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EXPERT REVIEWS

Nerve growth factor, pain, itch and inflammation: lessons from congenital insensitivity to pain with anhidrosis

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NGF is a well-known neurotrophic factor essential for the survival and maintenance of primary afferent neurons and sympathetic neurons. NGF is also an inflammatory mediator associated with pain and itch. Congenital insensitivity to pain with anhidrosis is a genetic disorder due to loss-of-function mutations in the *NTRK1* gene encoding TrkA, a receptor tyrosine kinase for NGF. Since patients with congenital insensitivity to pain with anhidrosis lack NGF-dependent unmyelinated (C-) and thinly myelinated (Aδ-) fibers, and their dermal sweat glands are without innervation, they exhibit no pain, itch, signs of neurogenic inflammation or sympathetic skin responses. Based on the pathophysiology of congenital insensitivity to pain with anhidrosis, this article indicates how NGF-dependent neurons are essential for the establishment of neural networks for interoception and homeostasis, and play crucial roles in brain–immune–endocrine interactions in pain, itch and inflammation. In addition, it refers to involvements of the NGF-TrkA system in various disease states, and potential pharmacological effects when this system is targeted.

Keywords: hereditary sensory and autonomic neuropathy type IV • interoception • NGF-dependent primary afferent neurons • *NTRK1* gene • polymodal receptors • receptor tyrosine kinase for NGF • sympathetic neurons • TrkA protein

Pain is an unpleasant sensory and emotional experience, associated with actual or potential tissue damage, which activates specific afferent neurons termed nociceptors. Nociceptors also respond to various stimuli, including mechanical, thermal, chemical and electrical stimuli, and are therefore regarded as polymodal receptors. Nociceptors can become sensitized to these stimuli and respond more vigorously upon acute activation. Chronic pain is a major healthcare problem, with moderate-to-severe chronic pain occuring in 19% of adult Europeans, seriously affecting the quality of social and working life [1]. Recent progress using animal models and genetic studies has advanced our understanding of the mechanisms of pain [2,3]. However, the findings of pain studies when using animal models are known to be affected by a wide range of factors that must be taken into account. In addition, it is known that rodents lack specific brain structures crucial for the experience of pain in humans [4–6]. These considerations have encouraged the study of pain, not only in animals, but also in humans.

Itch (pruritus) can be defined as an unpleasant cutaneous sensation associated with the immediate desire to scratch [7,8]. Chronic itch disrupts sleep, reduces the quality of life and undermines the health of those who suffer from it [9]. Clinically, itch is one of the most common symptoms of skin diseases, and markedly affects quality of life [8,10]. Current evidence clearly indicates the existence of an interactive network between the skin and the peripheral nervous system, as well as the CNS, regulating and responding to pruritic stimuli [8]. Itch may be interpreted as a defense mechanism by which potentially dangerous organisms or stimuli in the skin and adjoining mucosa are disposed [8]. Although it is clearly distinct from pain as a sensation and also with respect to the stimuli producing it [11], itch can markedly decrease quality of life in some pathological conditions, and thus

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require treatment [12]. Chronic pruritus of any origin is frequently seen in daily medical practice, and treatment of it is challenging. Recent studies of pruritus may yield neurophysiological and neurochemical therapeutic models, and the possibility of treating patients with refractory itching of various origins [13].

Pain and itch share many mediators and/or receptor molecules, as well as primary afferent neurons and processing centers, and induce similar autonomous skin reactions [7,14]. Chronic pain and central sensitization to itch appear to be neurophysiologically related phenomena [12,14,15]. Scratching highlights the close relation of pain and itch, and itch appears to be under tonic inhibitory control by pain-related signals [8,14,15]. However, itch and pain serve different purposes. In contrast to pain-related withdrawal reflexes, itching stimuli provokes a characteristic scratch reflex, both related to the protection of the body against tissue damage. This close connection suggests that the neuronal apparatus for itch has developed as a nocifensive system for the removal of irritating objects and agents assaulting the skin; thereby protecting the body's integrity (e.g., against parasites, insects, sharp objects, irritants and allergens). Thus, the possession of skin capable of inducing the symptom of itch may have afforded a substantial advantage during evolution [14].

NGF plays a pivotal role in controlling the survival and differentiation of the nervous system during embryonic development and in the early postnatal stage. NGF is a neurotrophic factor essential for the survival and maintenance of various types of neurons; including the nociceptive neurons, autonomic sympathetic neurons and some neurons of the CNS [16–19]. Discovered as a target derived survival factor, it is known to control cell fate and axon growth and guidance, and is required for the survival of nociceptors during development. However, it may also play an important role during inflammatory processes in adult animals [18]. NGF has two receptors: the p75 neurotrophin receptor ($p75^{NTR}$), a member of the tumor necrosis factor receptor superfamily; and TrkA, a receptor tyrosine kinase. There is considerable evidence for functional involvement of $p75^{NTR}$ in mechanisms of NGF-induced neuronal modulation, nerve fiber sprouting and degeneration [19,20]. This article, however, describes a disorder due to genetic defects in TrkA, and thus focuses on this receptor. Target-derived NGF mediates biological effects by binding to and activating the TrkA receptor at nerve terminals [19,21–26]. The activated TrkA receptor then exerts local effects at nerve terminals and retrograde effects at the neuronal cell bodies that often reside at considerable distances from the terminals. Recent experiments have suggested that the major retrograde signal required for survival and expression of various genes is of activated TrkA itself [19,21–26].

Genetic studies of pain pathways have complemented the traditional neuroscience approaches of electrophysiology and pharmacology to yield fresh insights into the molecular basis of pain perception [27]. Genetic variants that interfere with pain have implications for pain medicine [28]. Congenital insensitivity to pain with anhidrosis (CIPA; also known as hereditary sensory and autonomic neuropathy type IV) is an autosomal recessive genetic disorder characterized by insensitivity to noxious stimuli, anhidrosis (inability to sweat) and mental retardation [29–36]. CIPA is due to loss-of-function mutations in the *NTRK1* (also known as *TRKA*) gene encoding a receptor tyrosine kinase (TrkA) for NGF [32–35,37–41]. Patients with CIPA lack NGF-dependent neurons, including primary afferent neurons with thin fibers, sympathetic postganglionic neurons and possibly several types of neurons in the brain [30–35]. NGF-dependent primary afferent neurons with thin fibers (NGF-dependent primary afferents) are defined as primary afferent neurons with small-diameter, thinly myelinated Aδ-fibers or unmyelinated C-fibers that depend on the NGF-TrkA system during development. These neurons include polymodal receptors [42], and probably a subpopulation of C-nociceptors, which do not respond to mechanical stimuli, and thus are not polymodal, but exhibit discharge patterns associated with the sensation of itch [43] and nociceptors with low electrical thresholds, and are thus unlikely to be mechanically insensitive fibers, which also mediate itch in humans [44,45]. Due to a lack of NGF-dependent primary afferents, patients with CIPA lack both pain and itch sensation, as well as axon reflexes in the skin associated with neurogenic inflammation [30,31,33–35]. Inflammatory responses in patients with CIPA differ from those in nonaffected individuals, and thus provide unique opportunities to explore the functions of NGF-dependent neurons in pain, itch and inflammation not available with animal studies. Although CIPA patients and TrkA gene knockout mice share some characteristic behaviors and features, some behaviors and clinical features in humans, such as anhidrosis, are not apparent or recognized in these mutant mice [33–35]. The reason for this might involve species differences or alternatively, technical difficulties in the analysis of mice. Indeed, gene knockout mice die within a month, hampering extended behavioral and neurophysiological studies of them. Patients with CIPA might, therefore, provide clues regarding use of the NGF-TrkA system as a target to treat pain, itch and inflammation.

The NGF-TrkA system is important for evolutionarily conserved biological mechanisms, including interoception, homeostasis, emotion and stress responses. All these biological mechanisms probably underlie acquired human pain states, itch and inflammation. This article is intended to provide some perspective on the roles of the NGF-TrkA system in itch, pain and inflammation. NGF itself plays important roles in inflammation and disease states and probably causes neuronal sensitization in both pain and itch. NGF and/or its receptor TrkA may, therefore, be useful as targets for therapeutic intervention in alleviating these uncomfortable conditions.

Interoception, sympathetic neurons & homeostasis

NGF-dependent primary afferent neurons have small-diameter, thinly myelinated Aδ-fibers or unmyelinated C-fibers, with cell bodies located in the dorsal root ganglion (DRG) alongside the spinal cord or in the trigeminal ganglion (Figure 1). A subset of NGF-dependent primary afferents in the glossopharyngeal nerve (IX) and the vagus nerve (X) transmit visceral afferent information to the brain from the head and neck, and from the thoracic and abdominal cavities, respectively. NGF-dependent primary afferents innervate all tissues of the body, including skin, muscle,

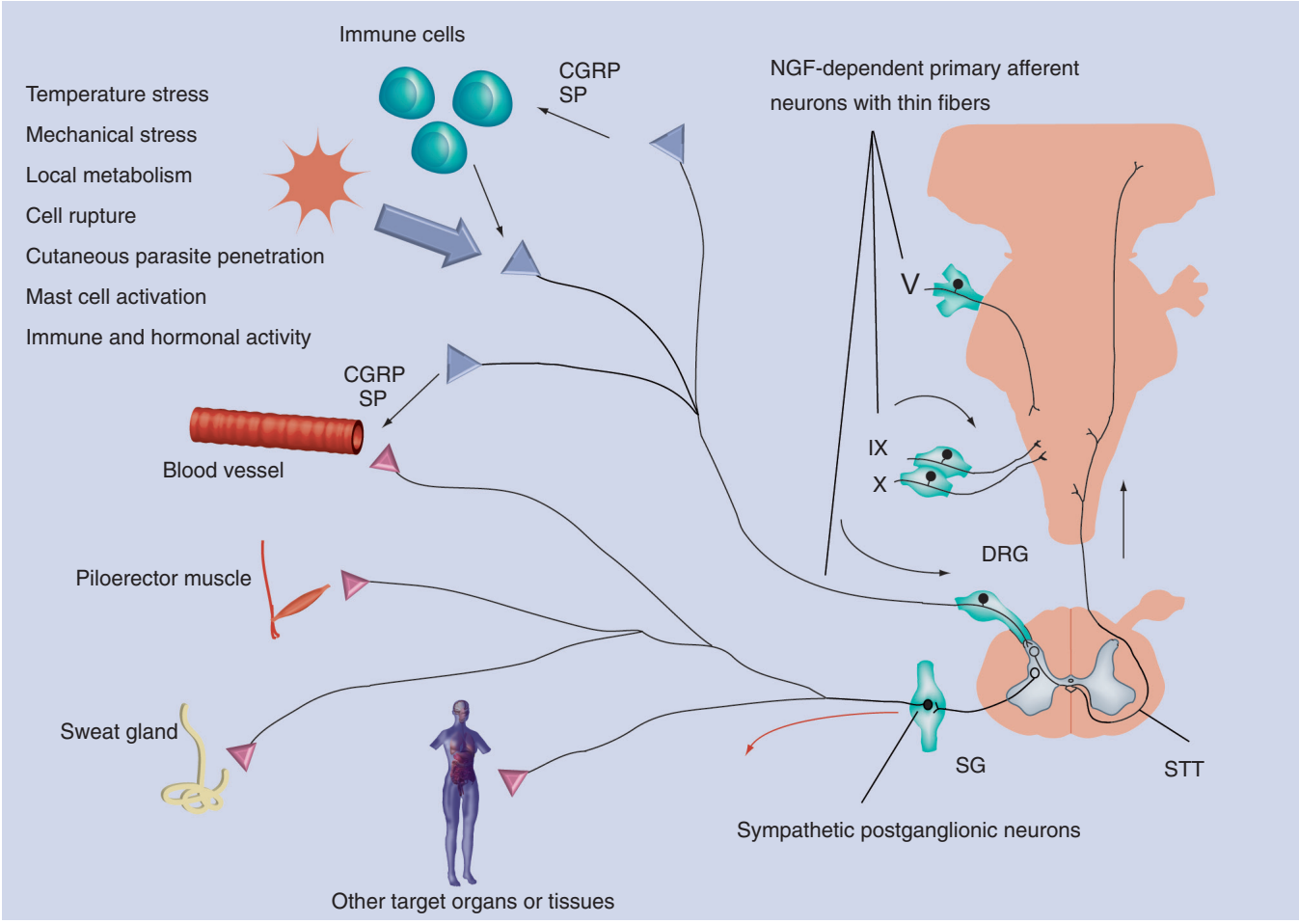

Figure 1. Patients with congenital insensitivity to pain with anhidrosis lack NGF-dependent primary afferent neurons with thin fibers (NGF-dependent primary afferents) and autonomic sympathetic postganglionic neurons. NGF-dependent primary afferents are DRG neurons or trigeminal ganglia (V) neurons with free nerve endings. A subset of neurons in the glossopharyngeal nerve (IX) and the vagus nerve (X) are probably NGF-dependent neurons. Sympathetic postganglionic neurons innervate blood vessels, piloerector muscle and sweat glands, as well as other target organs or tissues in the body. Postganglionic fibers to sweat glands are exceptionally cholinergic. Trigger factors (shown by bold arrow) may directly or indirectly stimulate NGF-dependent primary afferents. Upon stimulation, these neurons release neuropeptides (SP and CGRP), which modulate inflammation, pain and itch. Sympathetic postganglionic neurons can also influence inflammation.
CGRP: Calcitonin gene-related peptide; DRG: Dorsal root ganglia; SG: Sympathetic ganglion; SP: Substance P; STT: Spinothalamic tract.

joints, teeth and visceral tissue, and mediate various sensations, including pain, temperature and itch [11,12,46,47]. NGF-dependent primary afferents also innervate blood vessels (Figure 1). Recent studies have yielded important evidence that NGF-dependent primary afferents also transmit sensation of the body's interior; the interoceptive sense [4,6]. They are thus also referred to as 'interoceptive polymodal receptors' [35]. NGF-dependent primary afferents terminate in lamina I of the spinal dorsal horns and trigeminal nucleus, conducting information on numerous types of physiological conditions via intervening pathways (such as the spinothalamic tract) to the brain (Figure 1).

The interoceptive system is considered a homeostatic afferent pathway representing the physiological status of all tissues of the body, including the mechanical, thermal, chemical, metabolic and hormonal status of the skin, muscle, joints, teeth and viscera [4,6]. The interoceptive polymodal receptors convey slow activity that transmits changes in a wide variety of physiological conditions – not only temperature and mechanical stress, but also local metabolism (acidic pH, hypoxia, hypercapnia, hypoglycemia, hypo-osmolarity and lactic acid), cell rupture (ATP and glutamate), cutaneous parasite penetration (histamine), mast cell activation (serotonin, bradykinin and eicosanoids) and immune and hormonal activity (cytokines and somatostatin) [4,6]. Exogenous or endogenous trigger factors, including those described above, may directly or indirectly stimulate NGF-dependent primary afferents (Figure 1). Thus, interoceptive polymodal receptors comprise a homeostatic afferent pathway, rather than simply a nociceptive pathway.

Autonomic sympathetic nerves are involved in the regulation of blood circulation, lymphatic function and various internal organs, as well as the regulation of skin appendages, including sweat glands, apocrine glands and hair follicles. Sympathetic postganglionic neurons, whose cell bodies are located in the sympathetic ganglion

(SG), are also NGF-dependent neurons and innervate blood vessels, piloerector muscle and sweat glands, as well as other target organs and tissues in the body (Figure 1). Most postganglionic nerve fibers are adrenergic, while those to sweat glands are cholinergic. Sympathetic postganglionic neurons regulate sweat gland function and vasoconstriction, and thereby temperature homeostasis [10]. The blood vessels of orofacial tissues are also innervated by cranial parasympathetic nerves [10,48]. Peripheral sympathetic nerve endings are known to release neuropeptide Y; alone or with catecholamines, such as adrenaline and noradrenaline, which have synergistic effects on immune cells [49]. Thus, interoceptive polymodal receptors report the physiological status of the various tissues of the body to the brain and the brain maintains homeostasis in the body along with other autonomic, neuroendocrine and behavior mechanisms [4,6,50]. In turn, integrated feedback from the entire body plays a role in emotional experience [4,6,50–53]. NGF-dependent primary afferents and autonomic sympathetic postganglionic neurons, therefore, form an interface between the nervous system and the body [35].

Congenital insensitivity to pain with anhidrosis

Congenital insensitivity to pain with anhidrosis is the first human genetic disorder for which the molecular basis of congenital insensitivity to pain has been identified. CIPA is caused by loss-of-function mutations in the *NTRK1* gene encoding the TrkA receptor for NGF [32–35,37–41]. Defects in NGF-TrkA signal transduction lead to apoptosis of various NGF-dependent neurons during development. Consequently, patients with CIPA lack NGF-dependent neurons, and thus provide a rare opportunity to explore the developmental and physiological functions of the NGF-TrkA system in behavior, cognitive and mental activities in humans (for review, see [35]).

Patients with CIPA lack NGF-dependent primary afferents, including interoceptive polymodal receptors (Figure 1) [35]. Therefore, they are unable to respond to changes in the physiological conditions of all tissues of the body. Patients exhibit insensitivity to both superficial and deep painful stimuli, including visceral perception, but touch, vibration and position senses are normal. A subpopulation of afferents with C-fibers is believed to mediate sensual (pleasant) touch. Patients with CIPA can experience a tickling sensation. However, it remains to be determined whether they can perceive sensual (pleasant) touch. Motor function is normal, although repeated trauma can result in secondary dysfunction of the motor system. Repeated fractures, dislocations and deformities of large weight-bearing joints are slow to heal and often result in Charcot joints (i.e., neuropathic arthropathy). In addition, osteomyelitis frequently occurs in patients with CIPA.

Patients with CIPA lack an itch pathway because Aδ- and C-fibers are absent, and therefore patients do not exhibit axon reflexes (whether histamine-mediated or induced by other stimuli) (Figure 1) [33–35]. Interestingly, it is known that humans can experience itch without axon reflexes [44,45]. Histamine is a well-recognized mediator of acute inflammation and a potent pruritic agent. Various immune cells, including mast cells and Langerhans cells, as well as other cells, such as keratinocytes and fibroblasts, contribute to the multiple features of acute, chronic and allergic inflammation (Figure 1). The axon reflex is an efferent function of the NGF-dependent primary afferents, in which release of neuropeptides, such as substance P (SP) and calcitonin-gene related peptide (CGRP) (Figure 1), from the peripheral terminal induces vasodilation and extravasation of plasma [54]. The term 'neurogenic inflammation' means that signs of inflammation (e.g., tumor, rubor, calor and dolor) develop upon activation of neurons and the consecutive release of neuronal mediators (e.g., SP and CGRP) [55,56]. Neuropeptides released from NGF-dependent primary afferents induce vasodilation. It is interesting to note that these neuropeptides do not activate mast cells in humans, as shown previously [57,58]. Patients with CIPA lack the axon reflexes responsible for neurogenic inflammation. In normal individuals, CGRP-containing nerve fibers are also intimately associated with immune modulatory cells, such as mast cells, Merkel cells and Langerhans cells, suggesting a locus of interaction between the nervous system and immunological function [10]. These inflammatory processes result in modulation of immune cell function and regulation of mediator release (cytokines, chemokines and growth factors) from keratinocytes and Langerhans cells [10]. Thus, patients with CIPA might not exhibit protective inflammatory reactions due to a defect in their axon reflexes.

Patients with CIPA also lack sympathetic postganglionic neurons (Figure 1) [33–35]. Sweating is controlled by the sympathetic nervous system and is important in maintaining body temperature, especially in humans. Because patients with CIPA do not sweat, they tend to develop hyperthermia when they are in a hot environment. Patients lack not only the thermal sweating, but also emotional sweating responses observed on the palmar and plantar surfaces [35]. Clinical and behavioral studies suggest that patients with CIPA also lack sympathetic innervation of various target tissues, including internal organs. In normal individuals, pain and itch also induce activation of the sympathetic nervous system, including the adrenal medulla, and are thus involved in various protective body reactions. Systemic responses of the sympathetic nervous system are also known as the emergency 'fight-or-flight response'. Together, these findings suggest that patients with CIPA lack the 'fight-or-flight response'. Thus, patients with CIPA cannot properly maintain a variety of neural processes, including those related to autonomic, neuroendocrine and behavioral responses in the body.

Children with CIPA are mentally retarded and exhibit severe learning deficits [33–35]. The emotional and learning problems observed suggest defects of NGF-dependent neurons in the brain, although there is no direct evidence that mentally retarded CIPA patients lack NGF-dependent neurons. It is interesting to note that the corresponding gene knockout mice lack basal forebrain cholinergic neurons (BFCNs) and striatal cholinergic neurons [59]. Neither BFCNs, nor striatal cholinergic neurons in the knockout mice, mature fully in the absence of NGF/TrkA signaling [60]. Observations of disturbances in autonomic function and behavioral abnormalities in CIPA patients, as well as some differences from gene knockout mice, such as *Ngf*, *p75* and *Trka*, have been previously described in more detail in various references (for reviews, see [33–35]).

In summary, patients with CIPA lack NGF-dependent neurons, including NGF-dependent primary afferents, sympathetic postganglionic neurons and probably several types of neurons located in the brain. Consequently, they lack interoception, homeostatic regulation and emotional responses of the body. They are always at a disadvantage because of this, with threats to their survival. Thus, NGF-dependent neurons constitute a part of a neural network for interoception and homeostasis, and probably play important roles in emotion and adaptive behavior. Together, these findings indicate that the NGF-TrkA system is essential for the establishment of neural networks for interoception and homeostasis.

Brain, immune & endocrine systems

The nervous, immune and endocrine 'super-systems' engage in multiple interactions in the responses of the body to acute and chronic stress [61,62]. The brain is the central organ of stress, while the brain and the immune system are essential for homeostatic regulation and survival [61]. The endocrine system is engaged in coordinating and controlling complex responses of the brain and the immune system [61–69]. The central components of the stress system are located in the hypothalamus and the brainstem, while the peripheral limbs of the stress system are in the hypothalamic–pituitary–adrenal (HPA) axis, together with the efferent sympathetic/adrenomedullary systems and components of the parasympathetic system [63–65,69]. The brain and the immune system are involved in functionally relevant cross-talk, the main function of which is to maintain homeostasis. The brain affects the immune system through neuroendocrine humoral outflow via the pituitary, and directly via the sympathetic and sensory innervation of peripheral tissues, including lymphoid organs and blood vessels [66]. The parasympathetic portion of the autonomic nervous system also plays important roles in the control of immunity and inflammation [10,68]. For instance, noradrenaline and adrenaline, through stimulation of the β_2-adrenoreceptor-cAMP-protein kinase A pathway, inhibit the production of type 1/proinflammatory cytokines, such as IL-12, TNF-α and IFN-γ, with antigen-presenting cells and T helper (Th) 1 cells, while they stimulate the production of type 2/anti-inflammatory cytokines, such as IL-10 and TGF-β [61]. SP stimulates most macrophage functions and upregulates TNF-α and IL-12 production by monocytes and macrophages, while CGRP downregulates pro-inflammatory TNF-α and IL-12 production and potentiates IL-6 and IL-10 secretion [66]. Exposure of human macrophages to acetylcholine, the principal cholinergic neurotransmitter, inhibits the release of the pro-inflammatory cytokines TNF-α, IL-1 and IL-18 in response to endotoxin, without affecting the anti-inflammatory cytokine IL-10 [68]. Evidence accumulated over the last two decades indicates that sympathetic and cholinergic neurons of the autonomic nervous system and NGF-dependent primary afferents modulate several immune parameters, and play important roles in homeostasis and inflammation [49,61–69]. In accordance with the concept of 'super-systems', NGF-dependent neurons, such as polymodal receptors and sympathetic postganglionic neurons, are considered communication routes between the brain and immune systems (Figure 1). These NGF-dependent neurons are also essential for interoception and homeostatic regulation of the body [35]. The NGF-TrkA system thus contributes to the establishment of a neural network between the brain and immune system.

Injury or tissue damage, activating NGF-dependent primary afferents, causes the sensation of pain and leads to systemic activation of the HPA axis, together with arousal and sympathetic responses. These responses are involved in various reactions that protect the body, including withdrawal reflexes and vasoconstriction. The systemic response of the sympathetic nervous system to danger is the 'fight-or-flight response', as described above. Invasion of parasites and insect bites also activate NGF-dependent primary afferents and causes an itch sensation, leading to the desire to scratch the skin. Injury or microbial invasion results in the local release of numerous chemicals that mediate or facilitate inflammatory processes [10,47,70]. Autonomic sympathetic nerves innervate various cells in the body, and thereby maintain homeostasis and regulate inflammation, as well as host defenses. Thus, mediators derived from NGF-dependent primary afferents or peripheral autonomic neurons, including sympathetic postganglionic neurons, probably play important regulatory roles in the body under many physiological and pathological conditions.

Upon stimulation, NGF-dependent primary afferents release various neuromediators or neuropeptides (e.g., SP and CGRP) that modulate inflammation, pain and pruritus (Figure 1). In turn, these neuromediators trigger the release of pro-inflammatory mediators that might amplify or facilitate inflammation by enhancing vasodilation, blood flow, vascular leakiness and leukocyte trafficking to sites of inflammation [67]. They also influence the expression of NGF and its secretion from keratinocytes [71]. Mast cells are located perivascularly, close to SP- and CGRP-containing neurons [62]. Mast cells are thus ideally equipped and placed to integrate and relay signals from all three super-systems during the peripheral tissue responses to psychological, as well as pathological, stress [62,69]. Mast cells are resident cells in various tissues and critical effector cells in inflammation. They can contribute to multiple features of acute and chronic, as well as allergic, inflammation [72]. Various inflammatory mediators derived from mast cells induce inflammation and also stimulate NGF-dependent primary afferents of the nose, skin and airways, resulting in sneezing, itching or coughing [72]. Since mast cells depend on NGF for homing, survival and differentiation, increased synthesis of NGF in inflamed tissues critically influences the number and activities of mast cells involved in inflammation [73].

Both pain and itch sensations are related locally to tissue damage and inflammatory responses. The nervous system integrates the inflammatory response: it gathers information about tissue-damaging events from several local sites, mobilizes defenses and creates memory of the event to improve chances for survival [67,68]. Pain and itch sensations also provoke emotional responses in the brain and probably contribute to the creation of memories surrounding tissue-damaging events. It is likely that patients with CIPA lack these neural processes. Again, they are always at a disadvantage as this threatens survival.

Inflammation is considered to be a protective response of the body to activate the immune system, although excessive inflammatory and immune responses can cause morbidity and shorten

lifespan. Thus, inflammation and immune responses must be fine-tuned and regulated with precision. Activation of the HPA axis and autonomic nervous system dampens inflammatory immune responses and restores host homeostasis [67]. Cortisol is a well-known anti-inflammatory hormone and is released from adrenal glands through activation of the HPA axis. It acts on virtually all of the components of inflammatory immune responses [64]. Indeed, analogs of this hormone are used to suppress inflammatory responses associated with various clinical conditions.

The brain is the central organ in the perception of, and in response to, stressors, including tissue damage and microbial invasion, and determines both behavioural and physiological responses to them. The endocrine system is engaged in coordinating and controlling complex responses of the brain and the immune system. It is thus important to understand the mechanisms of pain and itch from the perspective of the inflammatory response, and interactions among the brain and immune and endocrine systems.

Pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, according to the definition of the International Association for the Study of Pain. Pain is also essential for the proper development of drives and instincts, and probably for the development of related decision-making strategies [51]. It might thus be related to the survival of the organism via multiple neural processes, especially those related to homeostatic regulation.

Recently, major pain syndromes have been distinguished and characterized by stimulus-response relations and pain mechanisms [74]. Pain is usually an adaptive response, alerting one to real or impending injury and triggering appropriate protective responses. By contrast, some types of pain are maladaptive, in the sense that they neither protect nor support protective responses. Maladaptive dysfunctional pain, including conditions such as fibromyalgia and irritable bowel syndrome, is considered to be an amplification of nociceptive signaling in the absence of either inflammation or neural lesions [74]. However, sensitization of sensory pathways by inflammation or NGF may also contribute to the development of hypersensitivity in neighboring organs at an early stage. Then, prolonged sensitization processes may underlie the coexistence of pain syndromes in patients with functional diseases, even after inflammation ceases. An animal study has indicated that inflammation or transient overexpression of NGF in one tissue triggers hypersensitivity in referral sites [75]. The peripheral stress mediator noradrenaline may also induce visceral hypersensitivity to colorectal distension in response to chronic stress through increasing the expression of NGF in the colon wall, thus sensitizing primary afferents in the absence of an inflammatory response [76].

Neuropathic pain is caused by metabolic, traumatic, viral or toxic lesions or dysfunction affecting the somatosensory system, thereby altering nociceptive signal processing. Immune cell products may play crucial roles, not only in inflammatory pain, but also in neuropathic pain caused by injury to peripheral nerves or the CNS [77]. Neuropathic pain, including postherpetic neuralgia, is considered a maladaptive type of pain. The spontaneous and evoked types of pain in neuropathy have been frequently attributed to injured nociceptive afferents that become sensitized and hyperexcitable, or to low-frequency ectopic firing in residual 'uninjured' nociceptors. A third alternative has also been proposed: that pain is due, at least in part, to ectopic afferent discharge generated in low-threshold, myelinated, rapidly conducting Aβ touch afferents [78]. Postherpetic neuralgia is one of the most common conditions seen in pain clinics [79]. Intriguingly, a recent study described a patient with CIPA suffering from herpes zoster [80]. This patient, a 3-year-old boy, had developed varicella at 2 months of age. Lesions of herpes zoster were characteristically confined to the trigeminal nerve-innervated maxillary region. Varicella-zoster virus (VZV) was identified by virus isolation. This patient has never complained of pain or itch sensation before or after herpes zoster, despite suffering severe herpetic skin lesions. Postherpetic neuralgia was not observed in this patient. It is of interest that VZV infects epidermal cells and causes herpes zoster in this patient, since patients with CIPA lack NGF-dependent primary afferents, as well as sympathetic postganglionic neurons. Patients with CIPA have touch sensation and intact primary afferent neurons with large myelinated Aβ-fibers in their skin. It is known that the VZV virus ascends the sensory nerve from the skin sensory nerve endings during primary infection, and migrates up the DRG, where it usually remains latent for the lifetime of the individual [79]. It is thus likely that VZV ascends the sensory nerves with Aβ-fibers and migrates up the DRG, based on clinical case reports of CIPA [80]. This may indicate an important feature of the mechanism of VZV latent infection in the DRG and neuropathic pain syndromes, including postherpetic neuralgia. In most cases of herpes zoster, preferential loss of large myelinated fibers appears to occur, with or without postherpetic neuralgia [79]. Thus, NGF-dependent afferent neurons are required for the establishment of pain sensation, but probably not for latent infection by VZV and the development for herpes zoster.

Postherpetic pain and other types of neuropathic pain are characterized by persistent pain following inflammation or nerve injury, and are evoked by stimuli that are normally perceived as innocuous. A small subset of primary sensory neurons with C-fibers may play a crucial role in the painful sensitivity to touch or pressure that follows injury or inflammation in animals [81]. These neurons respond to innocuous mechanical stimuli, such as light touch, rather than noxious stimuli. This suggests that a subset of primary sensory neurons with C-fibers can change from eliciting innocuous sensation of light touch to evoking pain following inflammation or injury. Primary afferent neurons with C-fibers are NGF-dependent neurons, at least during the developmental stage. Thus, patients with CIPA lack NGF-dependent neurons and consequently all pain sensation, including injury-induced mechanical hypersensitivity.

Itch

Itch is an uncomfortable sensation that causes a desire to scratch the skin, and is often associated with invasion of parasites or insect bites. Itch probably evolved as a defense mechanism against insects. Unlike pain, which elicits a withdrawal response, itch draws attention to a particular area of the skin and elicits scratching. It

may, thus, serve to remove insects and any stingers, eggs or other deposits they leave behind [9]. NGF-dependent primary afferent C-fibers and probably certain subtypes of Aδ-fibers appear to be crucial for mediating various peripheral stimuli to the spinal cord and the brain, resulting in the symptoms of itching, although the roles of Aδ-fibers in this are still poorly understood [10]. There is no universal peripheral itch mediator, with sets of disease-specific mediators existing instead [8]. In addition, numerous mediators of skin cells can activate and sensitize pruritic nerve endings, and can even modulate their growth.

Although itch and pain are different sensations tied to different behaviors, both are conveyed from the periphery to the spinal cord by NGF-dependent primary afferents. Histamine, released from tissue mast cells by tissue damage or microbial invasion, is a well-recognized mediator of acute inflammation and a potent pruritic agent. Intradermal injection of histamine causes a strong sensation of itch in normal individuals. Patients with CIPA lack both pain and itch sensation, since they lack NGF-dependent primary afferents. This is also demonstrated by a defect in histamine-mediated axon reflexes [33], as described above.

There has long been debate concerning the basic mechanisms of itch and the interaction between pain and itch, raising an important conceptual problem [82]. A subpopulation of afferent neurons with C-fibers were considered the peripheral 'itch' fibers, whereas activation of polymodal receptors, responding to a range of noxious stimulation, as well as to non-noxious stimulation, could generate the perception of itch [82]. The question remains whether there are separate neuronal pathways for itch and pain [15,82]. It is known that lesions of the spinothalamic tract pathways (STT) always impair both itch and pain sensations [83]. A specialized class of dorsal horn neurons projecting to the thalamus has been demonstrated to respond strongly to histamine administered to the skin by iontophoresis [83]. The presence of a small subset of histamine-responsive neurons in the lamina I spinothalamic tract neurons has been reported in cats, arguing for a 'labeled line' for itch [83,84]. Intriguingly, in atopic dermatitis (AD), one of the most common pruritic diseases, itch can often be induced mechanically, in contrast to the mechanoinsensitivity of the histamine-sensitive C-fibers [15]. Recent studies in primates, however, have found that all histamine-sensitive STT neurons are responsive to noxious stimuli, arguing against a labeled line for itch [85,86]. Consistent with these findings, a further study reported that primary afferent neurons expressing capsaicin receptor (TRPV1) are equipped with multiple signaling mechanisms that respond to different pruritogens [87]. Intriguingly, itch sensation can be elicited by dermal application of the algogen capsaicin [88]. To dissociate the pruritic and nociceptive sensory effects of chemical activation of sensory neurons, chemicals were applied in punctiform fashion to the skin, using individual heat-inactivated cowhage spicules treated with various concentrations of capsaicin or histamine. Spicules, containing capsaicin or histamine, produced similar qualities and magnitudes of sensation. The similar pruritic and sensory effects of punctate application of each chemical suggest the function of a common subset of peripheral nerve fibers or common central mechanisms that result in similar qualities of sensation. These studies have linked itch research and pain research on a basic mechanistic level.

Other recent studies have suggested that gastrin-releasing peptide receptor (GRPR) is an itch-specific protein in the spinal cord [89]. A subsequent study by the same group on GRPR has also suggested that the neurons expressing GRPR in the spinal cord neuron differ from the STT neurons that have been the focus of the debate on a 'labeled line' for itch [90]. These GRPR-expressing neurons probably represent a previously unrecognized subpopulation of lamina I neurons that confer specificity of itch at the spinal level. However, it is uncertain whether these neurons are projection neurons or interneurons. Detailed understanding of the anatomic basis of these neurons and their relationship with STT neurons will require further study.

It has not been possible to morphologically differentiate fibers specific for pain from those specific for itch in normal individuals [12,15]. It remains unknown whether there are separate neural pathways specific for pain and itch in normal individuals. However, molecular and physiological studies of patients with CIPA suggest that NGF-dependent primary afferents are responsible for mediating pain and itch sensations.

Neural sensitization in pain & itch

It is a common experience that itch sensation can be reduced by a painful sensation caused by scratching [7]. Cold stimulation also reduces itch sensation, although warming the skin often leads to exacerbation of itch. Itch and pain thus appear to share many receptors and processing centers, although they remain two distinct sensations [7,11]. There is a broad overlap between pain- and itch-related peripheral mediators and/or receptors, suggesting similar mechanisms for neuronal sensitization in the peripheral nervous system and CNS [7,10,12,15]. NGF probably alters the response properties of itch-signaling neurons, as well as pain-signaling neurons [7]. Acute peripheral sensitization processes involving NGF and inflammation participate in pain and itch. In addition, NGF probably contributes to central sensitization processes and plays pivotal roles, particularly in the context of neuropathic pain [91–93].

Pain and itch are uncomfortable sensory and emotional experiences, often provoking changes in activation of the autonomic sympathetic nervous system. Pain can also be seen as a homeostatic emotion causing adverse behavioral responses, such as autonomic reflexes, motor responses and psychosomatic reflexions. The activation of NGF-dependent primary afferents and postganglionic sympathetic neurons of the peripheral nervous system during an immune response might be aimed at localizing the inflammatory response through induction of neutrophil accumulation and stimulation of more specific immune responses [68]. Axon reflexes mediated by NGF-dependent primary afferents probably play important roles in these local responses. By contrast, uncomfortable emotional memories associated with various experiences of pain and itch are probably useful in inducing preventive behaviors against potential injury or tissue damage, and thus contribute to homeostatic processes and the survival of the organism. Although inflammation is a local, protective response to microbial invasion

or injury, it must be fine-tuned and regulated precisely, since deficiencies in or excessive inflammatory responses cause morbidity and shorten lifespan [67,68]. By the same token, pain and itch must be tuned and regulated appropriately. Deficiency of these sensations may otherwise cause morbidity and shorten lifespan, as observed in patients with CIPA, while excess sensation of this type can cause maladaptive morbidities, such as dysfunctional or neuropathic pain and chronic itch.

It is known that acute stress and chronic psychoemotional stress can trigger or enhance pruritus [14,62,94]. Stress responses are known to be learned, to involve cortical centers and to activate the HPA axis [14,69]. Psychoemotional and physical stress can induce itchiness of the skin, exacerbate inflammatory skin diseases and inhibit would healing [95]. Plasticity of the cutaneous peptidergic innervation, in response to stress exposure, appears to be a prerequisite for the enhancement of cutaneous inflammatory responses observed in individuals with stress [95]. The importance of the roles of learning processes in the development of both chronic pain and chronic itch has also been recognized, and the experience of increased pain and itch upon stressful events also leads to conditioning of pain and itch, thereby aggravating and perpetuating stress-induced pain and itch [14].

NGF & inflammation

NGF is a well-known neurotrophic factor that regulates the long-term survival, growth and differentiation of function of both nociceptive neurons (or more broadly NGF-dependent primary afferents) and sympathetic postganglionic neurons. NGF is thus essential for the establishment of neural pathways for pain and itch, as well as for homeostatic regulation of the body via the sympathetic nervous system in the developing animal. NGF-dependent primary afferents and sympathetic postganglionic neurons influence inflammation by secreting pro-inflammatory or anti-inflammatory substances into sites of inflammation [14,61–69]. These NGF-dependent neurons play critical roles in neurogenic inflammation. Indeed, axon reflexes are absent in patients with CIPA, as described above. This suggests that neurogenic inflammation does not occur without NGF-dependent neurons.

Expression of NGF is high in injured and inflamed tissue, and activation of the NGF receptor tyrosine kinase TrkA on nociceptive neurons triggers and potentiates pain signaling through multiple mechanisms [96–98]. NGF is conveyed via retrograde axonal transport to the DRG; where gene expression of neuropeptides, receptor molecules, such as the vanilloid receptors (TRPV1), and brain-derived neurotrophic factor (BDNF) is increased [70,98–101]. Numerous studies have also demonstrated that axonal ion channels contribute to pain, and that NGF alters their local expression [102–107].

NGF also initiates nerve fiber sprouting, and thus alters the morphology of sensory neurons in localized pain and hypersensitivity. In addition, inflammation induces the activation of the sympathetic nervous system [108,109]. The sympathetic nervous system is involved in various protective reactions of the body that are associated with pain, but not in the generation of pain by activation or sensitization of afferent neurons. However, this system may also be involved in the generation of pain in certain pathological conditions [108]. It is known that NGF increases sympathetic fiber density and peripheral innervation [110,111], enhances sympathetic sodium currents [112] independently of their activation/inactivation kinetics [113], maintains sympathetic calcium currents and enhances frequency discharges of action potentials by decreasing spike latency/inter-spike intervals [114], and decreases sympathetic potassium current amplitude [115]. Thus, the cross-talk between autonomic sympathetic nerves and NGF may contribute to the generation of pain in certain pathological conditions. Patients with CIPA probably do not exhibit this type of cross-talk since they lack sympathetic postganglionic neurons.

NGF is now known to influence the main mediators of neurogenic inflammation through direct or indirect biologic activities in both the nervous and immune systems [18,73,99,116]. The direct effects of NGF on TrkA-expressing neurons involves both peripheral sensitization and the induction of altered central pain processing, while its indirect effects involve immune cells, including mast cells and neutrophils (or eosinophils in allergic inflammation), as well as sympathetic postganglionic neurons.

Cross-talk between NGF and a proinflammatory cytokine, such as TNF-α, has been also proposed, contributing to intercellular positive-feedback loops of these factors among neural cells, glial cells and immune cells [117]. NGF is produced continuously during allergic inflammation, and thus might act as a long-term modulator, amplifying inflammatory signals between the nervous and immune systems during neurogenic inflammation [73,116]. NGF can modulate NGF-dependent primary afferents by stimulating the production of neuromediators or neuropeptides, especially SP and CGRP [7,73]. NGF-dependent primary afferents and sympathetic postganglionic neurons release neuromediators and activate specific receptors on many target cells in the skin or lung, and thereby modulate inflammation, cell growth and immune responses [10,73]. Neuropeptides such as SP are also capable of activating keratinocytes, resulting in production of a number of proinflammatory cytokines [10]. Thus, neuropeptides released by NGF-dependent primary afferents modulate a broad range of functional responses of immune cells, including lymphocytes, eosinophils, mast cells and macrophages, as well as keratinocytes, leading to activation and differentiation of these cells (Figure 1).

The biological activities of NGF in inflammation described above only include some of its effects. Over the past decade, considerable evidence has accumulated in both humans and animals that NGF is a peripheral pain mediator, particularly in inflammatory pain states (for reviews, see [18,99]). NGF is upregulated in a wide variety of inflammatory conditions, and NGF-neutralizing molecules are effective analgesic agents in many models of persistent pain, as described below. NGF thus plays critical roles as a neurotrophic factor during development, but also as a significant mediator and modulator of pain, itch and inflammation throughout life.

NGF & diseases

NGF functions as a mediator of inflammation in various diseases of the skin, such as AD (for review, see [10]), in those of the airways, such as asthma and rhinitis (for reviews, see [116,118,119]) and

those of the musculoskeletal system, such as various inflammatory and degenerative diseases, including autoimmune and rheumatic diseases (for review, see [120]).

Atopic dermatitis

Atopic dermatitis is a chronic skin disease characterized by symptoms such as red scaly eczema and a strong itching sensation. Pruritus is the most common and least tolerated symptom of AD, and even partial reduction of pruritus can result in significant improvement in quality of life for patients [121]. NGF plays an important role in regulating the activity of immune cells in normal skin and in a number of pathological conditions, including wound healing, inflammation, psoriasis and AD, as well as in allergic, autoimmune and stress-induced skin responses [122,123]. Recent studies have suggested that NGF may play a role in the pathophysiology of AD [10]. Expression of NGF is increased in the skin of patients with AD [124–127], with animal studies reporting similar findings [128–134]. In addition, studies using electron microscopy have revealed increased intradermal fiber density in patients with AD [135,136]. Skin inflammation modulates neuronal plasticity and regeneration via a cytokine/NGF axis. Alterations of NGF signaling, for example, by cytokines, may account for many inflammation-associated changes in cutaneous innervation [95]. Potent proinflammatory cytokines can upregulate the cutaneous expression of NGF, and may thus contribute to a vicious cycle of proliferative and proinflammatory events that maintain and promote chronic inflammatory diseases. NGF plays an important role in the neuroimmune network regulating allergic skin responses [122]. NGF expression thus modulates interactions of epidermal keratinocytes with cutaneous nerves, as well as mast cells in the skin, contributing to vicious cycles that amplify allergic skin inflammation [73].

Airway inflammatory diseases

NGF may participate in airway inflammation, alterations in bronchial responsiveness, and airway remodeling, which are all important features of allergic rhinitis [137–143] and asthma [96,118,119]. Airway hyper-responsiveness (AHR) and inflammation are essential clinical features of allergic asthma, and contribute strongly to the morbidity of this disease. Following irritation, activation of sensory airway nerves occurs and triggers an axonal response that acts as an immediate protective mucosal defense mechanism, resulting in coughing and sneezing [116]. Coughing, sneezing and other avoidance mechanisms clear the upper and lower airways of offending agents. Changes in airway sensory innervation are under the control of inflammatory mediators released during allergic inflammation, and neurotrophin expression is intensively upregulated in the inflamed lung [116]. NGF increases the contents of neuropeptides in sensory nerves. *In vivo* studies in models of asthma in the guinea pig and mouse have also demonstrated that NGF may play a role in AHR through activation of the TrkA receptor [144–147]. Animal studies have demonstrated that NGF also increases the excitability of lower airway parasympathetic neurons in diseased or inflamed lower airways [148,149]. NGF may be involved in amplification of the effects of axon reflexes in the airways, enhancing neurogenic inflammation and contributing to the pathophysiology of bronchial asthma [119]. Thus, neurotrophins contribute to AHR through increasing the activity of the sensory airway nerves [116].

Recent studies suggest that NGF has important effects on neuronal activity in airways and sensory innervation, and acts as a growth factor for inflammatory cells, including mast cells, T cells and eosinophils, in the bronchial mucosa [73,118,119,150–152]. In addition, NGF may act on structural cells and, therefore, participate in the bronchial remodeling that occurs in the airways of patients suffering from allergic diseases, particularly asthma [118]. Potential cellular sources of increased neurotrophin production are resident lung cells and invading immune cells [116]. Fibroblasts and airway smooth muscle cells may also be additional sources of NGF during inflammatory activation [116,118,119,153,154]. Furthermore, the NGF-TrkA system might be involved in common respiratory infections, such as that by respiratory syncytial virus [119,155,156]. Changes in NGF expression in the respiratory tract may represent an important link between viral infection in early life and childhood asthma [157]. Together, these findings suggest that NGF plays roles in the inflammation, AHR and remodeling processes observed in airway inflammatory diseases [73,116,118,119].

Rheumatic diseases

Inflammatory and degenerative diseases of the joints are major causes of chronic pain [158]. In younger patients, inflammatory diseases in particular, such as rheumatoid arthritis, are causes of joint pain, whereas elder individuals mainly suffer from pain due to osteoarthritis [158,159]. Autoimmune diseases and a variety of degenerative rheumatic disorders are characterized by chronic inflammatory events [158,160,161]. The joints are equipped with large numbers of Aδ- and C-fibers (i.e., NGF-dependent primary afferents) able to encode painful stimuli. Sympathetic postganglionic neurons also innervate the joint capsule and synovium. The nervous system is not just a passive sensor of painful processes, and instead exhibits interaction with non-neuronal events in inflamed joints [161]. Inflammation, whether primary/autoimmune or secondary/degenerative, leads to peripheral sensitization and stimulation, which may in turn lead to central sensitization, neurogenic amplification of inflammatory responses and activation of the neuroendocrine axis [160]. Proinflammatory cytokines, including TNF-α, play important roles in rheumatoid arthritis. Their antagonists have been introduced as new therapeutic agents for patients with rheumatoid arthritis.

NGF is overexpressed in many inflammatory and degenerative rheumatic diseases. NGF concentrations are increased in body fluids and tissues derived from patients with these diseases, and correlate with the extent of inflammation and/or clinical activity [120,162–168]. Several clinical trials of anti-NGF treatments have already been conducted in pain diseases, as described below. The NGF-TrkA system might thus be a useful target in the treatment of various rheumatic diseases.

Expert commentary

NGF acts as an inflammatory mediator, in addition to exhibiting neurotrophic effects. The NGF-TrkA system, acting on the nervous, immune and endocrine systems, might play critical roles in maintaining homeostasis in the body. Complete loss of the effects of NGF acting through TrkA receptors can be detrimental to the survival of the organism, as exemplified by the clinical phenotypes of patients with CIPA. However, various chronic inflammatory diseases may cause hyperactivity of the NGF-TrkA system, contributing to vicious cycles of pain or itch associated with neurogenic inflammation. Thus, NGF antagonists may offer novel therapeutic approaches to inflammatory diseases associated with chronic pain and itch.

NGF-dependent neurons are involved in reciprocal communication between the brain and the body, modulating inflammation, immune responses during host defenses, pain and pruritus (Figure 1). This reciprocal communication between the body cells and the brain mediates homeostatic regulation in physiological, as well as pathophysiological, conditions. The NGF-TrkA system might be an important participant in crucial neurological pathways and mediators, provoking adaptive or maladaptive responses in the body. Hopefully, integrated understanding of the neuroimmunoendocrine system will lead to new innovative approaches to the treatment of many diseases associated with chronic pain, as well as chronic itch.

NGF is now considered an inflammatory mediator that sensitizes and regulates gene expression in NGF-dependent neurons [18]. NGF is upregulated in a variety of inflammatory conditions, including autoimmune and rheumatic diseases [10,73,116,118–120]. NGF levels are elevated in injury, inflammation and chronic pain states [98], and administration of NGF provokes pain and hyperalgesia in humans [169]. Accordingly, various approaches to the antagonism of NGF have been developed in animal models. These include NGF-capturing agents, antagonists at the NGF-TrkA binding site and antagonists of TrkA function to inhibit TrkA signaling (for review, see [98,170,171]). These selective antagonists of the NGF-TrkA system are expected to be highly effective therapeutically in many pain states due to their distinct mechanisms of action [172–174]. NGF-neutralizing molecules are effective analgesic agents in many models of persistent pain [96,174–183]. Analysis of NGF antagonists improves understanding of NGF-induced inflammation and may yield many new therapeutic strategies. Targeting NGF is thus a promising candidate in the search for novel therapeutics [98,170–172].

Recently, many analgesics have been developed based on the biological mechanisms of various types of pain. In addition, new drugs against itch have been developed based on the biological mechanisms of itch [7]. Molecular and biological analyses of various pain syndromes and itch states, as well as the pathology of CIPA, have suggested that the NGF-TrkA system might be involved in both maladaptive pain and chronic itch. Indeed, clinical investigations have demonstrated that NGF and SP levels are increased in the plasma of patients with AD or prurigo nodularis skin [184], and that these may be useful markers of disease activity [185]. Indeed, a novel antipruritic strategy to target the neurokinin receptor 1 (NKR1), a receptor for SP, has been recently reported to show promising results in patients with treatment-refractory pruritus [186]. The use of this NKR1 antagonist, aprepitant, may present a novel, effective treatment strategy based on the pathophysiology of chronic pruritus. NGF may play important roles in the pathogenesis of AD-like lesions in the NC/Nga mouse, a model of AD [187]. In these mice, nerve fibers were found to be significantly increased in the epidermis of skin with lesions, and the NGF content of serum and skin was significantly elevated. Anti-NGF antibodies significantly inhibited the development of skin lesions and epidermal innervation. These findings suggest that inhibiting the physiological effects of NGF, or suppressing increase in NGF production, may provide a new therapeutic approach for amelioration of the symptoms of AD [188].

Considering the broad overlap between pain- and itch-related peripheral mediators and/or receptors, and the similarity in their mechanisms of neuronal sensitization in the peripheral nervous system and CNS, combinations of centrally acting drugs counteracting sensitization and topically acting drugs counteracting inflammation appear to be promising in ameliorating pain and itch [7,11,12]. Combined approaches that target both the peripheral production of inflammation-induced pain or itch signals and the peripherally-incited vicious cycles that perpetuate pain or itch and cause spinal and central sensitization are needed. Thus, the combination of peripherally active anti-inflammatory agents with drugs that counteract chronic central sensitization is a particularly sensible approach beyond the use of NSAIDs, opiates and antihistamines. These considerations together encourage the development and testing of selective inhibitors of the NGF-TrkA system for human diseases associated with pain, itch and inflammation. Thus, naturally occurring TrkA missense mutations with loss of function provide considerable insight into structure–function relationships and aid in the development of drugs that target the NGF-TrkA system [32–35,37–41].

With targeting the molecular mechanisms of NGF-TrkA signal transduction, may come the hope of developing novel approaches to the treatment of a variety of persistent pain and itch syndromes. However, clinical application of inhibitors of the NGF-TrkA system might have a range of untoward effects, given the function of NGF-dependent neurons in several brain regions observed in animal studies [35,189,190]. In humans, growing evidence suggests that an imbalance in the expression of NGF and TrkA might be one of the crucial factors underlying dysfunction of cholinergic basal forebrain neurons in Alzheimer's disease [96,191]. Indeed, significant downregulation of TrkA expression during the development of Alzheimer's disease has been demonstrated [192]. In addition, a Phase I clinical trial has been undertaken to examine the utility of *ex vivo* NGF gene therapy for Alzheimer's disease, which has shown promise in treatment and warrants additional clinical trials [193]. However, it is unclear whether exposure of the brain to a NGF-TrkA inhibitor will give rise to significant side effects in adults. Accordingly, drugs that inhibit signal transduction in the NGF-TrkA system might affect cognitive functions when delivered to target neurons in the brain. These effects may limit the utility of such drugs in the treatment of severe, but nonlethal,

chronic diseases associated with pain and itch. Thus, identification of specific inhibitors that act only on the peripheral nervous system may be desirable. However, if NGF-dependent neurons in the brain prove to be involved in mechanisms of chronic pain and itch, they could be targets in developing an unprecedented approach to treatment of chronic pain and itch. They might also be targets for therapeutic interventions in human diseases associated with emotional disturbances, which are often associated with chronic pain and itch.

The vanilloid receptor TRPV1 is a central integrator molecule in the pain and itch pathways [8]. TRPVI has been identified as a molecular target for the treatment of pain associated with inflammatory diseases and cancer. TRPV1 can be activated, not only by capsaicin, but also by heat, acid and various lipids [101]. Hence, TRPV1 antagonists have been considered for therapeutic evaluation in such diseases. Preclinical studies suggest that TRPV1 is an important component of several diseases, such as pain-related and airway diseases, playing roles in sensitization related to both pain and cough [194]. In addition, several synthetic antagonists of the TRPV1 channel have been developed and are currently under investigation. Unfortunately, one such molecule has caused marked hyperthermia in humans, preventing further development of it [195]. TRPV1 antagonists may also induce complete insensitivity to heat-related pain, and may thus be seriously harmful, since the mechanism for prevention of burns has been effectively eliminated. This suggests that TRPV1 regulates vasomotor tone and metabolic heat production, and may therefore play a pivotal role as a molecular regulator of body temperature in humans. TRPV1 mRNA is highly expressed in NGF-dependent primary afferents that are also considered homeostatic afferent neurons. NGF increases expression of the *TRPV1* gene and induces a long-lasting increase in the sensitivity of TRPV1 receptor when administered to somatic tissues [194,196]. NGF might be involved in thermoregulation by altering the sensitivity of other TRP channel proteins, such as TRPV2, expressed on NGF-dependent primary afferent neurons. Interestingly, warmth is detected through the activation of other TRP channels, such as TRPV3 and TRPV4, expressed in skin keratinocytes [197,198]. Accordingly, keratinocytes might play an active role in thermosensation by signaling thermal information to the sensory nerves. NGF can be released from keratinocytes and has been suggested to be a potential paracrine warmth signal [198]. Cool temperatures are primarily sensed by activation of TRPM8, and noxious cold can activate TRPA1 channels in a subset of TRPV1-expressing fibers [197,198].

One of the characteristic symptoms in patients with CIPA is recurrent fever, associated with anhidrosis. However, hypothermia is also observed in patients with CIPA in cold environmental temperatures. In addition, piloerection or 'goose bumps' does not occur in response to cold stimuli in these patients. NGF also acts on the sympathetic postganglionic neurons that regulate sweat glands, piloerector muscles and blood vessels, playing important roles in thermoregulation. It may thus be necessary to consider alteration of thermosensation, and consequent alteration of thermoregulation, when targeting the NGF-TrkA system.

According to animal studies, embryonic afferent neurons expressing TrkA receptors exhibit two distinct pathways of differentiation that lead to the formation of two classes of neurons – peptidergic and nonpeptidergic. The latter class switches off TrkA and expresses Ret, another receptor tyrosine kinase for glial cell-derived neurotrophic factor (GDNF) [199]. Nonpeptidergic neurons expressing Ret become GDNF-dependent neurons and can be identified by staining for isolectin-B4. By contrast, peptidergic neurons remain dependent on NGF and its TrkA receptor. A subset of primary sensory neurons with C-fibers that play a crucial role in the sensitivity to touch or pressure that follows injury or inflammation in animals does not appear to overlap with afferent neurons that bind isolectin-B4 [81]. Interestingly, patients with CIPA probably lack all of these afferent neurons. Recent studies have suggested that GDNF-dependent neurons modulate nociception [200–202]. It remains to be determined whether nonpeptidergic GDNF-dependent neurons exhibit any response to approaches targeting the NGF-TrkA system after switching off TrkA. Further studies are needed to answer this question.

Five-year view

NGF is a well known survival factor for NGF-dependent primary afferent neurons and sympathetic postganglionic neurons in the developing nervous system. In adults, NGF acts not only as an important neurotrophic factor for these NGF-dependent neurons, but also as a crucial inflammatory mediator. During inflammation, various tissues and immune cells produce and release NGF, and NGF delivers activating and survival signals, through TrkA receptors, to effector cells involved or associated with inflammation. Activating NGF signals are also mediated through p75 receptors [203]. NGF plays a crucial role in the generation of pain and hyperalgesia in several acute pain and chronic pain states. NGF also plays important roles in the neuroimmune network involved in the establishment of sensitization to itch in allergic skin diseases and AHR in airway diseases. NGF may thus contribute to a vicious cycle of proliferative and pro-inflammatory events that maintain and promote chronic inflammatory diseases, including allergic airway diseases, such as asthma and rhinitis, AD and various rheumatic diseases. More comprehensive investigation of the complex biological functions of the NGF-TrkA system might yield new opportunities for the development of novel strategies of therapeutic intervention.

Since there are many mediators and mechanisms that are potentially algogenic or pruritic in inflamed tissues or skin, many could provoke pain or itch in sensitized patients. Similar mediators and mechanisms probably contribute to AHR in allergic airway diseases. Thus, therapeutic approaches that only target a single pain or pruritic mediator do not appear to be promising for patients with chronic pain or itch or AHR. The main therapeutic implication of this is, in fact, that combinations of centrally acting drugs counteracting sensitization and topically acting drugs counteracting inflammation are more promising for ameliorating pain, itch and AHR. The NGF-TrkA system is probably not a direct cause of each disease involved, but may contribute to vicious cycles shared by many chronic inflammatory diseases or states. Consequently,

the NGF-TrkA system is a promising target for the treatment of various diseases associated with chronic inflammation, pain and itch. Indeed, several pharmaceutical companies have active drug-discovery and development programs based on a variety of approaches to antagonize NGF, including NGF 'capture', blocking the binding of NGF to TrkA and inhibiting TrkA signaling. Therapeutic approaches that target the NGF-TrkA system may provide a unique means of exploring new drugs against various inflammatory diseases associated with pain, itch or AHR, beyond those currently available.

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Key issues

- NGF is a well-known neurotrophic factor essential for the survival and maintenance of NGF-dependent neurons, including primary afferent neurons with thin fibers (for short, NGF-dependent primary afferents) and sympathetic postganglionic neurons.
- NGF-dependent primary afferents not only mediate transmission of both pain and itch sensation, but also play essential roles in interoception. NGF-dependent primary afferents and sympathetic postganglionic neurons thus contribute to homeostasis in the body, together with the immune and endocrine systems.
- Both pain and itch sensations are associated with inflammation and subsequent tissue damage. There is broad overlap between pain- and itch-related mediators and/or receptors, suggesting similar mechanisms of neuronal sensitization.
- NGF changes the response properties of NGF-dependent primary afferents, as well as sympathetic postganglionic neurons, and thus plays important roles in neuronal sensitization in both pain and itch.
- NGF plays critical roles as a significant mediator and modulator of pain, itch and inflammation. NGF may also contribute to a vicious cycle of various inflammatory diseases, including allergic and autoimmune diseases.
- Congenital insensitivity to pain with anhidrosis (CIPA) is a genetic disorder due to loss-of-function mutations in the *NTRK1* (also known as *TRKA*) gene encoding TrkA, a receptor tyrosine kinase for NGF.
- Patients with CIPA lack NGF-dependent neurons, including NGF-dependent primary afferents and sympathetic postganglionic neurons. They consequently lack both pain and itch sensations and neurogenic inflammation, as well as sympathetic functions.
- Patients with CIPA may offer the opportunity to consider potential pharmacological effects, as well as side effects, when the NGF-TrkA system is targeted, since the phenotypes of these patients can be assumed to reflect an extreme end of the broad spectrum of expected effects.
- With targeting of the molecular mechanisms of NGF-TrkA signal transduction may come the hope of developing novel analgesics and antipruritic drugs, as well as anti-inflammatory drugs.

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