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Review Article

Venom Derived Nerve Growth Factors and Their Potential Therapeutic Applications

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Abstract

Venom is a natural source of therapeutically active compounds, exhibiting pharmacological action. Nerve growth factors represent a group of proteins responsible for the upkeep and separation of thoughtful and tangible neurons of the fringe sensory system of vertebrates. Many arthropods have been the moderate source of nerve growth factors with contradictory outcomes. Many studies report many diverse nerve growth factors, which are therapeutically and biologically active but differ widely in their isoelectric properties, immunological cross-reactivity with antibodies to mouse b- NGF, endogenous levels of ester peptidase activity as well as molecular weight.

Keywords: Venom, Nerve Growth Factor, Aging and Atrophy, Anxiety and NGF, Alzheimer's Disease, and NGF

Introduction

Venom is consisting of a biologically active mixture of therapeutically active compounds such as polyamines, amino acids, peptides, neurotransmitters, and other receptors regulating lower molecular weight peptides [1]. This active complex is used by a variety of animals for defense, contestant prevention and predation [2]. However, we don't know about mammalian venom, while a fundamental pursuit of the Internet of Science Database (ISI Web of Knowledge) utilizing the inquiry term '"reptile venom" or "snake venom"' yields 4282 hits, a hunt of a similar database utilizing '" mammalian venom" or "platypus venom" and "vixen venom"' yields only 34 [3]. For centuries, science ignored the fact that mammals can be venomous and was not much studied but recently there started numerous studies in this field shows the interest in mammal venom has been increased [4]. This lack of interest in mammalian venom may be due to the unavailability of the techniques and technology to characterize the mammalian venom but now due to the advancement of the technology and techniques, the work in this area has been increased. Also, the review was written by renewed the attention by characterizing and describing the venom of mammalian order insectivore [5].

However, venom has variegated compositions and act by variegated means, all mammalian venoms share a similar history of condoning by science. For centuries there has been an extensive weighing that mammals could be as venomous as reptiles [6]. This belief, however, remained unnoticed by orthodox mammologists and was treated as folk tales. Numerous restoratively valuable

substances confined from reptilian venom give absence of mammalian venom thinks about is not because of nonattendance of offices for this sort of research [7]. One reason might be the fatalities caused by reptilian venom in humans, have gotten investigated inclination for the improvement of antisera against the reptilian venom as they are deadlier than mammalian venom. The second reason is the less amount of mammalian venom realistic for examination [8].

Neurotrophins characterize a family of structurally associated proteins, critical for neuronal expansion, restoration, endurance, death, and elasticity. According to the conventional neurotrophic supposition, neurotrophins are generated in less quantity and the endurance of inner vanning neurons is reliable on winning the struggle for enough amount of these factors [9,10]. Nerotropins include quality relatives like neurotropins-3 (NT-3), mind determined neurotrophic factor (BDNF), neurotrophin-4/5 (NT-4/5), and nerve development factor (NGF), as universal in the animal kingdom, neurotrophins are found both in vertebrates and invertebrates [11]. It is a fact that neurotrophins are very significant in the regulation of peripheral and central nervous systems, they also have many critical roles in the central nervous system, as in spermatogenesis, regulation of skin and immune system, and in kidney and cardiac development [12]. In mammals very, diverse organs and tissues can produce NGF (such as skin cardiomyocytes, epididymis and testes, salivary glands, and in addition to these also the cells of the invulnerable framework [13].

Nerve growth factors represent a group of proteins responsible for the upkeep and separation of thoughtful and tangible neurons of the fringe sensory system of vertebrates [14]. The nerve-development factor is a gathering of proteins that particularly energize the arrangement of nerve strands from the explants of thoughtful ganglia and embryonic dorsal root *in vitro* [15]. The finding that such substances exist was made by Levi-Montalcini and Burger in 1951 and from their part of work on the organic properties of nerve-development factors both *in vivo* and *in vitro* [16], has been expressed, much in them by Levi-Montalcini and her coworkers for a survey see [17]. The fundamental wellspring of NGF is the sub-maxillary organs of male mice and certain snake venoms [17,18]. NGF is distinguished to be communicated in smooth muscle cells, glandular cells like salivary organs, provocative cells, epithelial cells and fibroblast cells, pee, serum and salivation, and placenta and sex organs. NGF has likewise been distinguished in the honeybees, scorpions, and snake venom [19].

NGF is formed as a complex of 130,000 Mw (7s) in the murine submaxillary gland. This mixture contains three further units: α, β, and g, theses subunits separate at the acidic pH, which makes it possible to separate the active β subunit from the NGF complex [20]. The β subunit, additionally called b-NGF (2.5 s) is the dynamic segment of the NGF complex and has every one of the properties characterized for the NGF [21]. Many Snake species have been the moderate source of nerve growth factors with contradictory outcomes [22]. Many studies report many diverse nerve growth factors, which are therapeutically and biologically active but differ widely in isoelectric properties, immunological cross-reactivity with antibodies to mouse b- NGF, endogenous levels of estero peptidase activity as well as molecular weight [23]. These changes come from the abnormalities of different isolation procedures used or possibly due to the marked heterogeneity of the fractions used in these studies. Snake venoms have an adequate quantity of NGF [24]. There are three groups of snakes: Elapidae, Viperidae, and Crotalidae. Every one of the snakes from these families has distinctive isoforms of NGF. Many vertebrates' species at maturity make and store a huge quantity of GFs in specialized structures [25]. To the extent NGF is related, it is the top identified GF between constantly increasing GF molecule, it is available in all the three groups of snakes: Viperidae, Crotalidae, and Elapidae, it is available in the seminal plasma of bull and guinea pig and the prostate gland of guinea pigs [26].

NGF up-manages the statement of lattice metalloproteinase 9 (MMP-9; sort IV collagenase), which cuts crucial intercellular associations (α6, β4 integrin in hemidesmosomes and desmoglein in desmosomes, separating adherens intersections, desmosomes, and tight intersections) improve cell spreading, the way toward discharging cells from their environment and letting migration [3,27]; in the wake of injuring. Furthermore, it has been noticed that NGF improves the motility of an extensive variety of cells, including endothelial cells, human typical dermal keratinocytes, and fibroblasts [28].

NGF in saliva with other motility factors such as Trefoil Factor Family 3 (TFF3) can act as fast epithelial restoration seen in the oral cavity [29]. Epithelial cells must endure during the restoration process NGF can go about as a perseverance factor for human dermal keratinocytes through TrkA likely saving sufficient levels of hostile to apoptotic protein Bcl-2 [30]. By the compensation, expansion of different cell sorts, including fibroblasts, endothelial cells, and keratinocytes is vital for wound recuperating. NGF spurs multiplication of human ordinary skin keratinocytes in measurement subordinate way, and same is the case also for human oral keratinocytes [31]. The tissue remodeling and deposition of collagen is the last stage in wound healing. In these processes' fibroblasts play a dominant role. They make and secrete proteoglycans, collagens MMPs, and fibronectin. NGF up-controls the outflow of MMP-9 [32].

NGF can increase the Na+ uptake per mg 2 to 3 times that of untreated cells by increasing the sensitivity to cholinergic agonists. As cells can form long neurotic outgrowths in response to NGF, the uptake was normalized into cells grown under different conditions based on protein content [33]. The control NGF- treated and control cells both grew exactly at the same rate. In contrast to that Gunning et al. (1981a) stated that cells can gradually increase their protein to DNA ratio in response to NGF [34]. As the PC12 cells have a high affinity for muscarinic antagonist quinuclidinyl benzilate (QNB), treating the cells with β-NGF QNB binding sites are increased and after two weeks maximum binding was seen. Also, muscarinic antagonists have much more good inhibiting QNB quality than d-tubocurarine [35]. NGF treatment does not affect the quality of Na channels in PC12 cells, but it increases the quantity of Na channels [36].

High resistance is shown by the Na channels in the heart to TTX by several species. Enervated adult mice and fetal mammalian muscle Na channels also show resistance for TTX. Low-affinity TTX, Na channels in muscles are associated with innervation and muscle development [37]. After denervation of adult muscle, TTX-resistant Na channels appear that account for 25- 30% of the Na conductance. NGF can be noticed in human saliva and 1-10 ng/ml NGF has been valued in human saliva through enzyme-linked immunosorbent assay ELISA [38]. Human saliva contains different forms of pro-NGF and not mature NGF, while mice have mature NGF. Immunostaining of biopsies showed pro-NGF as the main form of NGF and not the mature NGF [39]. Typical oral mucosa demonstrates the occurrence of genius NGF in every single epithelial layer, whereas upper spinal and granular cells layers staining observed mature NGF. Fibroblasts and leukocytes, mutually in inflamed and healthy oral mucosa, express both mature NGF and precursor form [40].

NGF From Platypus

The uncommon indications of platypus envenomation give platypus venom may have remedially and possibly critical substances, however, we know next to know about platypus venom. The investigations up to have demonstrated that platypus venom has nineteen valuable peptides divisions alongside non-peptide parts [41]. Upton yet just three sorts of peptides C-sort natriuretic peptides (OvCNPs), defensin-like peptides (OvDLPs), and nerve development factor (OvNGF), have been perceived and completely sequenced however their correct capacity has not yet been known. The nerve development factor protein secluded from platypus venom is 13 kDa in estimate [42].

All the platypus venom tried for quality articulation design up-to yet, OvDLP-An is the main quality being communicated in the venom organ. OvCNP and OvNGF like those like OvDLP-B and OvDLP-C are the qualities that have venom-related capacities as well as have the different parts as they are communicated in various tissue [43]. These qualities are communicated both in males and females and have more extensive parts than just the venomous qualities.OvNGF is communicated in somewhat more elevated amounts in venom organs than in different tissues which give OvNGF might not have the capacity of poison [44]. OvNGF is likely communicated in the venom organs since it is glandular tissue. On the off chance that if OvNGF from platypus has venom part, then it might be the immunogenic impacts depicted before, for example, chemokine movement, pole cell granulation, and histamine discharge, in comparative route to that of OvDLPs, which are non-neuronal impacts [45].

Structural Assessment of Nerve Development Factor from Bothrops Jararacussu Venomous Gland

A section of c-DNA coding for an NGF isolated from B. jararacussu has 241 deposits of prepro-NGF and 118 buildups of the develop Bj.NGF. The association of expected BJ-NGF precursor indicates similarity to that of NGF precursor from N. naja, B. multicinctus, and A. h. Pallas with boundlessly shielded C-terminal range in the develop NGF protein [46]. Viperideae venom NGFs are glycoproteins, distinguishing them from mammalian and cobra venom NGFs. Asn23 is most likely an N-glycosylation site in NGFs from A. h. Pallas, B. jararacussu, C. d. terrificus, V. r. russelli, and B. multicinctus [47]. It is astounding that N-glycosylation area is so close to the invariant val21 and Trp20 deposits. Val21 is required for NGF, as evidenced by site coordinated mutagenesis studies on chicken NGF, and it may be associated with the NGF receptor restriction site [48].

Therapeutic Application of NGF

Aging Atrophy and NGF

Aged rats have reduced their spatial learning ability, greatly improved by using an intravenous dosage of OX-26NGF. NGF dose has characterization to increase the cholinergic body size in basal forebrain due to this increase the spatial learning ability of aged rats [49]. However, giving NFG to young rats cause intact cholinergic fibers sprouting, resulting in undescribed changes in basal forebrain system function and behavior changes [50]. Aged mice body size increases through OX-26NGF triggers the nuclear process to reduce junction in malnutrition aged cholinergic neurons. It was found that giving OX-256NGF dose to aged rat increase the cell size, not cell number [51].

Molecular Evolution of NGF in Advanced Snake Venoms

Enlistment of venom organ quality in venom creatures is not always dependent on the quality of duplication events. However,

in venom organs natural protein may be transmitted in huge amounts which imbedded in supplicate, exasperates the body's normal ability [52]. In propelling wind venom this method is used for the improvement of NGF even if NGF in venom organs is not overexpressed in all advanced snacked, the venom can still be harmful full and cells lacking tyrosine kinase (TrkA) receptor are susceptible to apoptosis [53].

Hematology and NGF

NGF and SP mechanism in which platelets shape change was not similar with important peptides such as polyornithine, which have a strange interface with the platelets layer. NGF and SP were also responsible for the alteration of platelet shape that was change not due to 5-HT released by platelets. 5-HT was receptor blocker methylsergide reduced 5-HT capacity to change shape, while having no effect on the capacity of MGF and SP [54]. NGF amount (EC50 5.7*10-7 M) use to change the shape of platelets was significantly larger than the amount requires to activate fiber outgrowth in isolated neuronal call (EC50 2*10-11M). In organ culture throughout ganglia, comparable fixation was predicted to increase tyrosine hydroxylase execution [55].

NGF and anxiety

NGF and anxiety relationship was checked by performing on an experiment in which animal model revealed that production of NGF in circulation during anabolic action due to aggressive activity, rather to lack of control in flight like situation, especially indicated by fear like reactions [56]. Furthermore, a high level of NGF in mice is reduced and subjected to frequent failure as compared to dominant attaching rat cognitive signals including uncontrollability can lead to an increase in NGF agonistic conflict. NGF concentration in circulation released by the submaxillary gland during flight conditions in male mice is strong evidence of NGF participation in neurobehavioral systemization in mammals. Moreover, this data suggest that social stress can affect NGF serum level [57].

More research suggested that panicogenic stimuli, which are most likely psychological substrates or are release into the blood stream. Particularly increase the amount of NGF after a fight between two male mice show a high degree of selectivity, while part of physiological alters the reaction of the organism to the stressful condition [58]. However, mice fighting NGF amount, and individual stress had a strong relationship regardless of aggressiveness, while the level of NGF serum in defeated animals was almost double then-dominant mice [59].

Elevated Level of NGF in Humans During Anxiety

Human NGF levels could be increased during emotional states. Soldiers who have never experienced parachuting have a higher level of NGF in their plasma as compared to the control one. Surprisingly, soldiers who participated in parachuting had not only an increased level of circulating NGF in the plasma after the jump, but they were also found to have an elevated level of NGF in the plasma in the blood before the jump, implying that not only anxiety but also anticipated anxiety, can raise blood NGF concentration [60].

Adrenocorticotropic hormone and cortisol levels are the opposite case, which only increased after the parachutes' jump in blood. These finding matches with the other data, that NGF level is increased with the drug withdrawal in drug-addicted persons, which suggests that there is a correlation between drug addiction and withdrawal distress [61]. Additional conditions characterizing anxiety in humans such as quitting smoking or caring for a seriously ill wife, both are stressful conditions associated with anxiety and an increased level of NGF in the blood is observed in these conditions [62].

NGF In Oral Pit and Role in Wound Mending

NGF various types introduced in the spit are known as "luminal reconnaissance peptides" because they can reach their receptors in the basolateral film exposed by mucosal damage. When injured, the star NGF and NGF receptors show on keratinocytes, in normal conditions can't get to because they are closed from the oral liquid compartments [63]. Because of the seepage caused by the lesion, plasmin compound is produced, which separates the dormant type of NGF: expert NGF from the dynamic type of NGF and develops NGF. When NGF reaches TrkA receptors on the injury's margins, it promotes healing and compensation [64].

In the 1970s, it was demonstrated that removing the submandibular organs from testing mice reduced the recovery time from cautiously administered damage. When NGF was applied topically, it incredibly expanded the speed of twisted recovery in sialoadenectomized animals, demonstrating NGF's role as a cutaneous injury healer [65]. After 20 years of this, works same outcomes were acquired in people. For the treatment of infinite skin ulcers and endless corneal neurotrophic factors, researchers used murine NGF restricted from murine submaxillary organs (mNGF) [66]. When mNGF was applied topically to both conditions, it demonstrated amazing results in curing them, but conventional medications had absolutely little effect on them. After this, NGF was used to treat wounds in healing-impaired diabetic mice, and healing was considerably improved. Additionally, m NGF showed promising outcomes in the treatment of diabetic foot ulcers, leg ulcers, and corneal ulcers in diabetic people. m NGF applying treatment has the advantage of having no negative effects in the patient before or after the experiment, as well as causing no antibodies against the murine NGF [67].

Treatment of Corneal Neurotropic Ulcer Through NGF

A human corneal neurotrophic ulcer is an optical pathology that causes vision loss due to a wide range of exogenous and endogenous abuse. Since the late 1990s, a steady stream of corneal ulcer patients (more than 200) has found NGF effective as eye drops, when regular treatments such as antitoxins, artificial tears, delicate contact focus point swathing, and eye fixing have proven to be ineffectual. Ulcer severity or depth in the stromal layer, as well as the reason for the ulcer and the patient's age, did not affect NGF recovery. There were no major side effects or antibodies against NGF during the treatment [68].

Treatment of Ischemia Through NGF

Myocardial ischemia causes a two-fold increase in mRNA levels, which is followed by reperfusion. During hind limb ischemia caused by femoral artery obstruction, and increased articulation of NGF in the gastrocnemius and adductor has been seen. R revascularization process begins when the patient receives numerous subcutaneous injections of NGF, which increases the number of arterioles [69]. This research was the first to show that NGF increases the number of arterioles in ischemia of the hind leg. Reparative vascularization is accomplished through the upregulation of NGF, which occurs because of femoral artery occlusion in mice due to ischemia. Immunosorbent assay and ELISA were used to assess the upregulation of NGF and TrkA receptors in ischemic muscles [70].

Murine Neutrophils Function Improvement Through NGF

(2.5s Nerve Development Factor Upgrades Survival, Phagocytosis, and Superoxide Creation of Murine Neutrophils) NGF increased the survival of neutrophils separated from the peripheral blood and peritoneal pit. NGF is not detectable in the blood of adult mice under normal conditions, but it is elevated to 5300 ng/ml after stress, such as fighting. neutrophils level is increased by the NGF in the bloodstream, excitement, exercise, epinephrine administration, and many other types of stress cause neutrophilia, therefore the number of neutrophils increases in the blood [71]. Furthermore, the NGF is released by the fibroblasts, growing nerves, and the amount of NGF secretion in various neuronal cells containing tissues is increased after the injuries in these tissues. NGF also stimulates PMA and opsonized zymosan-induced superoxide generation by peritoneal neutrophils [72], with protein kinase C acting on post-receptor sites and PMA acting as a direct activator of protein kinase C. Alternatively, opsonized zymogen is responded upon by surface membrane receptors [73].

NGF Metalloproteinase

Many NGFs have been isolated from all three snake families: Elapidae, Viperidae, and Crotalidae. Like the activity of snake venom vascular endothelial growth factor (VEGF), venom produced NGFs replicated capillary sprouting, migration, and further angiogenic activities, and this may be the finest medical tool to explore NGF actions [74]. Nerve growth factors suppress venom metalloproteinase-dependent proteolysis, due to the presence of greater NGF in viper venom than metalloproteinase is assumed to be owing to NGF's preventative role in venom autolysis [75].

Nerve Development Factor in Various Scleroses

Numerous types of sclerosis are safe interceded state of the focal sensory system, in different sclerosis, the myelin sheath of nerve filaments is devastated. Mind inferred neurotrophic components (BDNF) [76], Nerve development factors (NGF) are thought to have parts in favoring remyelination, recovery, and keeping the neuronal passing and recuperation procedure. Various scleroses are degenerative and incendiary ailments, arranged by assorted procedures of demyelination axonal misfortune. Through examinations, it was demonstrated that NGF could bring myelin repair. Neurotropic components are discharged amid intense activities in both sound and MS patients which might be included in the gainful impacts of vigorous preparation [77]. h-NGF presentations through intracerebral-ventriculer (ICV) into the non-human primates have turned out to be powerful in decreasing demyelination, different research is yet going ahead to watch advantages of NGF in numerous sclerosis illness, through hyper responses of an insusceptible framework in various sclerosis, harm to neurons happens which have observed to be switched by NGF [78].

NGF-Based Quality Treatment for Alzheimer's Malady

NGF organization specifically into the CNS is a promising course to intercede the disturbance of NGF development or debasement in clinical trials. Tuszynski et al. demonstrated that 22 months following the implantation of autologous fibroblasts hereditarily changed to express human NGF into the forebrain of six subjects, a change in the rate of psychological decay was watched [7,79]. This trial proposes that NGF may diminish cholinergic neuron misfortune in Advertisement. Another investigation on quality treatment for Promotion gave an account of the conveyance of NGF using an NGF-delivering, hereditarily built typified human cell line [80]. At a year, the inserts were effectively evacuated and industrious NGF emission was examined in half of the patients. Also, adeno-related infection (AAV) is the most generally utilized vector for quality treatment in clinical trials concentrated on Advertisement [81]. One investigation gave an account of the utilization of AAV2 as the vector to convey NGF quality into the reciprocal core basalis of Meynert of Promotion patients. Following 2 years, positron outflow tomographic imaging and neuropsychological testing demonstrated no proof of quickened decrease [82].

Conclusion

Venomous animals are excellent candidates for the derivation of pharmacologically active compounds. Both in vitro as well as *in vivo* investigation recognizes their vital role in the development of new therapeutic compounds. Nerve Growth Factor is a Nerve-development factor, gathering of proteins that particularly energize the arrangement of nerve strands. In this review, an attempt was made to explore the therapeutic involvement of nerve growth factors in different diseased and unusual conditions.

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