as a key factor during painful states is emphasized. As the primary homeostasis center of the brain, the brainstem integrates and modulates trigeminal pain transmission and other sensory modality processing such as internal (interoceptive) or external (exteroceptive) stimuli. One of the functions of pain is to facilitate recovery from injury and/or illness by stimulating recuperative behaviors (reflex of withdrawal from the aggressor, immobilization of the injured area, activation of body defense mechanisms, healing). To optimize this process, nociceptive modulation is required for beneficial adaptation to the painful stimulus. In this context, the brainstem conducts bimodal modulation in the form of inhibition or facilitation of nociception [14].

The hippocampus is also being attributed a role in pain via an endogenous peptide: the nociceptin [15], despite the fact that the hippocampus is not part of the brainstem.

Recent brain imaging studies have shown that noxious stimulation in humans can activate several cortical regions, including the somatosensory cortex, insula and anterior cingulate cortex [16]. Nociceptive neurons have also been reported in various cerebral regions, such as the insula, anterior cingulate cortex, prefrontal lobe and various limbic centers which have been implicated in the affective dimension of pain [17].

In contrast to this classical view of acute pain, chronic pain is considered as part of a multi-system disease resulting from a disturbance in the homeostatic mechanisms of the body thus reflecting an imbalance in the cross talks between the immune and the nervous systems. This new concept has been supported by experimental

evidence [18]. Another concept followed this one and emerged from anatomical comparisons suggesting that chronic pain is a homeostatic emotion [19].

#### THE SYMPATHETIC NERVOUS SYSTEM IN ACUTE PAIN

Noxious stimuli can be considered as a stressful event. The resulting pain sensation affects the activity of the sympathetic nervous system. The sympathetic activation pattern is characterized by an instantaneous defense behavior. As a biochemical correlate to such stress, catecholamines are released from the adrenal medulla into the circulation together with other metabolic changes. In experimental studies, strong sural nerve stimulations have been used to induce a spinal polysynaptic defense response characterized by heart rate increases and withdrawal of the extremity away from the noxious stimulus, the so-called nociceptive withdrawal reflex [20].

An additional complication in understanding the influence of attention on pain is the observation that pain itself modifies an individual's ability to focus attention. Pain is in general an attention-demanding modality, so that when a person is asked to divide his/her attention between pain and another sensory modality, attention to pain dominates [21].

Finally in animal studies in the orofacial area it was found that the sympathetic system helped maintaining the inflammation in temporomandibular joint arthritis [22]. It has also been shown that the sympathetic system participates in the immunomodulation in inflammatory states by exerting a tonic regulatory effect over lymphocyte proliferation and migration in the rat dental pulp [23].

In all these conditions, it seems that the role of the autonomic nervous system is to try and restore a balance when the normal circuits of the nervous system are not sufficient, injured or destroyed. The involvement of the sympathetic system seems to play this role of replacement thus producing sympathetically maintained pain symptoms due to the sprouting of the sympathetic fibers to reach the peripheral nervous system. This sprouting is helped by the presence of several neurotrophins like the nerve growth factor (NGF), neurotrophin 3 (NT3) and the brain-derived neurotrophic factor (BDNF). This process opens new channels for chronic pain where adrenaline release (which is not painful in normal situations) starts to produce pain in stressful conditions [24-25].

#### THE SYMPATHETIC NERVOUS SYSTEM IN CLUSTER HEADACHE

Cluster headache is a severe strictly unilateral head pain localized in general in the orbital, supraorbital and/or temporal areas. It can sometimes switch from side to side. It is characterized by relatively short-lived attacks (15-180 min) following a circadian rhythm. In the episodic form the frequency of headaches occur daily for some weeks (usually 6-12 weeks) followed by a period of

remission that can last up to a year. In the chronic form the remission periods are fewer in time and numbers. It has a relapsing-remitting course with seasonal variations. Headache is accompanied by one of the following symptoms ipsilateral to the pain side : conjunctival injection or lacrimation, nasal congestion and/or rhinorrhoea, eyelid oedema, forehead and facial sweating, miosis and/or ptosis, sense of restlessness and agitation. Finally, historical, physical and neurological examinations do not suggest any other disorder [4]. Disease is more prevalent among women with a 3:1 ratio. Age of onset is 28-30. Alcohol, histamine and nitrates can trigger an attack [26]. Current smoking has been the most common lifestyle feature associated with prevalence of the disease. A speculative hypothesis of a probable link between a genetic predisposition to nicotine addiction and the predilection to the disease is proposed [27]. Treatment in acute crisis is 20 min inhalation of 100% oxygen (minimum 7 L/min up to 15 L/min) in a sitting upright position. About 60% of cases respond to this treatment within 20-30 min [28-29]. One placebo-controlled, double blind trial study showed, however, that it is not an effective treatment [30]. Sumatriptan when injected subcutaneously is effective in 75% of cases in 20 min [31-32]. Intranasal lidocaine, although not very efficient (only 33% response), has also been used [33-34].

The choice of treatment is time and efficiency dependent. Side effects are also another factor. Oxygen therapy seems effective and has no side effects but is related to the presence of pressurized oxygen. Sumatriptans are effective but should not be prescribed to patients with cardiovascular or cerebrovascular disorders or untreated arterial hypertension [26].

Verapamil seems to be the established treatment of choice as a preventive measure. Dose vary between 240-320 mg but can go as high as 720 mg. An increase of 80 mg every 3 days is recommended with the full effect expected in 2-3 weeks [35-36]. (For more detailed information see [26]).

To unravel the role of the sympathetic nervous system one has to understand the pathophysiology of the disease. Cluster headache should be explained according to three axes, "*trigeminal distribution of the pain, ipsilateral cranial autonomic features and episodic pattern of attacks. The vascular theory, which is based on an inflammation of the walls of the cavernous sinus (the only peripheral anatomical location where a single pathology could involve trigeminal C fibers and sympathetic fibers), has been superseded by recognition that neurovascular events and some central impulse generator or oscillator seem to be more important. The severe unilateral pain is likely to be mediated by activation of the first (ophthalmic) division of the trigeminal nerve, whereas the autonomic symptoms such as lacrimation are due to activation of the cranial parasympathetic outflow through the seventh cranial nerve. The sympathetic paralysis (miosis and ptosis) may be due to a neurotoxic injury of postganglionic fibers in most patients. Currently at least*

*three possible sources of the autonomic symptoms are under investigation : (1) the autonomic dysregulation might originate centrally in association with a hypothalamic disturbance, (2) a vasodilation or perivascular oedema (due to trigeminal-parasympathetic overactivity during attacks) compromises the carotid canal and consequently the traversing sympathetic fibers, and (3) the autonomic symptoms are secondary to trigeminal discharge.*" [26, p. 844]. Finally the circadian cycle and the periodicity suggest that the hypothalamus or maybe the suprachiasmatic nuclei in the ventral hypothalamus are responsible of the triggering of acute attacks [26]. Prevalence of the disease three times more in women than in men could be related to data extrapolated from animal studies to humans showing that sprouting of sympathetic fibers into the hippocampus following neural injury is more restricted in males than in females [37].

#### THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN CHRONIC CENTRAL TRIGEMINAL NEUROPATHY

Also called atypical odontalgia, but more recently referred to as a traumatic trigeminal neuralgia, this clinical condition can be present with or without sympathetically maintained pain. Since the majority of patients have a relief of pain after a sympathetic block the type associated with the sympathetic system is more prevalent. This condition can be considered as a form of sympathetically maintained pain with a history of trauma. At the time of examination there is no obvious local cause of the pain or any radiological abnormality. There is usually a three months history of unresolving pain in a tooth or tooth site. Although variable, the pain is continuous but not paroxysmal and usually shows up after a tooth extraction, root canal treated tooth or apicectomy. In absence of any diagnostic test available, the condition is diagnosed by exclusion and is classified as a complex regional pain syndrome type I [16, 38].

Treatment of this condition is still unclear and not very effective. Typically, the patient sees several medical and dental practitioners before coming to consult a pain specialist. Several invasive medical and/or surgical procedures have been prescribed by those practitioners and include local anesthetic injections, topical capsaicin or psychotherapy. Tricyclic antidepressants, gabapentin and NMDA receptor antagonists have also been used [39-42].

#### CONCLUSION

In painful conditions, it seems that the autonomic system acts in parallel to the peripheral and central nervous systems to help in controlling the situation.

In acute pain the sympathetic system plays a role in triggering a fight or flight response in order to help the body avoid further injury or recover from it.

In chronic pain the condition is different and is expressed as a disease resulting from a homeostatic imbalance between the immune and the neuro-endocrine systems.

In the complex regional pain syndrome, substances such as adrenaline may be released from the sympathetic efferents that innervate many peripheral tissues and can modulate the excitability of the nociceptive afferents and thereby contribute to the pain [9]. “*In cluster headache, there might be an imbalance of the homeostasis of the hypothalamus, and the sympathetic paralysis (miosis and ptosis) might be due to a neuropraxis injury of postganglionic fibers in most patients*” [26, p. 845]. We already know that adrenoreceptors have been found on T cells, B cells and macrophages [43]. Could it be that these cells have a role to play between the immunological system and the autonomic nervous system in painful states ?

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