

# Peripheral sympathetic mechanisms in orofacial pain

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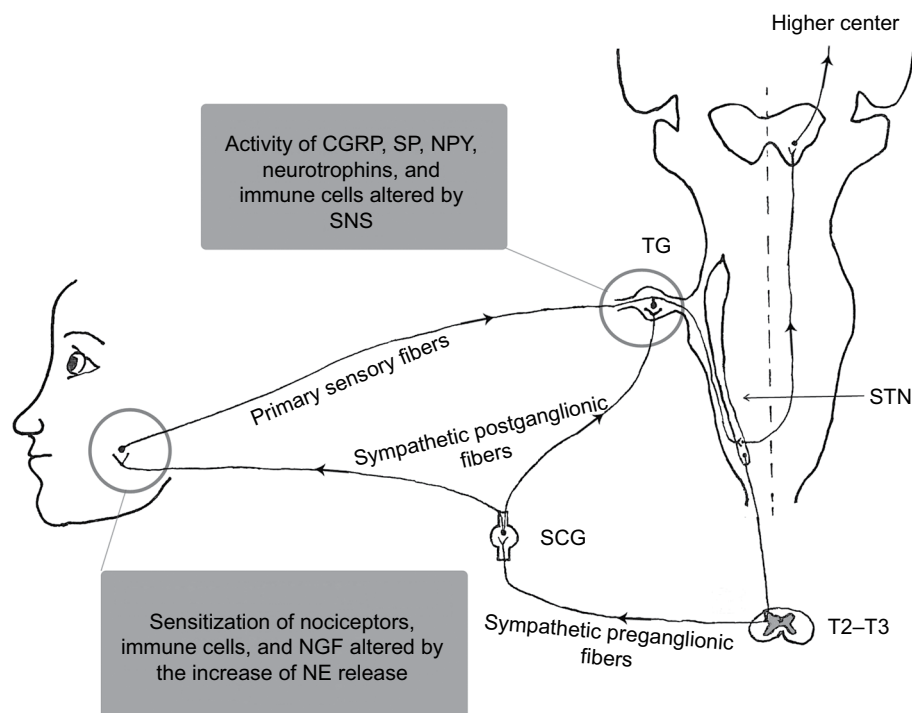
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**Abstract:** Sympathetic nervous system (SNS) is a part of the autonomic nervous system which involuntarily regulates internal body functions. It appears to modulate the processing of nociceptive information. Many orofacial pain conditions involve inflammation of orofacial tissues and/or injury of nerve, some of which might be attributed to SNS. Thus, the aim of this review was to bring together the data available regarding the peripheral sympathetic mechanisms involved in orofacial pain. A clearer understanding of SNS–sensory interactions in orofacial pain may provide a basis for novel therapeutic strategies for conditions that respond poorly to conventional treatments.

**Keywords:** sympathetic nervous system, norepinephrine, adrenergic receptors, orofacial pain

## Introduction

Sympathetic nervous system (SNS) arises from the spinal cord between the first thoracic vertebra and the second lumbar vertebra and travels to sympathetic ganglia, where it synapses with a postganglionic neuron. From there, the long postganglionic neurons extend across most of the body. The SNS, as a component of the autonomic nervous system, reaches most of the body's internal organs to maintain homeostasis together with the para-SNS.<sup>1</sup> The American Academy of Orofacial Pain (AAOP) defined the term “orofacial pain” as “pain conditions that are associated with the hard and soft tissues of the head, face, neck, and all the intraoral structures.”<sup>2</sup> Orofacial pain sensation from the intraoral and extraoral structures of the head and face is relayed to the central nervous system (CNS) by trigeminal nerve system. Primary sensory fibers innervating the orofacial region derive from neurons of the trigeminal ganglion (TG). The central processes of TG enter directly into the pons, where they descend in the brainstem to synapse in the spinal trigeminal nucleus (STN).<sup>3,4</sup> The secondary afferents from STN cross to the opposite side and project to higher center (Figure 1). SNS (visceral motor nerve) and the sensory nerves are generally regarded as discrete structures, but the efferent SNS and the afferent nociceptive interact in many ways. Activation of SNS can suppress or augment pain in pathological states, which might take place in the periphery or the CNS.<sup>5–7</sup> Considerable evidence has demonstrated that SNS might regulate peripheral sensitized nociceptors, immune cells, and neuroactive molecules, which are potentially relevant for the pathophysiology of orofacial pain. The purpose of this study was to present different lines of evidence for the role of SNS in orofacial pain studied to date. Possible peripheral mechanisms regarding the connection between SNS and orofacial pain are discussed.



**Figure 1** Schematic diagram of the SNS and possible sympathetic mechanisms in orofacial pain.

**Abbreviations:** CGRP, calcitonin gene-related peptide; NE, norepinephrine; NGF, nerve growth factor; NPY, neuropeptide Y; SCG, superior cervical sympathetic ganglion; SNS, sympathetic nervous system; SP, substance P; STN, spinal trigeminal nucleus; TG, trigeminal ganglion.

## SNS of orofacial region

The sympathetic innervation of the orofacial region originates in the most rostral intermediolateral horn cells of the spinal cord between segments T2 and T3. The axons of preganglionic neurons pass through anterior roots of the spinal cord, ascend in connectives of the sympathetic chain, and synapse with postganglionic neurons in the superior cervical sympathetic ganglion.<sup>8</sup> The postganglionic axons then distribute to their target organs in the orofacial region (Figure 1). In the neurotransmission of the SNS, preganglionic neurons use acetylcholine as a neurotransmitter, whereas postganglionic neuron nerve fibers release norepinephrine (NE) as a key neurotransmitter. There are five types of adrenergic receptors including  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$ ,  $\beta_2$ , and  $\beta_3$ . Of these five subtypes,  $\alpha_{2A}$ - and  $\alpha_{2C}$ -adrenoreceptors are expressed in TG of intact animals.<sup>9</sup> In fact, the neural transmission in the SNS involves the release of multiple neuroactive agents such as neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP), and nitric oxide.<sup>10,11</sup>

## Involvement of SNS in orofacial pain

Morphological study shows that primary sensory and sympathetic fibers innervate the temporomandibular joint (TMJ),

which suggests that sympathetic nerves could be responsible for allodynia or neuropathic pain caused by TMJ disorders.<sup>12</sup> Injury of the mental nerve, a branch of the trigeminal nerve, has been shown to result in sympathetic fiber sprouting in the upper dermis of lower lip skin, an area from which they normally are absent, and form close associations with sensory fibers.<sup>11,13-15</sup> It suggests that some active molecules released by these ectopic sympathetic fibers may sensitize nociceptive nerve endings, contributing to orofacial pain. Clinically, pain dependent on activity in the SNS is known as sympathetically maintained pain (SMP), which in particular is noted in many cases of complex regional pain syndrome (CRPS, reflex sympathetic dystrophy, causalgia). In SMP, procedures that interrupt the function of the SNS can relieve the pain and hyperalgesia.<sup>8</sup> In studies of traumatic neuralgias in the maxillofacial region, microsurgical exploration of injured trigeminal nerves in patients with neuralgia reveals that a sprouting of nerve collaterals from adjacent uninjured nerve could be responsible for SMP.<sup>16</sup> In addition, cervical sympathetic electrical stimulation causes excitation or suppression of cold-receptive cells in the trigeminal nucleus caudalis according to stimulation frequency.<sup>17</sup> Similarly, sympathetic stimulation affects muscle spindle afferent sensitivity to stretch in rabbit jaw closing muscles.<sup>18</sup> Clini-

cally, cervical sympathetic block reduces some pain in the orofacial region.<sup>19–23</sup> The data suggest that SNS is involved in modulating primary afferent neurons in orofacial region.

## Possible sympathetic mechanisms in orofacial pain

Under normal conditions, sympathetic activity results in the release of NE at the peripheral receptor sites and does not affect primary nociceptive neurons. However, if the primary neurons have been sensitized by neuroplastic changes, NE released by normal activity of the postganglionic sympathetic neurons can excite adrenergic receptors, which continue to excite these altered primary afferents and thus increase nociceptive input.<sup>24</sup> The exact mechanism of this peripheral pronociceptive effect is not well known. In TMJ inflammatory pain models, local sympathomimetic amines contribute to the inflammatory TMJ hyperalgesia by activating  $\beta_2$ -adrenoceptors,<sup>25–27</sup> since  $\beta_2$ -adrenoceptor antagonist or the depletion of NE in the sympathetic terminals can reverse this effect.<sup>25,26</sup> These results suggest that inflammation may sensitize nociceptors to NE and/or increase the release of the sympathetic amines. Furthermore, there is a study showing that  $\alpha_1$ -adrenoceptor upregulation in the dorsal root ganglion (DRG) after spinal nerve ligation may play an important role in the development of adrenergic sensitivity in injured sensory neurons.<sup>28</sup> Another study shows that after a chronic nerve constriction, DRG becomes a source of abnormal activity modulated by sympathetically released NE acting on  $\alpha_2$ -adrenoceptors in DRG somata. This neuropathic activity may contribute to cutaneous pain and hyperalgesia.<sup>29</sup> In contrast, an *in vitro* study shows that activation of  $\alpha_2$ -adrenoceptors can hyperpolarize TG neurons. The activation may have an inhibitory effect on nociceptive transmission in the trigeminal system.<sup>9</sup> There is no information about  $\alpha$ -adrenoceptor mechanism in orofacial pain models *in vivo*. It is worth to explore that which subtype of adrenoceptor in the periphery contributes to antinociception and which one to pronociception.

There is considerable evidence showing that the immune system plays an important role in pathophysiological pain conditions.<sup>30</sup> Haug et al's study shows that unilateral sympathectomy induces a significant increase in immune cell density both in the inflamed and in the uninflamed dental pulp bilaterally. The change of immune cells may induce inflammation and pain in teeth.<sup>31</sup> Furthermore, immune cells express several types of adrenoceptors.<sup>32</sup> Via these adrenergic receptors, NE is able to regulate the level of immune cell activity, which often involves a change in the level of gene expression

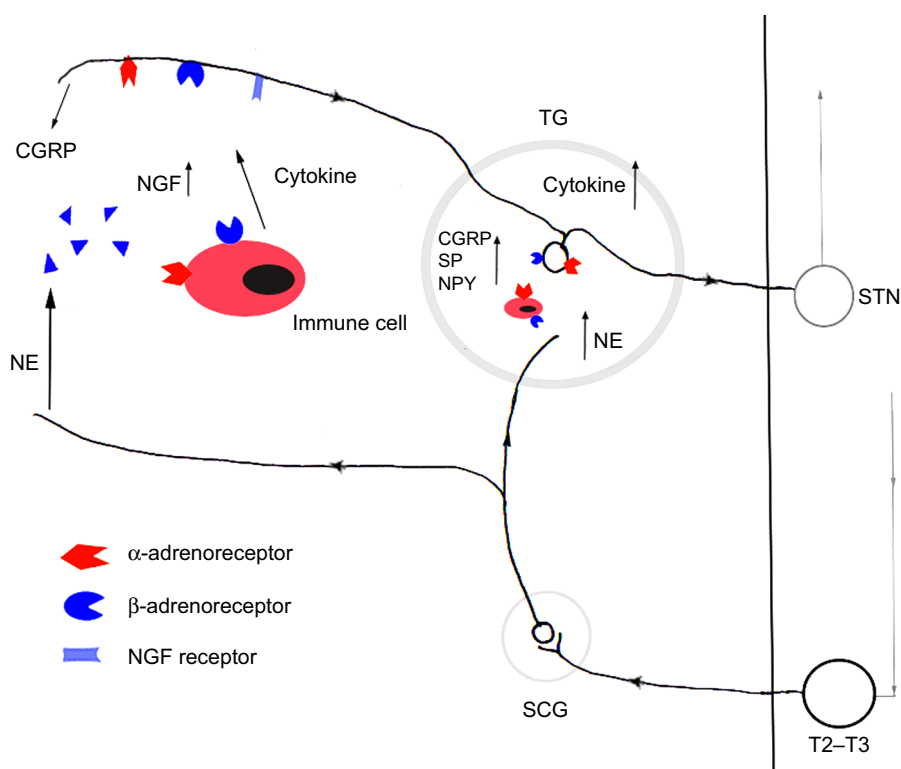
for cytokines and antibodies.<sup>33</sup> For example, among the cytokines produced by macrophages, the production and release of the inflammatory cytokine tumor necrosis factor- $\alpha$  is the primary cytokine that is regulated by the SNS.<sup>33</sup> Interestingly, TMJ inflammation induced by complete Freund's adjuvant activates resident macrophages in the TG,<sup>34</sup> but the authors did not detect whether SNS is involved in the mechanical allodynia of inflamed TMJ. Cytokines are now recognized as important mediators of inflammatory and neuropathic pain at the level of both nociceptor and neuronal cell bodies of sensory ganglion.<sup>35–37</sup> No data are obtained concerning how the peripheral NE acts on immune cells and then involves in orofacial pain, which needs to be investigated further.

Most nociceptive primary afferents are unmyelinated (C fibers) and subdivided into peptidergic and nonpeptidergic fibers. There is some evidence that neuropeptides have been implicated in the modulation and transmission of nociceptive input. Substance P (SP), CGRP, and NPY are thought to be important in nociceptive transmission.<sup>38–40</sup> The ectopic innervation of the upper dermis by sympathetic fibers occurs with SP fiber reinnervation following mental nerve injury.<sup>13</sup> It suggests that sympathetic–sensory interactions may be involved in the genesis of neuropathic pain. Under normal conditions, NPY resides in sympathetic postganglionic neurons but is absent from the cell bodies of sensory neurons. There are studies showing that NPY is upregulated in the TG neurons after chronic constriction injury of the mental nerve<sup>11</sup> or inferior alveolar nerve injury.<sup>41</sup> The upregulation in the neurons may come from sprouted sympathetic fibers or production of TG neurons, which might alter nociceptive transmission of primary afferent fibers. Capsaicin can activate transient receptor potential vanilloid type 1 (TRPV1, a ligand-gated ion channel) that mediates activation of the sensory neurons. Capsaicin increases the release of CGRP from dental pulp biopsies in a concentration-dependent manner, which provides a novel tool to determine the effects of pharmacological compounds on human nociceptor sensitivity.<sup>42</sup> Hargreaves et al's study demonstrates that NE inhibits capsaicin-evoked CGRP release in dental pulp, and the application of  $\alpha$ -adrenergic antagonist increases spontaneous release of CGRP. Since capsaicin-sensitive neurons are nociceptors, the result suggests that certain sympathetic neurotransmission may modulate pain.<sup>43</sup> In addition, CGRP and SP increase significantly in the rat primary trigeminal sensory neurons after sympathectomy.<sup>31,44,45</sup> The rise of CGRP and SP closely matches the process of the postsympathectomy pain observed clinically.<sup>46</sup> These findings lead

to the possibility that sympathetic terminals may modulate sensory peptidergic innervations and activity and then influence nociceptive processing, although in an *in vitro* study, NE influenced neither the basal release of CGRP nor the stimulated release of CGRP from the dura mater.<sup>47</sup> In the CNS, CGRP stimulates selectively noradrenergic sympathetic outflow.<sup>48</sup> In the periphery, whether CGRP increases the release of NE and plays a role in orofacial pain remain to be determined.

Neurotrophins (NTs) such as nerve growth factor (NGF), NT-3, and brain-derived neurotrophic factor are required for the growth and survival of specific populations of sensory and sympathetic neurons.<sup>49</sup> There is increasing evidence that NTs are peripheral pain mediators and involved in different pain states.<sup>50</sup> In the periphery, NGF and NT-3 are produced by target tissues, internalized by the innervating sympathetic and/or sensory neuron and retrogradely transported to the cell body.<sup>51</sup> At the same time, sympathetic input regulates NGF and NT-3 protein expression in peripheral targets.<sup>52</sup> Following nerve injury, satellite glial cells (glial cells

surrounding each sensory neuron in the sensory ganglia) upregulate the synthesis of NTs acting both as promoters of sympathetic sprouting within the ganglion<sup>53</sup> and as direct sensitizers of nociceptive neurons.<sup>54</sup> Spinal nerve injury in rat induces a widespread sympathetic nerve outgrowth in affected DRGs.<sup>55,56</sup> However, several studies have shown that there is no sympathetic sprouting in the rat TG following trigeminal nerve injury.<sup>57,58</sup> Overexpressing NGF in TG, new sympathetic axons extend into the TG of transgenic mice and form perineuronal plexuses surrounding only those neurons immunostained for NGF.<sup>59</sup> Intracerebroventricular infusion of NGF increases sympathetic ingrowth to the TG.<sup>60,61</sup> The data indicate that it is possible that there is not enough NGF in TG to induce sympathetic sprouting following trigeminal nerve injury. Overexpression of NGF and NT-3 in the skin induces novel sympathetic projections to primary sensory endings.<sup>62,63</sup> The enhancement of innervation may be regulated by both the low affinity (p75) and/or high affinity (trkA) NGF receptors in sympathetic and sensory neurons.<sup>62-67</sup> The increased NGF expression plays a



**Figure 2** The peripheral molecular mechanisms of SNS in orofacial pain.

**Notes:** After inflammation and/or nerve injury, adrenoceptors are sensitized. NE released by the normal activity of the sympathetic neurons can excite adrenergic receptors of afferent neurons and immune cell, which can alter some neuroactive molecule expression in neurons and peripheral tissues, and subsequently activates and sensitizes peripheral nociceptors further.

**Abbreviations:** CGRP, calcitonin gene-related peptide; NE, norepinephrine; NGF, nerve growth factor; NPY, neuropeptide Y; SCG, superior cervical sympathetic ganglion; SNS, sympathetic nervous system; SP, substance P; STN, spinal trigeminal nucleus; TG, trigeminal ganglion.

role in the development of sympathetic hyperalgesia,<sup>63,68,69</sup> although sympathectomy does not affect the early ectopic discharge from myelinated fibers in inferior alveolar nerve neuromas.<sup>70</sup> These results indicate that NGF may play a role in mediating the interactions between sympathetic nerve fiber and nociceptive fibers in orofacial pain. The role might be at the nociceptor level not neuronal soma, but the detailed mechanisms remain to be explored.

## Conclusion

Although the sensory nerves and SNS are generally regarded as discrete structures, the interaction between the SNS and sensory nerves has been associated with orofacial pain (Figures 1 and 2). SNS is involved in many but not all cases of CRPS in orofacial region. The precise mechanisms of SNS in orofacial nociception so far have not been clear, especially in atypical facial pain, stomatodynia, atypical odontalgia, and some forms of masticatory muscle and TMJ disorders. Most investigators focus on the pain mechanisms of SNS in spinal nerve system. However, much less is known about the sympathetic mechanisms in orofacial pain (trigeminal nervous system). The findings about the role of SNS obtained in the DRG could also be operative in the TG, which would be worthy to be confirmed, although the pathophysiology of the trigeminal nerve is in many ways different to that found in spinal nerves.<sup>71,72</sup> A better understanding of SNS and the mechanisms of sympathetic-sensory interactions could help us to treat orofacial pain more successfully in the future.

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## Disclosure

The authors report no conflicts of interest in this work.

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