

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-Montalcini¹ 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 cells¹⁵ 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 movement²⁶ 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* knock-out 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

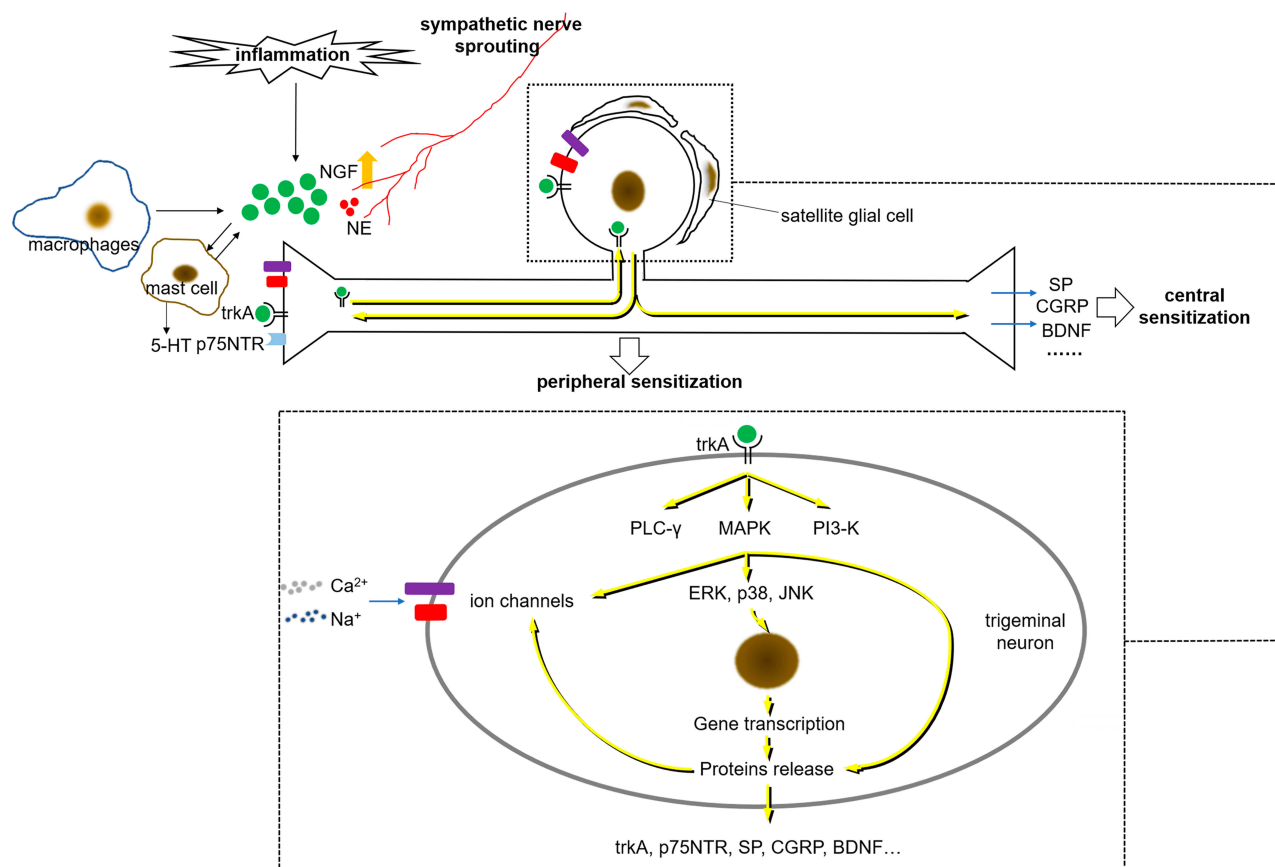


Figure 1 The picture mainly illustrates NGF contributes to orofacial pain via intracellular as well as extracellular mechanisms. NGF released from inflammatory cells increase following peripheral inflammation, initiating the trafficking event of trkA upon binding NGF from the axons to the soma. NGF subsequently 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 allodynia⁷³ and mechanical hyperalgesia.⁷⁴ Moreover, PLC- γ 1 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 μ g/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.

References

- Levi-Montalcini R, Meyer H, Hamburger V. In vitro experiments on the effects of mouse sarcomas 180 and 37 on the spinal and sympathetic ganglia of the chick embryo. *Cancer Res.* 1954;14(1):49–57.
- Cohen S. Purification of a nerve-growth promoting protein from the mouse salivary gland and its neuro-cytotoxic antiserum. *Proc Natl Acad Sci U S A.* 1960;46(3):302–311. doi:10.1073/pnas.46.3.302
- Skaper SD. The neurotrophin family of neurotrophic factors: an overview. *Methods Mol Biol.* 2012;846:1–12.
- Khan N, Smith MT. Neurotrophins and neuropathic pain: role in pathobiology. *Molecules.* 2015;20(6):10657–10688. doi:10.3390/molecules200610657
- Kumar A, Pareek V, Faiq MA, et al. Regulatory role of NGFs in neurocognitive functions. *Rev Neurosci.* 2017;28(6):649–673.
- Indo Y. Nerve growth factor, pain, itch and inflammation: lessons from congenital insensitivity to pain with anhidrosis. *Expert Rev Neurother.* 2010;10(11):1707–1724. doi:10.1586/ern.10.154
- Pezet S, McMahon SB. Neurotrophins: mediators and modulators of pain. *Annu Rev Neurosci.* 2006;29:507–538. doi:10.1146/annurev.neuro.29.051605.112929
- Ikoma A, Steinhoff M, Ständer S, Yosipovitch G, Schmelz M. The neurobiology of itch. *Nat Rev Neurosci.* 2006;7(7):535–547. doi:10.1038/nrn1950
- Sessle BJ. Acute and chronic craniofacial pain: brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates. *Crit Rev Oral Biol Med.* 2000;11(1):57–91. doi:10.1177/10454411000110010401
- Leeuw R, Klasser GD. *Orofacial Pain-Guidelines for Assessment, Diagnosis, and Management.* 5th ed. Quintessence Publishing Co. Inc; 2013.
- Romero-Reyes M, Uyanik JM. Orofacial pain management: current perspectives. *J Pain Res.* 2014;7:99–115. doi:10.2147/JPR.S37593
- Denk F, Bennett DL, McMahon SB. Nerve growth factor and pain mechanisms. *Annu Rev Neurosci.* 2017;40:307–325. doi:10.1146/annurev-neuro-072116-031121
- Pincelli C. Nerve growth factor and keratinocytes: a role in psoriasis. *Eur J Dermatol.* 2000;10(2):85–90.
- Leon A, Buriani A, Dal Toso R, et al. Mast cells synthesize, store, and release nerve growth factor. *Proc Natl Acad Sci U S A.* 1994;91(9):3739–3743. doi:10.1073/pnas.91.9.3739
- Ossipov MH. The perception and endogenous modulation of pain. *Scientifica.* 2012;2012:561761. doi:10.6064/2012/561761
- Bandtlow CE, Heumann R, Schwab ME, Thoenen H. Cellular localization of nerve growth factor synthesis by in situ hybridization. *EMBO J.* 1987;6(4):891–899. doi:10.1002/j.1460-2075.1987.tb04835.x
- Kurata S, Goto T, Gunjigake KK, et al. Nerve growth factor involves mutual interaction between neurons and satellite glial cells in the rat trigeminal ganglion. *Acta Histochem Cytochem.* 2013;46(2):65–73. doi:10.1267/ahc.13003
- Esposito D, Patel P, Stephens RM, et al. The cytoplasmic and transmembrane domains of the p75 and Trk A receptors regulate high affinity binding to nerve growth factor. *J Biol Chem.* 2001;276(35):32687–32695. doi:10.1074/jbc.M011674200
- Chen Y, Zeng J, Chen Y, et al. Multiple roles of the p75 neurotrophin receptor in the nervous system. *J Int Med Res.* 2009;37(2):281–288. doi:10.1177/147323000903700201
- Khodorova A, Nicol GD, Strichartz G. The TrkA receptor mediates experimental thermal hyperalgesia produced by nerve growth factor: modulation by the p75 neurotrophin receptor. *Neuroscience.* 2017;340:384–397. doi:10.1016/j.neuroscience.2016.10.064
- Muragaki Y, Timothy N, Leight S, et al. Expression of trk receptors in the developing and adult human central and peripheral nervous system. *J Comp Neurol.* 1995;356(3):387–397. doi:10.1002/cne.903560306
- Gibbs RB, Pfaff DW. In situ hybridization detection of trkA mRNA in brain: distribution, colocalization with p75NGFR and up-regulation by nerve growth factor. *J Comp Neurol.* 1994;341(3):324–339. doi:10.1002/cne.903410304
- Han HM, Kim TH, Bae JY, Bae YC. Primary sensory neurons expressing tropomyosin receptor kinase A in the rat trigeminal ganglion. *Neurosci Lett.* 2019;690:56–60. doi:10.1016/j.neulet.2018.10.009
- Shinoda M, Honda T, Ozaki N, et al. Nerve terminals extend into the temporomandibular joint of adjuvant arthritic rats. *Eur J Pain.* 2003;7(6):493–505. doi:10.1016/S1090-3801(03)00021-1
- Sullins JS, Carnes DL Jr., Kaldestad RN, Wheeler EF. Time course of the increase in trk A expression in trigeminal neurons after tooth injury. *J Endod.* 2000;26(2):88–91. doi:10.1097/00004770-200002000-00007
- O'Hara AH, Sampson WJ, Dreyer CW, Pierce AM, Ferguson IA. Immunohistochemical detection of nerve growth factor and its receptors in the rat periodontal ligament during tooth movement. *Arch Oral Biol.* 2009;54(9):871–878. doi:10.1016/j.archoralbio.2009.06.003
- Dos Reis RC, Kopruszinski CM, Nones CF, Chichorro JG. Nerve growth factor induces facial heat hyperalgesia and plays a role in trigeminal neuropathic pain in rats. *Behav Pharmacol.* 2016;27(6):528–535. doi:10.1097/FBP.0000000000000246
- Wong H, Dong XD, Cairns BE. Nerve growth factor alters the sensitivity of rat masseter muscle mechanoreceptors to NMDA receptor activation. *J Neurophysiol.* 2014;112(9):2275–2282. doi:10.1152/jn.00327.2014
- Svensson P, Wang MW, Dong XD, Kumar U, Cairns BE. Human nerve growth factor sensitizes masseter muscle nociceptors in female rats. *Pain.* 2010;148(3):473–480. doi:10.1016/j.pain.2009.12.009
- Pelegrini-da-Silva A, Oliveira MC, Parada CA, Tambeli CH. Nerve growth factor acts with the beta2-adrenoceptor to induce spontaneous nociceptive behavior during temporomandibular joint inflammatory hyperalgesia. *Life Sci.* 2008;83(23–24):780–785. doi:10.1016/j.lfs.2008.09.021
- Dong Y, Wang XM, Liu HC, Widmalm SE. The effect of experimental occlusal interferences on nerve growth factor levels in periodontal tissues. *Arch Oral Biol.* 2010;55(12):988–994. doi:10.1016/j.archoralbio.2010.08.007
- Anderson LC, Rao RD. Interleukin-6 and nerve growth factor levels in peripheral nerve and brainstem after trigeminal nerve injury in the rat. *Arch Oral Biol.* 2001;46(7):633–640. doi:10.1016/S0003-9969(01)00024-3

33. Shinoda M, Asano M, Omagari D, et al. Nerve growth factor contribution via transient receptor potential vanilloid 1 to ectopic orofacial pain. *J Neurosci*. 2011;31(19):7145–7155. doi:10.1523/JNEUROSCI.0481-11.2011
34. Ye Y, Dang D, Zhang J, et al. Nerve growth factor links oral cancer progression, pain, and cachexia. *Mol Cancer Ther*. 2011;10(9):1667–1676. doi:10.1158/1535-7163.MCT-11-0123
35. de Castro F, Silos-Santiago I, Lopez de Armentia M, Barbacid M, Belmonte C. Corneal innervation and sensitivity to noxious stimuli in trkA knockout mice. *Eur J Neurosci*. 1998;10(1):146–152. doi:10.1046/j.1460-9568.1998.00037.x
36. Iwata K, Dos Reis RC, Kopruszinski CM, Nones CFM, Aguiar DA, Chichorro JG. The opposing contribution of neurotrophin-3 and nerve growth factor to orofacial heat hyperalgesia in rats. *Int J Mol Sci*. 2020;31(1):27–33.
37. Evans LJ, Loescher AR, Boissonade FM, Whawell SA, Robinson PP, Andrew D. Temporal mismatch between pain behaviour, skin nerve growth factor and intra-epidermal nerve fibre density in trigeminal neuropathic pain. *BMC Neurosci*. 2014;15:1. doi:10.1186/1471-2202-15-1
38. Ginty DD, Segal RA. Retrograde neurotrophin signaling: trk-ing along the axon. *Curr Opin Neurobiol*. 2002;12(3):268–274. doi:10.1016/S0959-4388(02)00326-4
39. Chung G, Jung SJ, Oh SB. Cellular and molecular mechanisms of dental nociception. *J Dent Res*. 2013;92(11):948–955. doi:10.1177/0022034513501877
40. Marlin MC, Li G. Biogenesis and function of the NGF/TrkA signaling endosome. *Int Rev Cell Mol Biol*. 2015;314:239–257.
41. Giniatullin R, Nistri A, Fabbretti E. Molecular mechanisms of sensitization of pain-transducing P2X3 receptors by the migraine mediators CGRP and NGF. *Mol Neurobiol*. 2008;37(1):83–90. doi:10.1007/s12035-008-8020-5
42. Norman BH, McDermott JS. Targeting the nerve growth factor (NGF) pathway in drug discovery. Potential applications to new therapies for chronic pain. *J Med Chem*. 2017;60(1):66–88. doi:10.1021/acs.jmedchem.6b00964
43. Diogenes A, Akopian AN, Hargreaves KM. NGF up-regulates TRPA1: implications for orofacial pain. *J Dent Res*. 2007;86(6):550–555. doi:10.1177/154405910708600612
44. Wong H, Kang I, Dong XD, et al. NGF-induced mechanical sensitization of the masseter muscle is mediated through peripheral NMDA receptors. *Neuroscience*. 2014;269:232–244. doi:10.1016/j.neuroscience.2014.03.054
45. Merighi A, Carmignoto G, Gobbo S, et al. Neurotrophins in spinal cord nociceptive pathways. *Prog Brain Res*. 2004;146:291–321.
46. Pak DJ, Yong RJ, Kaye AD, Urman RD. Chronification of pain: mechanisms, current understanding, and clinical implications. *Curr Pain Headache Rep*. 2018;22(2):9. doi:10.1007/s11916-018-0666-8
47. Mizumura K, Murase S. Role of nerve growth factor in pain. *Handb Exp Pharmacol*. 2015;227:57–77.
48. Song C, Liu P, Zhao Q, Guo S, Wang G. TRPV1 channel contributes to remifentanyl-induced postoperative hyperalgesia via regulation of NMDA receptor trafficking in dorsal root ganglion. *J Pain Res*. 2019;12:667–677. doi:10.2147/JPR.S186591
49. Martins DO, Santos FM, Britto LR, Lemos JB, Chacur M. Neurochemical effects of photobiostimulation in the trigeminal ganglion after inferior alveolar nerve injury. *J Biol Regul Homeost Agents*. 2017;31(1):147–152.
50. Hung CY, Tan CH. TRP channels in nociception and pathological pain. *Adv Exp Med Biol*. 2018;1099:13–27.
51. Malin S, Molliver D, Christianson JA, et al. TRPV1 and TRPA1 function and modulation are target tissue dependent. *J Neurosci*. 2011;31(29):10516–10528. doi:10.1523/JNEUROSCI.2992-10.2011
52. Logashina YA, Korolkova YV, Kozlov SA, Andreev YA. TRPA1 channel as a regulator of neurogenic inflammation and pain: structure, function, role in pathophysiology, and therapeutic potential of ligands. *Biochemistry (Mosc)*. 2019;84(2):101–118. doi:10.1134/S0006297919020020
53. Wada N, Shimizu T, Shimizu N, et al. The effect of neutralization of nerve growth factor (NGF) on bladder and urethral dysfunction in mice with spinal cord injury. *NeuroUrol Urodyn*. 2018;37(6):1889–1896. doi:10.1002/nau.23539
54. Saloman JL, Singhi AD, Hartman DJ, Normolle DP, Albers KM, Davis BM. Systemic depletion of nerve growth factor inhibits disease progression in a genetically engineered model of pancreatic ductal adenocarcinoma. *Pancreas*. 2018;47(7):856–863. doi:10.1097/MPA.0000000000001090
55. Obata K, Katsura H, Mizushima T, et al. TRPA1 induced in sensory neurons contributes to cold hyperalgesia after inflammation and nerve injury. *J Clin Invest*. 2005;115(9):2393–2401. doi:10.1172/JCI25437
56. Blanke ML, VanDongen AMJ. Activation mechanisms of the NMDA receptor. In: Van Dongen AM, editor. *Biology of the NMDA Receptor*. Boca Raton (FL): Frontiers in Neuroscience; 2009.
57. Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesth Analg*. 2003;97(4):1108–1116. doi:10.1213/01.ANE.0000081061.12235.55
58. Li J, McRoberts JA, Nie J, Ennes HS, Mayer EA. Electrophysiological characterization of N-methyl-D-aspartate receptors in rat dorsal root ganglia neurons. *Pain*. 2004;109(3):443–452. doi:10.1016/j.pain.2004.02.021
59. Bai G, Kusiak JW. Nerve growth factor up-regulates the N-methyl-D-aspartate receptor subunit 1 promoter in PC12 cells. *J Biol Chem*. 1997;272(9):5936–5942. doi:10.1074/jbc.272.9.5936
60. Walsh GS, Kawaja MD. Sympathetic axons surround nerve growth factor-immunoreactive trigeminal neurons: observations in mice overexpressing nerve growth factor. *J Neurobiol*. 1998;34(4):347–360. doi:10.1002/(SICI)1097-4695(199803)34:4<347::AID-NEU5>3.0.CO;2-6
61. Shoemaker SE, Kudwa AE, Isaacson LG. Sympathetic ingrowth to the trigeminal ganglion following intracerebroventricular infusion of nerve growth factor. *Brain Res*. 2002;956(1):136–148. doi:10.1016/S0006-8993(02)03490-X
62. Nauta HJ, Wehman JC, Koliatsos VE, Terrell MA, Chung K. Intraventricular infusion of nerve growth factor as the cause of sympathetic fiber sprouting in sensory ganglia. *J Neurosurg*. 1999;91(3):447–453. doi:10.3171/jns.1999.91.3.0447
63. Davis BM, Goodness TP, Soria A, Albers KM. Over-expression of NGF in skin causes formation of novel sympathetic projections to trkA-positive sensory neurons. *Neuroreport*. 1998;9(6):1103–1107. doi:10.1097/00001756-199804200-00027
64. Smeyne RJ, Klein R, Schnapp A, et al. Severe sensory and sympathetic neuropathies in mice carrying a disrupted Trk/NGF receptor gene. *Nature*. 1994;368(6468):246–249. doi:10.1038/368246a0
65. Zhou XF, Rush RA. Endogenous nerve growth factor is required for regulation of the low affinity neurotrophin receptor (p75) in sympathetic but not sensory ganglia. *J Comp Neurol*. 1996;372(1):37–48. doi:10.1002/(SICI)1096-9861(19960812)372:1<37::AID-CNE4>3.0.CO;2-N
66. Walsh GS, Krol KM, Kawaja MD. Absence of the p75 neurotrophin receptor alters the pattern of sympathosensory sprouting in the trigeminal ganglia of mice overexpressing nerve growth factor. *J Neurosci*. 1999;19(1):258–273. doi:10.1523/JNEUROSCI.19-01-00258.1999
67. Dhanoa NK, Krol KM, Jahed A, Crutcher KA, Kawaja MD. Null mutations for exon III and exon IV of the p75 neurotrophin receptor gene enhance sympathetic sprouting in response to elevated levels of nerve growth factor in transgenic mice. *Exp Neurol*. 2006;198(2):416–426. doi:10.1016/j.expneurol.2005.12.022
68. Fan W, Zhu X, He Y, et al. Peripheral sympathetic mechanisms in orofacial pain. *J Pain Res*. 2018;11:2425–2431. doi:10.2147/JPR.S179327
69. Davis BM, Albers KM, Seroogy KB, Katz DM. Overexpression of nerve growth factor in transgenic mice induces novel sympathetic projections to primary sensory neurons. *J Comp Neurol*. 1994;349(3):464–474. doi:10.1002/cne.903490310

70. Randolph CL, Bierl MA, Isaacson LG. Regulation of NGF and NT-3 protein expression in peripheral targets by sympathetic input. *Brain Res.* **2007**;1144:59–69. doi:10.1016/j.brainres.2007.01.099
71. Qin F, Vulapalli RS, Stevens SY, Liang CS. Loss of cardiac sympathetic neurotransmitters in heart failure and NE infusion is associated with reduced NGF. *Am J Physiol Heart Circ Physiol.* **2002**;282(1):H363–H371. doi:10.1152/ajpheart.00319.2001
72. Zhu W, Oxford GS. Phosphoinositide-3-kinase and mitogen activated protein kinase signaling pathways mediate acute NGF sensitization of TRPV1. *Mol Cell Neurosci.* **2007**;34(4):689–700. doi:10.1016/j.mcn.2007.01.005
73. Kayama Y, Shibata M, Takizawa T, et al. Signaling pathways relevant to nerve growth factor-induced upregulation of transient receptor potential M8 expression. *Neuroscience.* **2017**;367:178–188. doi:10.1016/j.neuroscience.2017.10.037
74. Malik-Hall M, Dina OA, Levine JD. Primary afferent nociceptor mechanisms mediating NGF-induced mechanical hyperalgesia. *Eur J Neurosci.* **2005**;21(12):3387–3394.
75. Yamdeu RS, Shaqura M, Mousa SA, Schafer M, Droese J. p38 Mitogen-activated protein kinase activation by nerve growth factor in primary sensory neurons upregulates mu-opioid receptors to enhance opioid responsiveness toward better pain control. *Anesthesiology.* **2011**;114(1):150–161. doi:10.1097/ALN.0b013e318201c88c
76. Cheng JK, Ji RR. Intracellular signaling in primary sensory neurons and persistent pain. *Neurochem Res.* **2008**;33(10):1970–1978. doi:10.1007/s11064-008-9711-z
77. Zhang YH, Nicol GD. NGF-mediated sensitization of the excitability of rat sensory neurons is prevented by a blocking antibody to the p75 neurotrophin receptor. *Neurosci Lett.* **2004**;366(2):187–192. doi:10.1016/j.neulet.2004.05.042
78. Barrett GL. The p75 neurotrophin receptor and neuronal apoptosis. *Prog Neurobiol.* **2000**;61(2):205–229. doi:10.1016/S0301-0082(99)00056-8
79. Freund-Michel V, Frossard N. The nerve growth factor and its receptors in airway inflammatory diseases. *Pharmacol Ther.* **2008**;117(1):52–76. doi:10.1016/j.pharmthera.2007.07.003
80. Carter BD, Kaltschmidt C, Kaltschmidt B, et al. Selective activation of NF-kappa B by nerve growth factor through the neurotrophin receptor p75. *Science.* **1996**;272(5261):542–545. doi:10.1126/science.272.5261.542
81. Shu XQ, Mendell LM. Neurotrophins and hyperalgesia. *Proc Natl Acad Sci U S A.* **1999**;96(14):7693–7696. doi:10.1073/pnas.96.14.7693
82. Svensson P, Cairns BE, Wang K, Arendt-Nielsen L. Injection of nerve growth factor into human masseter muscle evokes longlasting mechanical allodynia and hyperalgesia. *Pain.* **2003**;104(1–2):241–247. doi:10.1016/S0304-3959(03)00012-5
83. Svensson P, Wang K, Arendt-Nielsen L, Cairns BE. Effects of NGF-induced muscle sensitization on proprioception and nociception. *Exp Brain Res.* **2008**;189(1):1–10. doi:10.1007/s00221-008-1399-4
84. Svensson P, Castrillon E, Cairns BE. Nerve growth factor-evoked masseter muscle sensitization and perturbation of jaw motor function in healthy women. *J Orofac Pain.* **2008**;22(4):340–348.
85. Exposto FG, Masuda M, Castrillon EE, Svensson P. Effects of nerve growth factor experimentally-induced craniofacial muscle sensitization on referred pain frequency and number of headache days: a double-blind, randomized placebo-controlled study. *Cephalalgia.* **2018**;38(14):2006–2016. doi:10.1177/0333102418758481
86. Dyck PJ, Peroutka S, Rask C, et al. Intradermal recombinant human nerve growth factor induces pressure allodynia and lowered heat-pain threshold in humans. *Neurology.* **1997**;48(2):501–505. doi:10.1212/WNL.48.2.501
87. Petty BG, Cornblath DR, Adornato BT, et al. The effect of systemically administered recombinant human nerve growth factor in healthy human subjects. *Ann Neurol.* **1994**;36(2):244–246. doi:10.1002/ana.410360221
88. Patel MK, Kaye AD, Urman RD. Tanezumab: therapy targeting nerve growth factor in pain pathogenesis. *J Anaesthesiol Clin Pharmacol.* **2018**;34(1):111–116. doi:10.4103/joacp.JOACP_389_15
89. Webb MP, Helander EM, Menard BL, Urman RD, Kaye AD. Tanezumab: a selective humanized mAb for chronic lower back pain. *Ther Clin Risk Manag.* **2018**;14:361–367. doi:10.2147/TCRM.S144125
90. Berenbaum F. Targeting nerve growth factor to relieve pain from osteoarthritis: what can we expect? *Joint Bone Spine.* **2019**;86(2):127–128. doi:10.1016/j.jbspin.2018.09.009
91. Schnitzer TJ, Easton R, Pang S, et al. Effect of tanezumab on joint pain, physical function, and patient global assessment of osteoarthritis among patients with osteoarthritis of the hip or knee: a randomized clinical trial. *JAMA.* **2019**;322(1):37–48. doi:10.1001/jama.2019.8044
92. Bannwarth B, Kostine M. Nerve growth factor antagonists: is the future of monoclonal antibodies becoming clearer? *Drugs.* **2017**;77(13):1377–1387. doi:10.1007/s40265-017-0781-6
93. Walicke PA, Hefti F, Bales R, et al. First-in-human randomized clinical trials of the safety and efficacy of tanezumab for treatment of chronic knee osteoarthritis pain or acute bunioneectomy pain. *Pain Rep.* **2018**;3(3):e653. doi:10.1097/PR9.0000000000000653
94. Lopes DM, Denk F, McMahon SB. The molecular fingerprint of dorsal root and trigeminal ganglion neurons. *Front Mol Neurosci.* **2017**;10:304. doi:10.3389/fnmol.2017.00304

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