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REVIEW

Role of Nerve Growth Factor in Orofacial Pain

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Abstract: Some chronic pain conditions in the orofacial region are common and the mechanisms underlying orofacial pain are unresolved. Nerve growth factor (NGF) is a member of a family of neurotrophins and regulates the growth, maintenance and development of neurons. Increasing evidence suggests that NGF plays a crucial role in the generation of pain and hyperalgesia in different pain states. This review investigates the role of NGF in orofacial pain and their underlying cellular mechanisms, which may provide essential guidance to drug-discovery programmes. A systemic literature search was conducted in Pubmed focusing on NGF and orofacial pain. Articles were reviewed, and those discussing in vitro studies, animal evidence, clinical course, and possible mechanisms were summarized. We found a hyperalgesic effect of NGF in peripheral sensitization in orofacial pain models. We also summarize the current knowledge regarding NGF-dependent pain mechanism, which is initiated by retrograde transport of the ligand-receptor complex, ensuing transcriptional regulation of many important nociceptor genes involved in nociceptive processing. Phase III trials suggest that anti-NGF drug is endorsed with anti-inflammatory and pain-relieving effects with good tolerance in a variety of pain conditions, including pain associated with osteoarthritis and chronic lower back pain. Based on the data reviewed herein, NGF is believed to be an important hyperalgesic mediator in orofacial pain. The identification of underlying mechanisms and pathways of orofacial pain opens new frontiers for pain management.

Keywords: nerve growth factor, orofacial region, pain, tyrosine receptor kinases A, mechanisms

Introduction

Nerve growth factor (NGF) was discovered in 1950 by Rita Levi-Montalcini[1] and subsequently purified in 1960.[2] NGF is one of neurotrophins (NTs) family members that also comprise brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4).[3] As its name suggests, NGF is essential for the neuronal survival, growth and development of neurons as well as the maintenance of neuronal phenotype in the mature nervous system via interaction with specific nerve surface receptors, such as tyrosine receptor kinases (trk) A.[4,5] Although NGF is a well-known neurotrophic factor, it also acts as a mediator of pain, itch and inflammation.[6–8]

This review investigates the role of NGF in orofacial pain and their underlying cellular mechanisms. A PubMed query on NGF, orofacial ("orofacial", "face", "neck", "jaw", "chin", "cheek", "buccal", "lip", "mouth", "plate", "tongue", "lingual", "teeth", "mental", "alveolar bone", "temporomandibular", "maxillary", "mandibular", "masseter", "salivary gland" and "trigeminal") and pain ("pain", "nociception", "hyperalgesia" and "sensitization") elicits 114 search results from 1992 to 2020. Using the listed

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keywords and after screening for eligibility, 85 articles were excluded and 29 papers were selected.

We provide current evidence for NGF as an important mediator in peripheral hyperalgesia in the orofacial region. A growing number of studies indicate the contribution of exogenous and endogenous NGF to hyperalgesia in the context of orofacial nociception. Then, we give a current knowledge of NGF-mediated pain mechanism underlying orofacial pain. Finally, the clinical validation of therapeutic drugs targeting NGF will be described.

Nociceptive Transmission of the Orofacial Region

Pain sensation from the orofacial region is relayed to nerve center by the trigeminal nerve system. The cell bodies of most trigeminal primary afferents are located in the trigeminal ganglion (TG, a cranial analog of the dorsal root ganglia, DRG), which is the first station of pain pathways in the orofacial region. The central processes of TG enter the pons, where they descend in the brainstem as the spinal trigeminal nucleus (STN). The STN is trigeminal second-order nociceptive neurons, from which the orofacial nociceptive information is conveyed to the higher center: the thalamus and somatosensory cortex.[9] Orofacial pain is a term defined by the American Academy of Orofacial Pain as "pain associated with the hard and soft tissues of the head, face, and neck".[10] Mechanisms of most orofacial chronic pain conditions are unresolved.[11] Understanding of the mechanism of orofacial pain is critical for performing successful management in such painful conditions.

NGF and Its Receptors

Elevated NGF level has been reported in multiple pathological states particularly in inflammation.[12] The cells that release NGF include keratinocytes,[13] mast cells,[14] fibroblasts, Schwann cells[15] and other target cells of the sensory and sympathetic neurons.[16] In addition, NGF mRNA can be observed in both neurons and satellite glial cells of TG following peripheral nerve damage, suggesting that NGF can be synthesized by them.[17]

Expressed on the cell membrane, the family of trk receptors is a class of proteins that consist of extracellular, intracellular, and transmembrane domains.[18] Three trk receptors have been identified and referred to as trkA, trkB and trkC, each of which has different affinities for particular NTs.[12] There are two types of NGF receptors, each with different preferences for NGF. One with high affinity is trkA and the other with low affinity is p75 neurotrophin receptor (p75NTR).[12] The p75NTR is also a transmembrane protein, which belongs to the tumor necrosis factor receptors superfamily. It has a similar affinity to all NTs and involves in mediating both cell survival and cell death in response to NGF.[19] Moreover, p75NTR acts as a coreceptor for trkA in eliciting neurotrophic actions by facilitating the affinity of trkA for NGF.[20]

The NGF receptors are mainly expressed in the distal axons of all NGF responsive cells in both the peripheral nerve system (ie, sympathetic and sensory neurons)[21] and expressed throughout the central neural axis.[22]

Involvement of NGF in Orofacial Nociception

Immunohistochemical study reveals that trkA as well as p75NTR are abundantly expressed in primary sensory neurons in the TG.[23,24] Sustained upregulation of trkA was observed in TG after tooth injury,[25] orthodontic tooth movement[26] and experimental temporomandibular joint (TMJ) arthritis,[24] indicating the critical role of NGF in modulating nociceptive responses in the orofacial region.

NGF may contribute to orofacial pain via direct mechanisms. NGF, a prominent hyperalgesic mediator in the trigeminal system, is involved in the development of facial heat hyperalgesia after NGF injection into the rat upper lip.[27] Administration of exogenous NGF into masseter muscle can produce a local mechanical sensitization or hyperalgesia in animals.[28,29] NGF-induced hyperalgesia could be attenuated by pretreatment with antibodies to NGF or antagonists of trkA.[27] In another study, co-injection of the non-specific trk receptor antagonists with NGF into the inflamed TMJ significantly reduces nociception.[30]

In addition to its direct effects, NGF can promote peripheral sensitization as a hyperalgesic mediator. For instance, experimental tooth movement and occlusal interference cause local increases in NGF.[26,31] The level of NGF after infraorbital nerve injury is positively correlative to the development of mechanical allodynia.[32] NGF concentration shows a significant increase in TG in the pain models of occlusal interferences and lower lip inflammation.[31,33] The role of NGF acting as a key endogenous molecule in cancer-induced inflammation and nociception is demonstrated in an animal model of oral cancer pain.[34] Administration with non-selective inhibitor of trk receptors into TG produced reversal of heat hyperalgesia in whisker pad skin.[33] A reduced response to mechanical, thermal and chemical

noxious stimuli was observed in the cornea of trkA knockout animals.[35] Evidence has accumulated to suggest that the sequestration of endogenous NGF significantly reduces hyperalgesia and pain perception in animal models of inflammatory and neuropathic pain in the orofacial region.[27,33,36] However, an animal study elegantly demonstrated that NGF does not contribute to hyperalgesia after unilateral mental nerve constriction.[37] p75NTR, on the other hand, appears to be of little relevance in orofacial pain conditions.[29]

Mechanisms of NGF Involved in Orofacial Pain

NGF-trkA Complex

NGF increases in peripheral tissues during the development of inflammation and then binds to trkA in the distal axons, forming NGF-trkA Complex. The ligand-receptor complex is internalized into neurons.[4,38,39] The process is known as endocytosis, by which NGF is incorporated into endocytic vesicles and retrogradely transported to the soma of sensory neurons. The increased NGF in the soma of neuron plays a role in transcriptional regulation of many important genes involved in pain processing.[40] The regulation increased the synthesis of nociceptive receptors such as transient receptor potential vanilloid (TRPV)1[27] and P2X3,[41] nociceptive transmitters (such as substance P or SP, calcitonin gene-related peptide or CGRP, and BDNF),[42] and ion channels such as the transient receptor potential ankyrin 1 (TRPA1)[43] and N-methyl-D-aspartic acid (NMDA) receptor.[44] Some gene products regulated by NGF are anterogradely transported to the distal axons and alter sensitivity of nociceptors (ie peripheral sensitization).[45] Meanwhile, some of them are released from central terminals and are implicated in central nociceptive processing (ie, central sensitization).[7,46] This regulation may be the underlying mechanism in orofacial pain (Figure 1).

TRPV1

TRPV1 is a critical contributor to nociceptor sensitization in peripheral tissues. It belongs to the transient receptor potential ion channel superfamily with high calcium permeability.[39] TRPV1 is mainly expressed in primary sensory neurons and can be activated by capsaicin, acid, noxious heat and various lipids, causing an influx of calcium and sodium, leading to the generation of the action potential.[47,48]

An animal experiment suggests that the expression of TRPV1 is consistent with the level of trkA after NGF administrated into the right upper lip.[27] Increased number of TRPV1-positive neurons innervating the lower lip after CFA injection can be reversed by NGF antagonists.[33]

Additionally, increasing intracellular calcium induced by TRPV1 leads to the release of several excitatory neuropeptides from trigeminal nerve terminals, including SP and CGRP, known as "neurogenic inflammation factors", which contribute to the development of peripheral hyperalgesia.[49] The data suggest that NGF may be involved in orofacial pain through regulating TRPV1 expression at the nociceptor level.

TRPA1

TRPA1 is a voltage-dependent, non-selective ion channel expressed by sensory neurons, which can be activated by low temperature and a number of noxious compounds, such as cannabinoids, mustard oil and allicin, to elicit nociception and inflammation.[50] Moreover, TRPA1 is responsive to various endogenous pain mediators, such as growth factors,[51] calcium ions, proinflammatory agents and gaseous transmitters.[52]

A current study indicates that the transcription of TRPA1 was significantly decreased after NGF inhibitor treatment in a pain model of spinal cord injury,[53] which is confirmed in the pancreatic ductal adenocarcinoma model,[54] CFA-induced peripheral inflammation and spinal nerve ligation model.[55] NGF may contribute to the development of hyperalgesia following nerve injury and inflammation in the orofacial region via the activation of TRPA1 channels. Diogenes et al provide evidence indicating that NGF functionally upregulates TRPA1 expression in TG neurons both in vivo and in vitro.[43] That NGF blockade decreased expression of TRPA1 was also indicated in oral cancer pain model.[34] The precise mechanisms of NGF contribution to nociceptor sensitization by upregulating TRPA1 are being unraveled in pain models.

NMDA

NMDA receptors are glutamate-activated cation channels with high calcium permeability that play important roles in the central sensitization of different types of pain.[56,57] However, recent studies suggest that NMDA receptors are also expressed in primary afferents terminals[29,58] and involved in peripheral sensitization.[44]

NGF may enhance the transcription of NMDA receptor via binding to trkA, leading to the increase of calcium

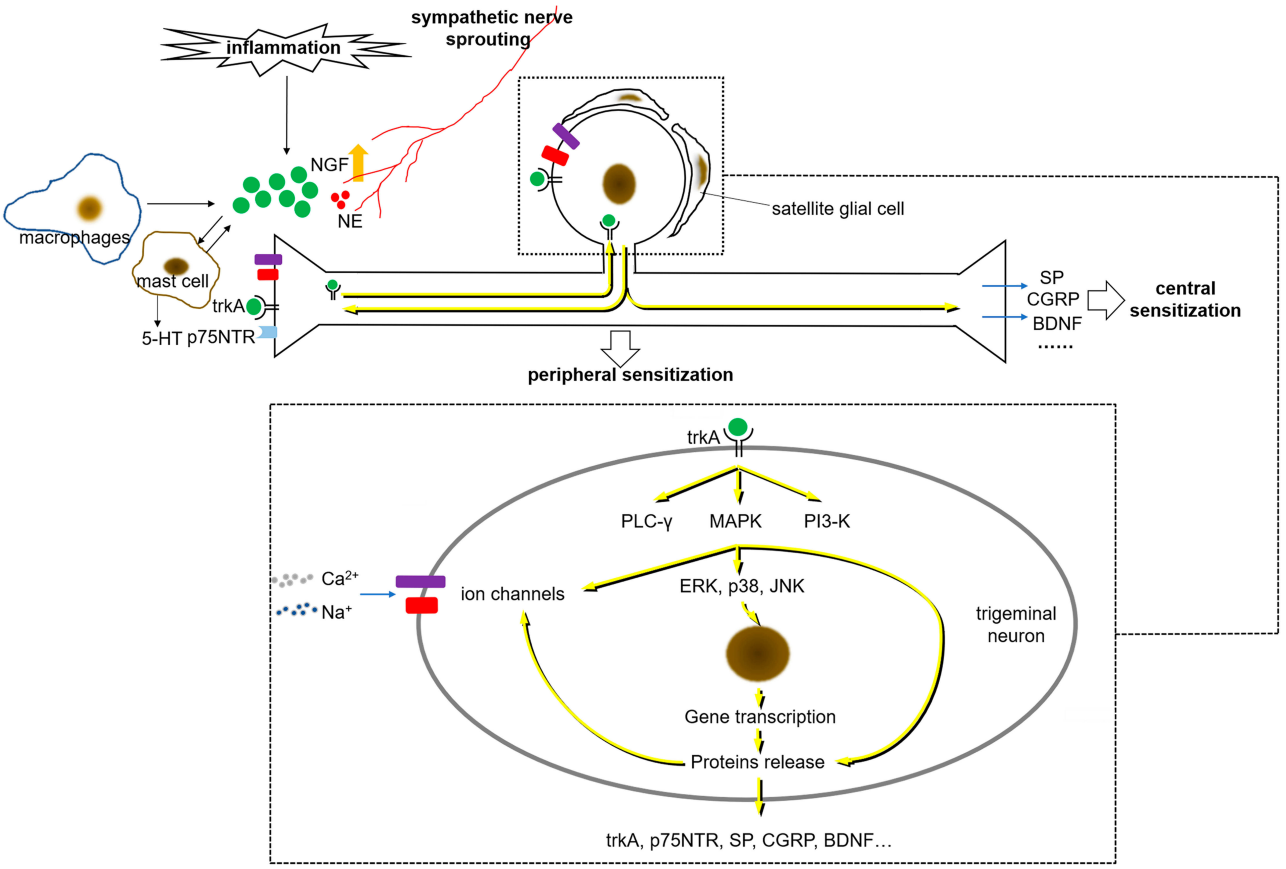

Figure 1 The picture mainly illustrates NGF contributes to orofacial pain via intracellular as well as extracellular mechanisms. NGF released from inflammatory cells increase following peripheral inflammation, initiating the trafficking event of trkA upon binding NGF from the axons to the soma. NGF subsequently regulate transcription of many important genes related to nociception. The synthesized proteins are anterogradely transported to the peripheral and central terminals involving in sensitization. Moreover, spouting of sympathetic fibers is involved too. The lower part shows the details of intracellular alteration induced by NGF, which includes signaling pathways, transcription, ion channels and receptors etc.

Abbreviations: NGF, nerve growth factor; trkA, tyrosine receptor kinases A; p75NTR, p75 neurotrophin receptor; NE, norepinephrine; 5-HT, 5-hydroxytryptamine; SP, substance-P; CGRP, calcitonin gene-related peptide; BDNF, Brain-Derived Neurotrophic Factor; PLC-γ, phospholipase C-γ; MAPK, mitogen-activated protein kinase; PI3-K, phosphatidylinositol 3-kinase; ERK, extracellular signal-regulated kinase; JNK, Jun N-terminal kinase.

influx and the phosphorylation of the NMDA receptors.[59] Following the injection of NGF into masseter muscle, the number of TG neurons expressing NMDA receptors increased while pretreated with its antagonists decreased NGF-induced sensitization.[44] In contrast, a previous study showed that the sensitization of masseter nociceptors by human NGF does not result from enhanced peripheral NMDA receptor activity.[29] Taken together, further investigation into the role of peripheral NMDA receptors in orofacial pain is merited.

The Spouting of Sympathetic Nerve Fibers

As its name suggests, NGF generated by target tissues promotes sympathetic sprouting. For example, new sympathetic axons extend into the TG of transgenic mice and form perineuronal plexuses surrounding only those neurons immunostained for NGF.[60] It was observed that intraventricular infusion of NGF increases sympathetic ingrowth to the TG.[61,62] Overexpression of NGF in the skin induces novel sympathetic projections to primary sensory endings.[63] The enhancement of innervation may be regulated by p75NTR and/or trkA in sympathetic and sensory neurons.[63–67] This raised the interesting possibility that perhaps NGF could link to pain by inducing novel sympathetic projection to sensory neurons. Evidence has accumulated to suggest that the sympathetic nervous system is involved in many orofacial pain conditions.[68] It has been shown that the increased NGF expression plays a role in the development of sympathetic hyperalgesia after nerve injury.[69] At the same time, sympathetic input regulates NGF expression in peripheral targets,[70] which might be mediated through a release of norepinephrine (NE) by

the sympathetic nerve.[71] Overall, these data suggest a regulatory role of NGF in the interactions between sympathetic nerve and nociceptive fibers in orofacial pain.

Intracellular Signaling Pathways

The underlying mechanism for NGF evoked pain and hyperalgesia involves several intracellular signaling pathways. As mentioned above, NGF sensitizes capsaicin receptor TRPV1 via trkA, the mechanisms linking which are related to activation of PI3K and MAPK pathways.[72,73] The NGF-trkA pathway activates PI3K and p38-MAPK, contributing to the development of cold allodynia[73] and mechanical hyperalgesia.[74] Moreover, PLC-γ1 pathway is a downstream effector in NGF-induced mechanical hyperalgesia.[74] In contrast, Yamdeu et al study showed that Local NGF through activation of the p38-MAPK pathway leads to adaptive changes in sensory neuron mu-opioid receptor and facilitates opioid-mediated antinociception in inflammatory pain.[75]

The intracellular signal pathways involved in the roles of NGF in the induction and maintenance of pain may attribute to their transcriptional and post-transcriptional regulations in primary sensory neurons,[76] whose downstream effector pathways and roles in orofacial pain need to be further explored.

The p75NTR might also play a role in generating inflammatory effects mediated by NGF.[77] On the one hand, a possible cooperative role between p75NTR and NGF/trkA signaling responses has been suggested in NGF-induced pain.[78,79] On the other hand, the binding of p75NTR to NGF may involve the activation of NF-kappa B (a transcription factor) in rat Schwann cells, which regulates gene transcription via binding to specific DNA sequences.[80] However, the signal pathways underlying the sensitization by NGF-p75NTR in animal models of orofacial pain remain elusive.

In addition to the direct mechanisms described above, NGF can promote peripheral sensitization by eliciting the degranulation of mast cells through the 5-lipoxygenase pathway, which may be relevant to the early stages of thermal hyperalgesia.[81] Briefly, NGF expression and release at sites of injury appear to sensitize peripheral nociceptive terminals and alter transcription of TG neurons. The nociceptive signals subsequently transmit to the central nervous system, where the pain signals are processed and developed into pain sensation in the orofacial area.[15] Yet studies on the interaction between NGF and nociceptors in the orofacial region are still limited.

Clinical Evidence

Evidence based on human studies provides strong support for a link of NGF with pain mechanism. It is likely that NGF plays a key role in pain hypersensitivity at the peripheral level as demonstrated in NGF-evoked mechanical sensitization in humans after intramuscular injected into the masseter muscle.[82–85] Intradermal injection of NGF to healthy volunteers generalized sensory hypersensitivity around the injected site and resulted in a decrease in the heat-pain threshold.[86] It is noteworthy that systemic administration of even low doses of NGF (above 1 μg/kg) evokes dose-dependently muscle pain, which includes pain with swallowing, pain in the masseter muscles increased by chewing, sore throat, and pain with eye movements.[87]

Therefore, NGF may become an optimal therapeutic target for the management of painful conditions. The NGF/trkA signaling appears to be one of the desirable targets for pain therapy. *Tanezumab*, a recombinant humanized monoclonal antibody to NGF, is a potential therapeutic drug for chronic pain states.[88] It is a new class of analgesics which shows an inhibitory effect on peripheral nociception in early clinical trials. This new agent was developed to reduce pain by blocking the interaction between NGF and its receptors.[15,89] Today, *Tanezumab* is being evaluated in Phase III trials to assess the safety profile.[90] Although this anti-NGF drug still awaits clinical validation, its efficacy has been demonstrated in osteoarthritis pain of the hip and knee joint as well as chronic low back pain.[88,91,92] Moreover, it is characterized by its good tolerability profile with less side effects in tanezumab-treated patients with chronic pain.[93] There is no data about clinical trials of the anti-NGF drug for orofacial pain. The efficacy and risks of anti-NGF for the treatment of orofacial pain such as TMJ arthritis are needed to confirm.

Conclusions

In summary, NGF seems to play a role in underlying orofacial pain conditions. Studies on NGF involved in orofacial pain (trigeminal sensory system) are much less than it is in the trunk and/or limb pain (spinal system). Despite being overwhelmingly similar, there are many differences between orofacial pain and trunk and/or limb pain in many ways.[94] On the one hand, the data about the role of NGF obtained in the DRG might be operative in the TG, which would be worthy to be confirmed. On the other, the precise mechanisms of NGF involved in orofacial pain so far have not been clear. This paper reviews the

critical role of NGF in participating in orofacial pain in both animals and humans, which gives us implications in orofacial pain management. Further studies must be performed in the trigeminal sensory system not only in different pain models but in clinical experiments. A deeper and updated understanding of the role of NGF in orofacial pain helps to find out the target molecules and to develop new analgesics for the prevention and/or treatment of different pain states of humanity.

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Disclosure

The authors report no conflicts of interest in this work.

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