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Review Article

Targeting nerve growth factor for pain relief: pros and cons

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ABSTRACT

Nerve growth factor (NGF) is a neurotrophic protein that has crucial roles in survival, growth and differentiation. It is expressed in neuronal and non-neuronal tissues. NGF exerts its effects *via* two types of receptors including the high affinity receptor, tropomyosin receptor kinase A and the low affinity receptor p75 neurotrophin receptor highlighting the complex signaling pathways that underlie the roles of NGF. In pain perception and transmission, multiple studies shed light on the effects of NGF on different types of pain including inflammatory, neuropathic, cancer and visceral pain. Also, the binding of NGF to its receptors increases the availability of many nociceptive receptors such as transient receptor potential vanilloid 1, transient receptor potential ankyrin 1, N-methyl-D-aspartic acid, and P2X purinoceptor 3 as well as nociceptive transmitters such as substance P and calcitonin gene-related peptide. The role of NGF in pain has been documented in pre-clinical and clinical studies. This review aims to shed light on the role of NGF and its signaling in different types of pain.

Keywords: Acute Disease; Chronic Disease; Inflammation; Low Back Pain; Musculoskeletal; Neoplasms; Nerve Growth Factor; Neuropathic Pain; Orofacial Pain; Osteoarthritis; Pain.

INTRODUCTION

1. Overview of nerve growth factor (NGF) and its role in pain perception

In the early 1950's, NGF was discovered by Rita Levi-Montalcini in a tumor tissue [1]. The discovery of NGF was considered a landmark achievement in neurobiology. Since then, the diverse roles of NGF were determined in multiple era including the pain field. NGF belongs to a large family of proteins that include, in mammals, neurotrophin-3, neurotrophin-4/5 and brain-derived neurotrophic factor [2]. NGF is important for the survival, growth and differentiation of sympathetic and sensory afferent neurons during development and in the modulation of nociception in adulthood [1]. It is expressed in neuronal and non-neuronal tissues. In more detail, it is widely expressed in the central nervous cells, peripheral Schwann cells, glands, endothelial cells, immune cells and skeletal muscles [3]. Notably, there is shift in the role of NGF from neuronal growth to the regulation of the sensitivity of the peripheral nervous system to noxious stimuli [4]. NGF has two receptors including the high affinity receptor, tropomyosin receptor kinase A (TrkA) and the low affinity receptor p75 neurotrophin receptor (p75NTR) [5]. Through its interaction with the high-affinity receptor TrkA, NGF suppresses the synthesis of p75. This neurotrophic protein is produced as pro-NGF that

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has more affinity to p75NTR compared to NGF that binds with higher affinity to TrkA [5]. TrkA receptor is highly expressed in dorsal root ganglion (DRG) neurons during embryogenesis and its role declines post-natally [6]. Accordingly, NGF is a major contributor to pain signaling and transmission [2,7]. In this regard, it was found that rats develop hyperalgesia when degradation of NGF is blocked by matrix metalloproteinases-2 inhibitor through a peripheral mechanism [8]. The role of NGF in neuronal development and the perception of localized tissue pain has been highlighted in multiple studies [2]. Also, investigators found that increased NGF levels are linked to inflammation, persistent pain, injuries, and discomfort [7]. To add, multiple studies showed that NGF is a marker for the peptidergic nociceptors that express TrkA compared to non-peptidergic nociceptors that express glial cell line-derived neurotrophic factor [9]. Furthermore, several lines of evidences implicated the role of NGF in different types of pain such as inflammatory, neuropathic, cancer, orofacial, musculoskeletal, and low back pain (LBP) [10–13]. In fact, earlier reports pointed to the critical role of NGF-mediated signaling in the initiation and maintenance of chronic pain [2]. Thus, this review is written to shed light on the role of NGF and its signaling in different types of pain.

MAIN BODY

1. Signaling pathways of NGF

NGF plays a key role in nociception through several mechanisms including the release of inflammatory mediators, increase in the activity and availability of many nociceptive ion channels and receptors [14]. The binding of NGF to TrkA increases the availability of nociceptive receptors such as transient receptor potential vanilloid 1 (TRPV1), transient receptor potential ankyrin 1 (TRPA1), N-methyl-D-aspartic acid, and P2X purinoceptor 3 as well as nociceptive transmitters such as substance P and calcitonin gene-related peptide (CGRP) [15,16]. Thus, NGF plays a crucial role in peripheral and central sensitization. It sensitizes nociceptors directly in the short term and/or changes gene expression in the long term [2]. Earlier reports showed that NGF binds to TrkA receptor and participates in the initiation and maintenance of nociception through several intracellular signaling pathways, including mitogen-activated protein kinases (MAPKs)/extracellular signal-regulated kinases and phosphoinositide-3-kinase(PI3K) [14]. Furthermore, NGF increases the release of serotonin, histamine, prostaglandin E2, and NGF itself, that collectively binds to their receptors on the peripheral terminals of nociceptors [17]. Also, it sets off a cascade of events that cause nociceptive pain. Furthermore, TrkA binds NGF which is then retrogradely delivered to the cell bodies of neurons. Within these cell bodies, it regulates the expression of TRPV1, bradykinin receptors, voltage-gated sodium channels, acid sensing ion channel 2/3, and other receptors [18]. The nociceptive receptors on the surface of these cells that are involved in nociception trigger peripheral sensitization and increase pain perception [19]. Meanwhile, central sensitization is produced by changes in gene expression induced by NGF-TrkA signaling [2]. In conclusion, NGF plays a key role in pain perception by regulating the expression of genes related to pain, controlling the activity of key channels/receptors in pain and increasing the pro-inflammatory mediators (**Fig. 1**).

2. Types of pain associated with NGF

1) Musculoskeletal pain

(1) Osteoarthritis (OA) pain

OA is an age-related chronic joint disease that leads to cartilage destruction caused by several factors including inflammation [20]. Inflammation is correlated to the role of NGF in increasing the sensitivity of nociceptive neurons in the area, thus regulating the production of pain molecules centrally and peripherally [10,11]. In more detail, it is well-known that pro-NGF controls both inflammation and apoptosis [21]. Further, neuropeptides, neurotransmitters, and immune-active cytokines are all produced due to NGF release and inflammation [11]. Also, the innate and adaptive immune responses are directly impacted by NGF, since it interacts with several cells that are involved in the immunological response, such as macrophages, lymphocytes, and mast cells [3]. Depending on the presence or absence of its receptors, NGF may promote or reduce inflammation. Accordingly, it is considered an endogenous molecule that serves two separate purposes initiating pathways that regulate inflammation/restrict tissue damage and stimulating immune responses. NGF has a role in the treatment of chronic inflammatory illnesses as it increases the pain that is associated with neurogenic inflammation of tissues [18]. In this regard, several lines of evidences highlighted the key roles of NGF in OA albeit controversy in its role as a pro-inflammatory [22] or anti-inflammatory media-

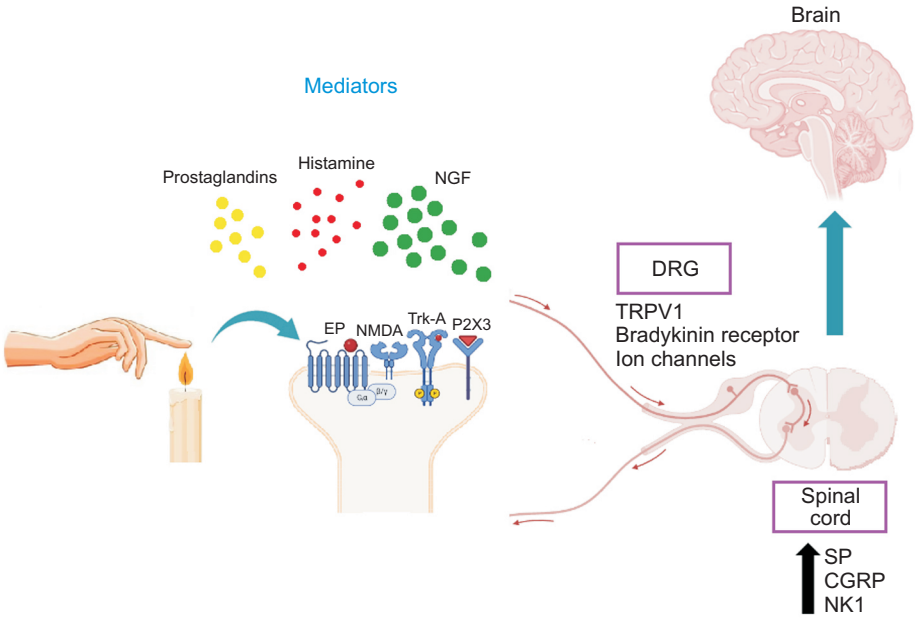

Fig. 1. Signaling pathways of NGF in pain. NGF: nerve growth factor, EP: prostaglandin E2 receptor, NMDA: N-methyl-D-aspartic acid, TrkA: tropomyosin receptor kinase A, P2X3: P2X purinoceptor 3, DRG: dorsal root ganglion, TRPV1: transient receptor potential vanilloid 1, SP: substance P, CGRP: calcitonin gene-related peptide, NK1: neurokinin-1.

tor [23]. The following paragraphs are details about the involvement of NGF in inflammatory pain. For instance, it was found that NGF receptors are expressed by joint cells [24]. Also, a large body of evidences showed that the lack of NGF leads to the loss of sympathetic and sensory neurons similar to TrkA-knocking down in animals [6,25]. People with inflammatory or degenerative rheumatic illnesses, including rheumatoid arthritis, OA, and spondyloarthritis, have elevated levels of NGF in their synovial fluid. Further, a meta-analysis of thirteen placebo-controlled trials examining OA of the hip or knee was carried out by Schnitzer and Marks, 2015 [26]. The researchers discovered that blocking NGF significantly reduced pain when compared to a placebo. In a mouse model of medial meniscus destabilization (MMD) associated with OA, the effects of NGF and its soluble receptor, TrkAd5, on pain rating were examined. The study demonstrated that TrkAd5 effectively decreased discomfort in mice with OA [27]. In 2015, it was found that canine-specific anti-NGF mAb could cure degenerative joint disease in dogs [28,29].

Investigators tested the efficacy of several intra-articular and intraperitoneal injection of an anti-NGF into the knees of rats and reported the effectiveness in reversing OA-induced pain [30]. Also, Dakin et al. [31] revealed that blocking NGF reduced pain behavior in two OA rat models. In addition, the effects of tanezumab on weight-bearing and cartilage degradation were shown in a study using the rat medial meniscal tear model whereby rats with meniscal injury had a less aberrant gait after receiving tanezumab treatment, regardless of dosage and increase in the incidence of subchondral bone sclerosis and cartilage degradation [32]. According to Xu et al. [33], it was revealed that anti-NGF mAb reduced the severity and discomfort of OA but increased cartilage destruction compared to the control group. This effect was particularly seen in the early stages of the disease [33]. After joint or orthopaedic surgery, Majuta et al. [34] showed that using anti-NGF in the knee enhanced limb performance in a mouse model and reported that NGF has two distinct roles in development and maturity [34].

After injecting NGF antibody in the knee, it was revealed that there was a shift in the levels of CGRP in DRGs, a matter that causes interference with walking patterns [34]. Furthermore, a new NGF vaccination was effective in reducing the spontaneous pain behaviour in mice with surgically induced OA. Overall, these findings support the idea that inhibiting NGF signaling might be beneficial in alleviating chronic pain, particularly in OA patients [35]. Additionally, previous studies showed that NGF decelerated chondrocyte differentiation and improved ligament healing [36,37]. In a study conducted on chondrocytes, the authors reported that the mechanical loading of cartilage accompanied with an increase of visfatin/nicotinamide phosphoribosyltransferase and interleukin 1β (IL-1β) aggravated OA pain though the stimulation of NGF expression and release by these cells [38]. Also, it was reported that there was a decrease in patient's OA symptoms including pain when anti-NGF-treatment was used [39].

Lane and Corr [40] discussed the efficacy of NGF inhib-

itors in reducing musculoskeletal pain. Additionally, Wise et al. [13] reviewed the clinical studies evaluating NGF inhibitors' efficacy, such as tanezumab, in chronic pain states like OA pain and discussed the significant pain relief observed in clinical trials and the associated risks of rapidly progressive OA. Meng et al. [41] reviewed the efficacy of NGF inhibitors in the treatment of OA, while Pallav et al. [42] published that anti-NGF mAbs (tanezumab, fasinumab, and fulranumab) caused a significant decrease in pain and physical function scores compared to the control groups. These studies collectively underscore the therapeutic potential of NGF inhibitors in managing chronic musculoskeletal pain.

(2) LBP

LBP is a type of pain that imposes huge burdens in the society. In 2007, the US estimated that 100–200 billion dollars are lost every year due to loss of productivity of employees or absence from work caused by LBP. Thus, various studies were conducted to find treatments for LBP. Nonradicular LBP is one kind of musculoskeletal pain that tanezumab showed promise in treatment. Anti-NGF showed low to moderate effects in alleviating LBP in patients [43]. In this regard, Markman et al. [44] discussed the safety and efficacy of tanezumab in treating nonradicular LBP that persists after medication. Another meta-analysis study revealed that the use of NGF agents improved the symptoms of LBP patients [45]. Researchers compared 5 or 10 mg of tanezumab administered subcutaneously every 8 weeks against 100 to 300 mg of tramadol taken orally once in a day. In contrast to tramadol, tanezumab at a dosage of 10 mg reduced the severity of LBP after 16 weeks. Complete joint replacement surgery was necessary for seven patients (1.4% of the total) in the 10 mg group compared to other groups. Tanezumab seems to be effective for chronic LBP [46]. In a study conducted in patients with chronic LBP, it was reported that tanezumab provided more improvement in pain and global assessment scores compared to the groups that received a placebo and naproxen [47]. On the other hand, other studies demonstrated the other side of NGF effects. In these studies, NGF was used to create a model of LBP in rats associated with mechanical somatosensory changes [48].

2) Cancer pain

Over 60 years ago, during a transplantation experiment with a malignant mouse sarcoma, NGF was first discovered by Levi-Montalcini indicating the role of NGF in cancer. NGF alone cannot promote the growth of neoplasms cells. Indeed, it plays a substantial role in the development of neoplasms when expressed in conjunction with substances that promote neoplasms. Several lines of evidence indicate the key role of NGF in cancer. For instance, sortilin, a membrane receptor, has been associated with carcinogenesis by acting as a co-receptor for proNGF in cooperation with p75NTR to promote cancer cell invasion [10]. Further, neuropilin-1, found in many nociceptors, is considered a key player in the TrkA-mediated pain signaling cascade [49]. In the pancreatic ductal adenocarcinoma model, it was found that there is a reduction in TRPA1 transcription after treatment with NGF inhibitor [50].

The role of TrkA and/or p75NTR receptors in enhancing pro-survival signaling in tumors vary [51]. In breast cancer, NGF plays an important role by promoting cell proliferation *via* TrkA and cell survival *via* p75NTR [51]. Furthermore, earlier studies revealed that the activation of p75NTR enhances the ability of breast cancer cells to withstand chemotherapy-induced cell death [52]. Stimulating the Ras (rat sarcoma) pathways, which are mediated by TrkA, allows cells to survive and nerve fibers to proliferate. Also, this pathway was implicated in the TrkA-activated PI3Ks pathway leading to proliferation, invasion, and metastasis [21]. In prostate cells; it was found that p75NTR promotes cell death and inhibits tumor growth in normal prostate cells [21]. Further, there is strong evidence that NGF affects liver cancer progression and metastasis [53]. NGF modulates signaling pathways linked to cell migration, cytoskeleton structure, and liver cancer cell polarity [53]. At high NGF levels, cells are shielded from planned cell death and detachment-induced cell death, and undergo cellular metamorphosis, which is characterized by increased mobility and susceptibility to directional and structural alterations [53]. Furthermore, the use of anti-NGF mAbs has been explored in many preclinical trials as a potential remedy for cancer-related discomfort [54]. Scientists showed that, in contrast to conventional morphine treatment, a new NGF sequestering antibody significantly reduced pain-related behaviors in a bone cancer mice model [55]. It was revealed that anti-NGF treatment considerably mitigated functional connectivity alterations and reduced cancer [56]. Another study highlighted the connections between oral cancer pain, proliferation, cachexia, and NGF. Also, it was shown that cancer pain reduced when anti-NGF medicine was administered at the early and late stages of the disease, according to Jimenez-Andrade et al. [56]. In a

mouse model of cancer-induced bone pain, Guedon et al. [57] investigated the effects of anti-NGF and found that anti-NGF mAbs reduced skeletal pain-related behaviors and affected cutaneous hypersensitivity.

3) Neuropathic pain

According to the International Association for the Study of Pain: neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" regardless of the cause [58]. The number of people suffering from neuropathic pain reached two million people according to US estimates [59]. In animal models of neuropathic pain, allodynia and thermal hyperalgesia were reduced by the intrathecal administration of NGF [60]. Meanwhile, in human clinical trials of peripheral neuropathic pain, NGF showed positive effects on neuropathic pain and pain sensitivity in human immunodeficiency virus (HIV)-associated sensory neuropathy [61]. Furthermore, NGF was effective in preventing the progression of peripheral neuropathies that are associated with HIV or diabetes [62]. Anti-NGF mAb therapy has been the subject of several preclinical investigations for the treatment of neuropathic pain including cancer-induced neuropathic pain. Research by Dai et al. [63] showed that inhibiting NGF reduced the activities of p65 and MAPK and alleviated neuropathic pain associated with chronic constriction injury. Additionally, local application of anti-NGF decreased the severity of heat-induced hypersensitivity in rats with trigeminal neuropathic pain, according to a study conducted by Dos Reis et al. [64]. As shown by Sainoh et al. [65], anti-NGF antibodies have the potential to be a useful tool in the management of neuropathic cancer pain.

4) Orofacial pain

Several lines of evidences show the role of NGF in orofacial pain. Jasim and co-workers conducted an examination to assess the levels of NGF in the saliva and plasma of 39 patients with chronic temporomandibular disorder (TMD)-myalgia and 39 pain-free individuals and found that the salivary levels of NGF decreased in TMD-myalgia patients [66]. Also, injecting NGF into the masseter muscle increased mechanical sensitization in women more than men indicating that NGF-induced muscle pain is sex-related [67]. Patients with multiple extractions of teeth perceived an increase in pain, particularly mechanical hyperalgesia, which might be prevented by using antibodies that reduce NGF activity. Furthermore, it was found that the trigeminal ganglia (TG) and periodontal tissues had elevation in the levels of NGF expression and that the application of mechanical stimuli to periodontal fibroblasts increased NGF production [68]. Thus, NGF-based gene therapy was proposed as a mediator for the mechanical hyperalgesia that results from tooth movement [69].

According to this study, control volunteers reported significant changes in the excitability of the corticomotor, while NGF (injected to the masseter muscle of individuals suffering from teeth grinding) did not demonstrate any changes in the central regulation of motor pathways due to NGF-induced sensitization combined with a motor training assignment [70]. According to Mai et al, NGF is involved in orofacial pain via regulating TRPV1 expression at the nociceptor level [70]. In addition, NGF antagonists reversed complete Freund's adjuvant-induced increase in the number of TRPV1-positive neurons that innervate the lower lip [50]. Also, it was found that blocking NGF reduced TRPA1 expression in an oral cancer pain model suggesting that NGF may contribute to the development of hyperalgesia in the orofacial region via TRPA1 activation [71].

5) Visceral pain

Mixed results were reported for the effects of NGF on visceral pain. In patients suffering from diarrhea-predominant irritable bowel syndrome, it was found that NGF interacts with sensory nerve fibers and mast cells in mediating visceral hypersensitivity [72]. Also, NGF was found in high concentrations in the urine of patients suffering from visceral dysfunction [73]. Also, in a model of neonatal colon inflammation, NGF was correlated with gastric hypersensitivity and its levels increased in gastric fundus [74]. Attenuation of NGF with gastrula mAbs, especially when humanized, is being examined in clinical trials as an analgesic option for a variety of visceral pain conditions such as diabetes and post-surgery [75,76]. In bioelectrical rehabilitation, the results suggested that microneedling could also up-regulate the expression of NGF genes, hence playing a significant role in the accelerated process of nerve regeneration in addition to restoring the normal functioning of the peripheral nerves [77]. According to Liang et al. [78], the researchers explored the involvement of electroacupuncture in visceral pain management as well as NGF producing nanocomponents in colorectal pain and revealed that the nanocomponents displayed the capability to relieve visceral pain by increasing NGF expression.

3. Therapeutic implications of NGF in pain management

Elevated levels of NGF have been associated with various pain states making it a target for pain management [3,5]. Accumulating pieces of evidence have shown that the available drugs (*i.e.,* opiates and non-steroidal anti-inflammatory drugs [NSAIDs]) that are used for the treatment of chronic pain leads to long-term side effects such as cardiac, gastrointestinal, or renal adverse effects, suggesting the need to look for other alternatives [5,16]. Antibodies or neutralizing medicines that target NGF signaling and its ability to modulate pain in the long term, have been studied in animal models. Under the request to license the subcutaneous injection of 2.5 mg tanezumab, the Food and Drug Administration (FDA) approved its use on March 2, 2020 [79,80]. NGF inhibitors are safer and more cost-effective than joint replacement surgery, the conventional alternative treatment for knee and hip OA [79,80]. Multiple approaches were established for targeting NGF to relive pain such as preventing NGF binding, activation or inhibiting of TrkA binding/signaling and sequestration of free NGF [2,5]. NGF inhibitors were used as analgesics in chronic pain conditions such as chronic LBP and OA with better outcomes compared to NSAIDs [13]. Also worth mentioning is the importance of pointing to the different signaling of NGF in the acute and chronic phases of pain. For example, it was revealed that there is an increase in p75NTR-mRNA level in the chronic phase of the experimental model of autoimmune encephalomyelitis leading to an elevation in the p75NTR to TrkA at the chronic phase of this model [81]. Also, the expression of NGF protein increased slightly during the acute phase whereas the expression of TrkA in the brains of mice was stable during this phase [81]. Additionally, several reports showed that NGF drives local neuronal sprouting and increases the excitability of the nervous system (promotes sensitization of neurons) which is a key process in many conditions of chronic pain [2]. These findings indicate the importance of tailoring drugs that are used in the acute phase differently than the ones used for the chronic phase. Hirose et al. [12] discussed the development of analgesics targeting NGF/TrkA signaling, noting that this approach can be effective for treating intractable pain without the adverse effects that are commonly associated with traditional analgesic drugs. Also, several phase 2/3 studies have been done that target NGF and TrkA inhibitors. Furthermore, humanized anti-NGF mAbs (*i.e.*, tanezumab, fulranumab, and fasinumab) were used in phase III trials in OA [82]. Additionally, the use of anti-NGF antibodies in patients suffering from knee OA improved stiffness, physical function, and patient global assessment [68]. Chang et al. [2] reported the effectiveness of NGF inhibitors for neuropathic and other types of pain, such as cancer and visceral pain. Peach et al. [49] found that the co-receptor for NGF is responsible for the transfer of signals to TrkA receptors, and that neuropilin 1 antagonism in nociceptors is a new approach for NGF-mediated pain. Also, another study demonstrated that development of abnormal somatosensory behavior was prevented by anti-NGF, suggesting its beneficial effect in the treatment for central pain [83]. Another important aspect in designing valuable drugs is to understand the dual roles of NGF as a pro-inflammatory and anti-inflammatory mediator which is dependent on the type and expression of NGF receptors, cellular context, and the stage of the inflammatory process. Understating these roles is crucial to tailor the inhibition of NGF in the right place and to avoid inhibiting NGF when it has an anti-inflammatory effect. Providing more detail, El-Hashim et al. [84] pointed to the role of NGF (when administered by inhalation or intracerebroventricularly) in cough and airway obstruction in guinea pigs by increasing the phosphorylation of TrkA receptors in the bronchi. On the other hand, it was shown that the expression of anti-inflammatory mediators such as IL-10 can be induced by NGF [85].

4. Adverse effects of anti-NGF treatment

Despite the promising analgesic efficacy of anti-NGF mAbs, their development has been complicated by safety concerns, particularly regarding their long-term use. These concerns include the possibility of aggravating peripheral neuropathies and joint issues. Also, the use of anti-NGF mAbs (mainly tanezumab) in the treatment of OA was correlated with some side effects in clinical trials such as rapidly progressive OA of the knee and hip joints [13] or neurological effects [86]. Also, Bernard [87] used NGF vaccine in a mouse model of OA (destabilization of the medial meniscus) and reported the effectiveness of this vaccine in pain reduction.

Although the evidence of the efficacy for NGF inhibitors in knee OA is robust, the incidence of adverse effects increases with higher doses, longer exposure, and concomitant use of NSAIDs. In patients with musculoskeletal pain, according to Katz et al. [46], the intravenous administration of 200 μg/kg tanezumab plus an oral placebo twice a day showed analgesic effects with some adverse effects. Lane and Corr [40] discussed the efficacy of NGF inhibitors in reducing musculoskeletal pain and reported

some adverse effects associated with the use of these inhibitors, such as accelerated arthropathy. Thus, the FDA halted all anti-NGF trials due to reports of rare cases of rapidly progressive joint degeneration that necessitated joint replacement, especially in those co-treated with NSAIDs [38].

5. Future research directions

As discussed in this review, the use of anti-NGF therapy showed promising effects in alleviating different types of pain. At the same time, there are adverse effects for using this therapy. More research is needed to find out routes for applying anti-NGF directly to the site of pain and to decrease its systemic side effects. Nanoparticles can be useful in this regard. To add, combinational therapy using anti-NGF therapy with other drugs can be good area for future research. Also, there is a need to explore the efficacy of anti-NGF therapy in the long term. Additionally, it would be very beneficial if scientists could design and tailor personalized NGF therapies based on the proteomics, genetic, and metabolomics analysis of patients. Finally, more research is needed to elucidate the differential mechanisms of NGF in acute and chronic pain in order to tailor drugs specifically for each case.

CONCLUSIONS

Collectively, all of the aforementioned studies point to the effectiveness and the mechanisms of NGF in alleviating different types of pain. Future work is needed to find the adverse effects of NFG that appear when combining NGF and other drugs. Filling this gap can be effective in mitigating these problems.

DATA AVAILABILITY

Data sharing is not applicable to this article as no datasets were generated or analyzed for this paper.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Sahar Jaffal: Writing/manuscript preparation and figure preparation; Raida Khalil: Revising the manuscript.

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