Nerve growth factor regulates nociception in human health and disease

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In this review, evidence is marshalled for the hypothesis that nerve growth factor (NGF) regulates nociception in human health and disease. The data from humans complement the studies of NGF in animal inflammatory pain models described elsewhere in this issue. An attempt is made to unify the role of NGF in inflammatory and neuropathic hyperalgesia. Although largely speculative at this stage, human conditions are discussed that may present with pain related to alterations of NGF activity—these may provide suitable models for the study of mechanisms of NGF and pain in humans, and new NGF-related prophylaxis and therapies. The “hyperalgesic” conditions include arthritis, some small fibre neuropathies, painful hypertrophic scars, sunburn, urinary bladder pain, migraine and vascular head pain. The “hypoalgesic” group includes leprosy neuropathy. Other conditions, including the major neuropathies that occur after trauma and diabetes, are more complicated and may display different NGF-related features during their development.

A neurotrophic factor may be defined as an endogenous substance that plays a role in the development, maintenance or regeneration of the nervous system. Trophic factors act via their high-affinity receptors on specific nerve cells to influence their survival and gene expression. Recent studies have identified a number of neurotrophic factors which play specific roles in the development, maintenance and regeneration of subpopulations of peripheral nerve fibres [24, 39]. The classic neurotrophic factor, NGF, is a protein normally produced by cells in the target organs, such as skin, blood vessels and the bladder; the NGF is secreted, then taken up by sympathetic and small sensory fibres via a high-affinity receptor (trkA), and transported retrogradely to the cell body [2].

In adults, NGF is necessary for the survival of sympathetic fibres, and for phenotypic properties of small sensory fibres, such as expression of neurotrophic factor-related properties of peripheral nerve fibres (for example, it is chemotactic for cultured human melanocytes and enhances their dendricity [64]: transfer of pigment via dendrites to keratinocytes determines skin colour.

Key words

Nerve growth factor and nociception

Failure of neurotrophic interactions between the target organ and its innervation may result in nerve dysfunction, degeneration and abnormal sensation [3]. NGF deprivation in animal models of disease leads to reduced expression of neuropeptides substance P and calcitonin gene-related peptide (CGRP), and of components of axoplasm which are vital to the integrity of the distal axon, particularly cytoskeletal proteins. Accordingly, skin nociceptor function (e.g. axon reflex vasodilatation, which is at least partly mediated by substance P and CGRP in unmyelinated afferent fibres), is reduced in these conditions. In contrast, NGF excess, as found in animal models of inflammation, may produce hyperalgesia by (a) directly sensitizing nociceptors; (b) increasing levels of substance P and CGRP, which may play a role in central sensitization and neurogenic inflammation; and (c) local effects, such as release of histamine from increased numbers of mast cells. In a transgenic mouse, overexpression of NGF was associated with mechanical hyperalgesia similar to that in rats after a systemic injection of NGF (for a review of these mechanisms, see Lewin and Mendell [39]).

EFFECT OF NERVE GROWTH FACTOR ADMINISTRATION IN HUMANS

A recent study provided the first demonstration that systemically administered NGF in pharmacological doses may produce hyperalgesia in healthy humans [53]. The subjects were given recombinant human NGF (rhNGF), either i.v. or s.c., at doses ranging from 0.03 to 1 µg kg⁻¹. The systemic effects, which were dose dependent and more apparent in the i.v. group and in women, comprised mild to moderate pain with swallowing, pain in the masseter muscles increased by chewing, sore throat and pain with eye movements. The myalgias were less prominent in distal abdominal and limb muscles.

Petty and colleagues suggest two possible explanations for this topography: “the shorter sensory fibres are affected first, reflecting the...
different time for retrograde transport of NGF along axons of short versus long nerve fibres”, or, alternatively, that it reflected “the shorter distances from the affected regions’ dorsal root ganglion cells to their central connections”. Given that these effects began in the i.v. group about 60 to 90 min after administration, these are unlikely explanations. In my view the myalgic effects of rhNGF may be mediated via local inflammatory cells, such as mast cells, in these regions and consequent sensitization of muscle afferents. The description of these effects of rhNGF is reminiscent of the clinical and neurophysiological effects of inflammation in muscle, where lowered sensory thresholds have been invoked to explain the tenderness of inflamed muscle and movement-related pain [47]. Most free nerve endings in muscle are found in the walls of arterioles and surrounding connective tissues. Direct action of rhNGF on muscle nociceptors is possible, but unlikely: it could explain the topography only if the density of such endings, or local chemistry including availability of endogenous NGF, is relatively higher in these regions. The apparent susceptibility in women in this study has to be regarded with caution, as the numbers studied were small, and pharmacokinetic modelling was not possible. However, sex differences with respect to NGF activity are mentioned later in this review.

In the s.c. group, rhNGF produced an injection-site hyperalgesia about 2.5 cm in circumference, with the skin in this area described as “extra-sensitive” when leaning against the region, or when taking a shower (we are not told whether this is a hot or cold shower: we presume hot!). The duration of the local hyperalgesia ranged from 1 to 49 days, and was not associated with spontaneous pain, redness, warmth or swelling of the injection site. The local hyperalgesia following s.c. rhNGF is likely to be mediated by sensitized unmyelinated afferents bearing trkA receptors, and, in addition, central effects. It is similar to mechanical and thermal (heat) hyperalgesia after topical application of capsaicin, soon after local redness and spontaneous pain have subsided [7]. No quantitative sensory or sympathetic fibre test results are reported in the rhNGF administration study, in either the i.v. or s.c. groups, and generalized subclinical effects on nociception cannot be discounted.

Nerve growth factor and hypoalgesia

HUMAN SYNDROME OF “NERVE GROWTH FACTOR DEFICIENCY”

Anand and colleagues have described the first clinical syndrome attributed to the deficiency of a neurotrophic factor, nerve growth factor (NGF) [15]. The patient presented with autonomic failure, and was demonstrated to have complete loss of adrenergic sympathetic function and of sensory neuropeptides substance P and CGRP, with undetectable NGF in skin and sural nerve. Skin capsaicin and histamine-induced axon reflex vasodilatation were markedly diminished, and the patient did not find the injection of capsaicin painful (in contrast with inept venepuncture), at capsaicin doses that were marked 6-8/10 by most normal subjects on a visual analogue scale. Her warm and cool sensory thresholds were within normal limits, but heat pain threshold was elevated. Although the findings must be interpreted with caution, as she had significant loss of unmyelinated fibres on sural nerve biopsy, and quantitative mechanical nociception tests were not performed, NGF may particularly regulate chemical and heat nociception in humans.

LEPROSY

Leprosy affects between 10 and 15 million people, and is one of the commonest diseases of the peripheral nerves worldwide. The earliest reported nerve lesions in human leprosy and animal models are in unmyelinated fibres and their Schwann cells [57], along with early loss of pain and temperature sensation, skin flare responses and sweating. Schwann cells of unmyelinated fibres serve as the host for *Mycobacterium leprae*. Although antibacterial drugs are effective, failure of nerve regeneration, especially nociceptor sprouting within skin, leads to trophic ulcers and mutilation, which remain a major cause of disability. The skin lesions in the early indeterminate and tuberculoid forms of leprosy, which are superficial and relatively well circumscribed, provide a unique opportunity to study the role of NGF in neuropathy. These lesions show hypoalgesia and hypopigmentation, in addition to hypohidrosis.

The previous work of Anand and others provided indirect evidence that NGF is implicated in leprous neuropathy, both in humans and in animal models. We first studied sensory neuropeptide levels in a mouse footpad model of leprosy; substance P concentration was reduced in sciatic nerve and ipsilateral spinal cord [5]. Substance P-immunoreactive fibres were undetectable in skin biopsies from patients with leprosy: markers for the presence of nerve fibres (PGP 9.5, neurofilaments) were seen in all 14 cases of indeterminate type, 15 of 43 tuberculoid cases and 33 of 43 lepromatous cases [36]. However, substance P-immunostaining was completely absent. Our recent study shows that NGF concentration is indeed decreased in leprous-affected human skin and nerve [14].

A study in leprosy patients showed no difference in the number of melanocytes and amount of pigment in hypopigmented lesions when compared with adjacent normal skin: it was suggested that the hypopigmentation could be caused by defective transfer of melanin into keratinocytes [56]. Cell culture studies of melanocytes show that they express functional NGF receptors, that NGF is chemotactic to melanocytes and that NGF increases the dendricity of melanocytes [64]: pigment is transferred from melanocytes to keratinocytes to determine skin colour.

The evidence cited above has led to our hypothesis that nerve fibres and melanocytes are deprived of NGF in leprosy. It is of interest that a targeted mutation of the gene coding for the low-affinity NGF receptor in the mouse leads to markedly decreased substance P and CGRP innervation of
footpad skin, and to development of ulcers and mutilation of the feet [38]. NGF may provide a rational treatment to restore nociception in leprous neuropathy.

**Nerve growth factor and hyperalgesia**

**SUNBURN**

A number of the clinical and neurochemical changes in leprosy described above appear to be the opposite of changes in models of sunburn [32]. Ultraviolet irradiation of skin produces erythema, hyperpigmentation and pain: it induces NGF mRNA in cultured keratinocytes, and long-term increase in the CGRP concentration in the dorsal spinal cord. It may be speculated that sunburn is, in a sense, the “opposite” of leprosy, with NGF expressed by basal keratinocytes driving the changes. In acute or severe sunburn, pigmentedary changes may provide an in vivo “bioassay” of NGF activity in skin.

**ARTHRITIS**

There is good evidence that raised endogenous concentration of NGF is related to the hyperalgesia in animal models of arthritis, probably by sensitization of articular small afferent fibres, and central changes, possibly related to increased concentration of NGF-dependent substance P and CGRP in sensory fibres [25, 39].

In humans, there is a report of the presence of NGF in the synovium and synovial fluid of patients with chronic arthritis, but not in the control synovial fluid [1]. We have reported increased intradermal capsaicin-induced axon reflex vasodilatation over the joints of patients with rheumatoid arthritis, but not in regions distant to the joint [35]. The mechanisms involved in this phenomenon are uncertain and deserve further investigation, but findings in animal models may provide an explanation. Substance P, which is present in unmyelinated afferent fibres and at least partly mediates axon-reflex vasodilation, is increased in skin in a model of inflammatory arthritis [25]. Substance P, in turn, is regulated by NGF [40], as is capsaicin sensitivity of sensory neurones [63]. Increased NGF concentration in skin overlying inflamed joints may thus account for our findings.

**URINARY BLADDER PAIN**

There is evidence from animal models that urinary bladder inflammation and hypertrophy are associated with increased NGF concentration and related sensory changes [37, 61].

We have found increased concentrations of NGF in bladder biopsies of patients with painful inflammatory cystitis, and in two other conditions, sensory urgency and pain on bladder filling (“idiopathic sensory urgency”) and interstitial cystitis [13]. The control biopsies were from patients with stress incontinence. Immunostaining showed increased NGF expression in the basal urothelium in all disease groups. The mechanisms of pain in idiopathic sensory urgency and interstitial cystitis are not understood. Interstitial cystitis, which is an idio-

pathic condition with suprapubic pain and urinary frequency, is marked by increased mast cell numbers and suburothelial innervation; it has been suggested that the pain is the result of degranulation of mast cells [19]. There is also a suggestion that women with idiopathic sensory urgency may have early interstitial cystitis [29], although the hallmarks of the latter were not present in the biopsies of our patients with idiopathic sensory urgency. An increase of NGF concentration in these patients may explain the increased number of mast cells, their degranulation and sensitization of bladder afferents. Although intravesical instillation of capsaicin to desensitize afferents has been shown to be helpful in hypersensitive disorders of the urinary bladder [17], in support of our hypothesis, anti-NGF treatment may be more rational and consistently effective in such patients with intractable bladder pain.

**PAINFUL HYPERTROPHIC SCARS**

Postoperative painful scars are a common but underestimated and undertreated condition. They may be distinguished from nerve trunk injury and entrapment in fibrous tissue by the following definition: persistent pain in a healed postoperative scar of more than 3 months’ duration, with allodynia and hyperalgesia adjacent to the scar, and with no sensory loss other than over the scar itself. Painful hypertrophic scars may be exquisitely hyperesthetic, as well as spontaneously itchy and erythematous: such scars show increased substance P and CGRP innervation at the base of the epidermis, in contrast with non-hypertrophic insensitive scars [51]. There appears to be a local decrease of sensory neuropeptides in normal wound healing [55].

It may be proposed that in painful hypertrophic scars both the increased number of cells producing NGF, and inflammation, may lead to the hyperinnervation and hyperalgesia. (This may also explain the greater occurrence of chronic pain when skin incisions are associated with local infection or inflammation, and delayed healing.) The allodynia and hyperalgesia adjacent to the scar are likely to be the result of central changes driven by afferents within the scar tissue, as agents such as local anaesthetics usually produce dramatic and rapid relief of the adjacent hyperalgesia when injected carefully in small quantities within the scar itself, and, with or without corticosteroids, sometimes produce long-lasting relief. Corticosteroids are known to decrease NGF expression in cultured cells [50, 58]. Painful hypertrophic scars may provide a good model to study the effect of “anti-NGF” agents administered locally in human hyperalgesia.

**ERYTHEMOMELALGIC SMALL FIBRE NEUROPATHY**

The cause of symptoms in most patients with painful small fibre neuropathies is unknown, particularly in those patients with normal thermal thresholds [59]. In some patients, the burning sensation may be associated with warmth and erythema of the extremities, described by Weir Mitchell as “erythromelalgia”. Mechanical and heat stimuli exacerbate
the pain, which may be relieved by cooling. NGF-related mechanisms are involved in such cases, especially as we have observed an increase of capsaicin-induced axon reflex vasodilatation in this condition. The syndrome may also occur rarely in patients with recognized neuropathies, as discussed in the section on diabetic neuropathy below.

MIGRAINE AND VASCULAR HEAD PAIN
The nerve supply to cerebral blood vessels plays an important role in migraine and vascular headache, via sympathetic fibres containing the vasoconstrictors noradrenaline and neuropeptide Y (NPY), and sensory fibres containing vasodilators substance P and CGRP [21, 31, 48]. The mechanisms invoked in neurogenic inflammation in migraine are similar to those in skin [3, 7].

We have measured NGF-like immunoreactivity in postmortem human cerebral vessels [8]. NGF levels were lower in anterior compared with posterior cerebral vessels in the circle of Willis, with a significant age-related decline. Our working hypothesis, that NGF may regulate the presentation of vascular headache, is based on the following indirect evidence, which may explain a number of clinical features of migraine.

The frequency and severity of migraine declines with age, as do NGF and its dependent peptides substance P, CGRP and NPY concentrations in human cerebral vessels [26]. The target organ (i.e., the blood vessel) has been shown to be responsible for the reduced cerebral vessel innervation in aged rats, and NGF infusion can reverse this neuronal atrophy [30]. NGF is produced by vascular smooth muscle cells and fibroblasts. In a study of cultured vascular smooth muscle cells, the hourly pattern of secretion of NGF was found to be elevated by alphaadrenergic receptor activation [62]. Migraine shows a familial tendency. Genetic factors may set the concentration of NGF in different target tissues: resistance vessel gene expression of NGF is elevated in young spontaneously hypertensive rats with vascular noradrenergic hyperinnervation [27]. Migraine is commoner in women. Hormonal influences may affect NGF activity by modulation of its receptors: oestrogens/proestrus upregulate NGF receptor mRNA in sensory neurones [60]. Testosterone reduces NGF mRNA in cultured fibroblasts [58]. Biopsies of tender superficial temporal arteries in migraine may show oedema, attributed to local release of substance P, and in cluster headache show increased mast cells during headache-free intervals [48]: NGF sensitizes nociceptor fibres, produces neurogenic inflammation via substance P and CGRP and is associated with increased numbers of mast cells. Corticosteroids help inflammatory vascular headache, as in temporal arteritis, and also reduce NGF synthesis [50, 58].

Diabetic neuropathy
Diabetic neuropathy comprises a number of clinical presentations that are likely to be caused by different mechanisms, which may coincide in the same patient. It has been classified into symmetric and focal neuropathies. Risk factors for neuropathy include duration of diabetes, age, male sex and height.

SENSORY AND AUTONOMIC POLYNEUROPATHY
Autonomic and sensory polyneuropathy is the most common neuropathy in diabetic patients, for which no specific and effective treatment is available. Neurotrophic mechanisms are more likely to involve symmetric rather than focal neuropathy on a priori grounds. Diabetic neuropathy affects nerve fibres that are known to be dependent on NGF and those that are not. It was proposed that NGF deprivation may determine its pattern of presentation, although metabolic or vascular abnormalities may be the cause of the neuropathy [3]. The length-dependent effect may result from abnormalities of axonal transport, including retrograde transport of NGF, observed in diabetic rats. In support of this proposal, our recent studies [16] in insulin-dependent diabetics showed an early length-dependent symmetrical dysfunction in sensory small-diameter fibres, associated with skin substance P and NGF depletion. NGF depletion correlated significantly with decreased capsaicin-evoked skin axon-reflex vasodilatation. NGF immunostaining was strongest in the basal keratinocyte layer in control skin, and was decreased in diabetic skin. NGF deprivation, from target organ failure and decreased axonal transport, may thus reduce chemosensitivity and warm/heat pain sensitivity in early diabetic neuropathy, or even subclinically in asymptomatic diabetics. Ageing appears to recapitulate these clinicopathological changes, and exacerbates them in diabetic subjects. Insidious progressive loss of nociception and axon-reflex vasodilatation in the feet may contribute to foot ulceration [52], a major and serious complication, for which early and prolonged NGF treatment at an appropriate dose may provide prophylaxis.

Animal models fail to show a number of features of human diabetic neuropathy, particularly morphologically, but are in accord with this hypothesis [12, 33]: NGF is reduced in diabetic rat nerve [33], and both NGF and NGF mRNA are reduced in diabetic rat skin [28].

PAINFUL DIABETIC NEUROPATHY
In contrast with the above description, less than 10% of patients with diabetic neuropathy in most large series develop pain. Among these are relatively rare cases with acute or severe pain with distal hyperalgesia and allodynia (very rarely erythromelalgia), which usually have early or mild neuropathy, with preservation of large sensory fibre function. In some patients, pain may be precipitated, paradoxically, by treatment of the diabetes or improvement of its control [41], and the pain is usually self-limiting. If NGF-related mechanisms are involved in such cases, it may be that skin keratinocytes, and Schwann cells which express NGF on loss of contact with the axon, are still producing substantial quantities of NGF, and that sprouting fibres in skin and nerve are exposed to
“relative excess” of NGF, or are more susceptible to NGF, thus resulting in hyperalgesia. Morphological studies of such cases show marked sprouting of unmyelinated axons [18]. In a case of acute painful neuropathy after establishment of strict diabetic control, sural nerve biopsy shortly after the onset of the pain showed prominent regenerative activity on the background of neuropathy, with no active fibre degeneration [41]. It is of interest that a hyperalgesic phenomenon occurs early after induction of diabetes in the rat [20].

Most patients with severe diabetic neuropathy develop numbness and loss of nociception. However, some exceptional patients with severe neuropathy mainly affecting small fibres, with marked loss of temperature and pain sensation, may also complain of pain: in such patients, it is more likely that a “de-afferentation” phenomenon occurs, from cell loss and atrophy. Morphologically, these cases show marked loss and centripetal degeneration of small myelinated and unmyelinated axons, though larger fibres are also affected [54]. Such cases are likely to be associated with marked deprivation of NGF, as in the late stages of neuropathy the dying-back fibres or sprouts presumably no longer innervate and take up NGF from the normal target organ (e.g. basal keratinocytes in skin), and both the normal target organ, and presumably the surrogate target organ for sprouting fibres within nerve (Schwann cells), may fail to produce sufficient NGF, as is the case at later stages in diabetic rat models. Early and continued appropriate support with NGF may prevent such a painful neuropathy.

The majority of cases do not fall into the above clear categories, may have different neurotrophic mechanisms in operation simultaneously and show no simple correlation of pain with morphological change [42]. In such cases, systemic rhNGF treatment (at doses that just fail to produce local hyperalgesia) may “paradoxically” improve sensation progressively from short to long fibres, prevent pain in the long term, and, excluding the rare early cases with distal allodynia and hyperalgesia, even ameliorate pain. The mechanisms involved in the last could include normalizing “NGF-trkA afferent disproportion” (e.g., more axonal sprouts would re-contact Schwann cells, and down-regulate their NGF expression), reversing atrophic processes, and preventing secondary demyelination.

**Traumatic neuropathy**

There is an extensive literature reviewing the pain syndromes that may follow nerve trauma. A number of different lesions may result in NGF deprivation of sensory neurones, including the removal of the target organ, cutting or crushing the nerve and blockade of axonal transport [10, 11, 45]. Crushing a peripheral nerve results in the induction of NGF synthesis by Schwann cells at the site of the lesion and the distal stump: the up-regulation of NGF synthesis after injury has been attributed to factors released by invading macrophages, including interleukin-1 [34]. The amount of NGF available to the injured fibres is insufficient to restore normal substance P concentration; NGF receptor down-regulation in injured fibres may contribute to this insufficiency. However, when regeneration is complete, the target tissue is able to supply sufficient NGF to restore normal substance P concentration in sensory fibres.

We have studied NGF expression in patients with peripheral nerve injury [6]. In biopsies taken proximal and distal to the injured region from patients undergoing peripheral nerve repair, NGF concentration was reduced when compared with intact nerve, but was generally higher in distal when compared with proximal segments in the more complete nerve lesions. NGF staining was present in Schwann cells in distal segments, including pockets of high expression in neuromas, but not in proximal segments or control nerves. Using the same argument as for early diabetic neuropathy presented above, fewer axonal sprouts with less competition for normal or even reduced NGF concentration, but relative excess, may lead to hyperalgesia, either in nerve trunks or the target organ (it is not suggested that this is the sole mechanism, but a possible contributory factor). In cases of nerve injury, unlike diabetes, the target organs probably do not lose their ability to continue to produce NGF: we have measured the concentration and immunostained substantial amounts of NGF in Schwann cells of the distal nerve stump in a patient 9 months after complete Wallerian degeneration. In some patients, with re-innervation of the skin of the upper limb months to years after nerve repair, there is marked hyperalgesia and allodynia, and exquisite capsaicin sensitivity: this, too, may be explained if few sprouts enter into the skin and encounter a relatively high availability of NGF in the target organ, that is, “NGF-trkA afferent fibre disproportion”. The status of trkA on sensory and sympathetic fibres in human neuropathies is not known, nor is the effect of sympathetic fibre dysfunction, loss or regeneration on the processes described above.

There is evidence that some processes involved in determining the course of pain after nerve injury may not be related solely to NGF in the periphery. In comparing the consequences of nerve injury in human and rat neonates and adults, only the adults develop intractable neurogenic pain or autotomy; as there does not appear to be a qualitative difference in NGF changes in neonatal and adult injured nerve, the lack of chronic pain in neonates may result from spinal cord plasticity and adaptation, which may fail in adults [4].

**Regulation of nerve growth factor expression**

Cell culture studies suggest that NGF expression is highest in rapidly dividing keratinocytes.

In our recent studies, NGF concentration was higher in primary cultured keratinocytes than in freshly isolated keratinocytes or culture through multiple passages [9]. Viral transformation of keratinocytes with the simian virus (SV40), which induces simple epithelial differentiation, reduced the concentration of NGF. Thus, in situ hybridization
studies in rat skin [46], and immunostaining studies in human skin [16], demonstrate NGF production in the basal keratinocyte layer. The same region shows immunoreactivity for the low-affinity NGF receptor [49], which is co-expressed with a high-affinity NGF receptor trkA by unmyelinated sensory neurones. These studies support the view that NGF is trophic to the unmyelinated subpopulation of sensory fibres, which terminate in or adjacent to the region of the basal keratinocyte layer. NGF may stimulate keratinocyte growth in an autocrine manner [22, 23], and nerve sprouting in classic neurotrophic fashion in denervated skin [46].

Although a number of potential pathogenetic agents, including cytokines and growth factors, have been shown to affect skin-derived cultured cells [44], it is not known whether these mechanisms operate in human neuropathies, or whether particular agents are important in the pathogenesis of the conditions of interest. The effect of neuropeptides on NGF expression, and of chronic denervation or diabetes on keratinocyte growth, is unknown. It has been suggested that corticosterone may decrease NGF expression in diabetes, as it reduces NGF expression in cultured fibroblasts, and may be increased in streptozotocin-treated rats [50]. The relevance of this observation to human diabetes is not clear, and there does not appear to be a significant neuropathy in human diseases where the concentration of corticosteroids is markedly elevated. However, if corticosteroids do reduce NGF expression in different cell types in humans in vivo, this may help explain, at least partly, their effectiveness in relieving inflammatory pain. Sympathetic agents may increase NGF secretion by vascular smooth muscle cells [62], which has implications for vascular pain: activity-related neurotrophic changes need to be studied in the region of the basal keratinocyte layer. NGF may stimulate NGF in denervated skin [46].

Conclusions

There is increasing support for the hypothesis that NGF may regulate pain sensation in humans. NGF is increased in inflammatory conditions; re-innervation of pockets of relatively high NGF expression, disproportionately few regenerating fibres exposed to a normal concentration of NGF (with a relatively high quantity of NGF taken up by each fibre), or increased susceptibility of nerve sprouts to NGF, could also lead to hyperalgesia. This hypothesis unifies the role of NGF in inflammatory and neurogenic pain. NGF may produce hyperalgesia by peripheral and central effects. In such conditions, anti-NGF treatment may reduce hyperalgesia.

However, NGF may play a different role in the development of chronic pain that results from cell death or atrophy, and failure of adaptation in the spinal cord, for example, in de-afferentation pain. Such a mechanism may explain the much greater incidence of post-herpetic neuralgia with increasing age after the sixth decade, as neurotrophic support to small and large fibres may wane. Changes of NGF expression may, at the early stages of nerve injury or disease, form part of an adaptive response [10, 11]. Failure of this response, or of secondary adaptation in the dorsal spinal cord, may contribute to the development of chronic pain. NGF may thus, at an appropriate time, dose, site and mode of administration, provide prophylaxis and treatment in conditions that lead to chronic pain.
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