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NGF-dependent neurons and neurobiology of emotions and feelings: Lessons from congenital insensitivity to pain with anhidrosis

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ABSTRACT

NGF is a well-studied neurotrophic factor, and TrkA is a receptor tyrosine kinase for NGF. The NGF–TrkA system supports the survival and maintenance of NGF-dependent neurons during development. Congenital insensitivity to pain with anhidrosis (CIPA) is an autosomal recessive genetic disorder due to loss-of-function mutations in the *NTRK1* gene encoding TrkA. Individuals with CIPA lack NGF-dependent neurons, including NGF-dependent primary afferents and sympathetic postganglionic neurons, in otherwise intact systems. Thus, the pathophysiology of CIPA can provide intriguing findings to elucidate the unique functions that NGF-dependent neurons serve in humans, which might be difficult to evaluate in animal studies. Preceding studies have shown that the NGF-TrkA system plays critical roles in pain, itching and inflammation. This review focuses on the clinical and neurobiological aspects of CIPA and explains that NGF-dependent neurons in the peripheral nervous system play pivotal roles in interoception and homeostasis of our body, as well as in the stress response. Furthermore, these NGF-dependent neurons are likely requisite for neurobiological processes of 'emotions and feelings' in our species.

1. Introduction

Nerve growth factor (NGF) is a well-studied neurotrophic factor or neurotrophin and one of the first growth factors to be identified and characterized. For her discovery of NGF, Rita Levi-Montalcini was awarded the Nobel Prize in Physiology or Medicine in 1986 (Levi-Montalcini, 1987). NGF induces neurite outgrowth and promotes the survival and maintenance of peripheral sensory and sympathetic postganglionic neurons derived from the neural crest, as well as central cholinergic neurons of the basal forebrain (Levi-Montalcini, 1987). Recently, NGF has also been considered to be an inflammatory mediator and modulator of pain in adulthood (Dawes et al., 2013; McMahon, 1996; Pezet and McMahon, 2006).

TrkA is a receptor tyrosine kinase for NGF. *NTRK1 (*also known as *TRKA)*, the gene encoding TrkA, was identified as part of the human *trk* oncogene derived from colon carcinoma (Martin-Zanca et al., 1986). The nomenclature of *trk* (pronounced 'track') reflects its rearranged molecular structure: tropomyosin(t)-receptor(r)-kinase(k). TrkA was first reported to be a novel receptor tyrosine kinase for an as-yet-unknown ligand (Martin-Zanca et al., 1989). TrkA later proved to be a receptor tyrosine kinase for NGF (Kaplan et al., 1991; Klein et al., 1991). The survival and maintenance of NGF-dependent neurons are thus dependent on the normal function of the NGF–TrkA system during development.

Autonomic sympathetic postganglionic neurons are well-known for their NGF-dependency. However, the identity of the NGF-dependent sensory neurons has not been specified in previous studies (Levi-Montalcini, 1987). Cloning of the gene encoding NGF or TrkA and subsequent studies of knockout mice for each gene have revealed that the NGF–TrkA system is essential for the establishment of peripheral neuronal systems for pain and autonomic sympathetic regulation (Crowley et al., 1994; Smeyne et al., 1994). Mice lacking the gene for NGF or TrkA lack a discrete member of sensory neurons with thin fibers and fail to respond to noxious stimuli. Primary sensory or afferent neurons to detect and transmit noxious stimuli are classified into various subgroups according to physiological properties and/or the expression of various genes (Ringkamp et al., 2013). For convenience, these afferent neurons are categorized here in terms of their NGF-dependency. '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 are dependent on the NGF-TrkA system during development' (Indo, 2010). Thus, NGF-dependent neurons in the peripheral nervous system (PNS) include sympathetic postganglionic

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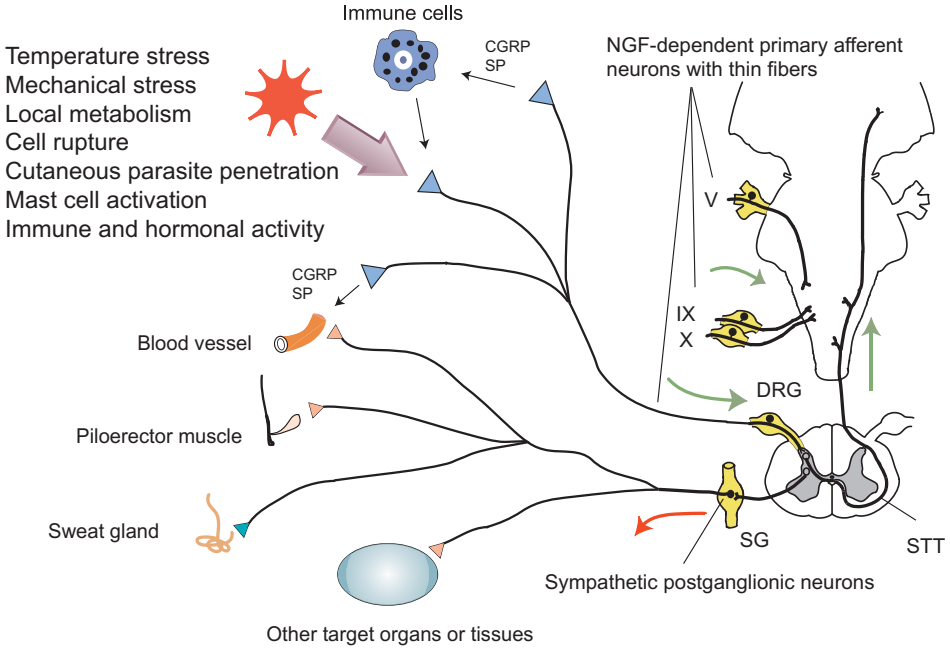

Fig. 1. Patients with congenital insensitivity to pain with anhidrosis lack NGF-dependent primary afferent neurons with thin fibers (NGF-dependent primary afferents) and autonomic sympathetic postganglionic neurons.
NGF-dependent primary afferents are dorsal root ganglia (DRG) neurons or trigeminal ganglia (V) neurons with free nerve endings. A subset of neurons in the glossopharyngeal nerve (IX) and the vagus nerve (X) are most likely NGF-dependent neurons. Sympathetic postganglionic neurons innervate blood vessels, piloerector muscles and sweat glands as well as other target organs or tissues in the body. Postganglionic fibers to sweat glands are cholinergic. Triggering factors (shown by bold arrow) may directly or indirectly stimulate NGF-dependent primary afferents. Upon stimulation, these neurons release neuropeptides (SP and CGRP) that 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. This figure has been reproduced, with permission, from Indo (Indo, 2012).

neurons and NGF-dependent primary afferents.

Congenital insensitivity to pain with anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV (HSAN-IV) is an autosomal recessive genetic disorder characterized by insensitivity to pain, anhidrosis (the inability to sweat), and various degrees of mental retardation, as well as characteristic behaviors (Axelrod and Gold-von Simson, 2007; Indo, 2002, 2008 Aug 5 [Updated 2014 Apr 17]; Swanson, 1963). A molecular genetic study found that CIPA is caused by loss-of-function mutations in *NTRK1*, the gene encoding TrkA (Indo et al., 1996). Mutations in *NTRK1* lead to the selective loss of NGF-dependent neurons in otherwise intact systems. The lack of pain and the presence of anhidrosis in CIPA are caused by the absence of NGF-dependent primary afferents and sympathetic postganglionic neurons, respectively (Fig. 1).

Pain was once regarded as a submodality of somatic sensation, along with touch, pressure and position sense. However, pain is a complex experience that involves cognitive and emotional processing by the brain. According to the International Association for the Study of Pain (IASP) (IASP Taxonomy), 'pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damages' (Merskey and Bogduk et al., 1994). Therefore, pain is discriminated from other somatic sensations in consideration of its inherent association with emotion. Pain warns of real or impending injury and triggers protective responses, thus playing critical roles in the survival of organisms (Julius and Basbaum, 2001). However, pain often becomes chronic and debilitating, reducing its usefulness as a warning system. Animal studies on pain using traditional electrophysiology, pharmacology and/or molecular biology have produced valuable insights into the molecular and neurobiological bases of pain (or nociception) (Basbaum et al., 2009; Mogil, 2009). However, the subjective and emotional aspects of pain are often difficult to evaluate in animal studies.

Small-diameter (Aδ and C) primary afferent fibers were initially considered to transmit pain as a 'nociceptive' pathway. Intriguingly, however, recent studies have indicated a conceptual shift in the recognition of the role of these afferent fibers as a 'homeostatic afferent pathway' (Craig, 2002). This homeostatic afferent pathway transmits 'interoception', which is defined as 'the sense of the physiological conditions of the entire body'. The 'interoceptive system' including a collection of nerve pathways and central nervous system (CNS) nuclei, detects and maps 'homeostatic signals, such as degrees of visceral muscle contraction and internal milieu chemical composition' (Craig, 2002). Coincidently, NGF-dependent primary afferents also almost entirely comprise Aδ and C primary afferent fibers and are thus referred to as 'interoceptive polymodal receptors' (Indo, 2009).

Pain is an emotional experience and activates the autonomic sympathetic nervous system. The 'fight-or-flight response' illustrates a strong emotional state associated with extreme excitation of the sympathetic nervous system and helps protect our physical body, often resulting in a conflict or fleeing from a conflict (Cannon, 1927; LeDoux, 1996). However, most emotional responses we experience in daily life occur at a subconscious level and probably contribute to our mental activity. A negative image or impression of emotions prevails in our daily life. However, Damasio proposes the 'somatic marker hypothesis', wherein emotions and feelings play critical roles in the decision-making and reasoning processes (Damasio, 1994). The close interconnection has been reported amongst the specific brain regions involved in the experience of pain and those more directly implicated in emotion and cognition (LeDoux and Phelps, 2008; LeDoux, 2000; Craig, 2008; Brodal, 2010a; Craig, 2015; Robinson et al., 2009). Recent progresses in neuroscience and its related fields is also providing intriguing insights into the unique aspects of interoception and the neurobiology of 'emotions and feelings' (Damasio and Carvalho, 2013).

Rare human genetic disorders can provide opportunities to explore pathological conditions in humans, as well as the underlying normal biological processes. The pathophysiology of CIPA may thus provide some clues to elucidate the various functions of NGF-dependent neurons in humans, which might be otherwise difficult to evaluate in animal studies. This review first describes the clinical and neurobiological aspects of CIPA and then examines the various roles that NGF-dependent neurons play under normal as well as pathological conditions in our species. NGF-dependent primary afferents together with sympathetic postganglionic neurons play critical roles in interoception and maintaining homeostasis of our body, as well as in the stress response. Furthermore, these NGF-dependent neurons in the PNS are essential for carrying out the neurobiological processes of 'emotions and feelings' in our mental experience.

2. NGF and neurotrophic theory

NGF is a well-known neurotrophic factor and has contributed to major advances in developmental neurobiology since its initial discovery (Bibel and Barde, 2000; Hamburger and Levi-Montalcini, 1949;

Huang and Reichardt, 2001). Neurons of the peripheral sensory and autonomic nervous systems are overproduced during embryonic development in mammals. The 'neurotrophic theory' proposes that immature neurons compete for target-derived trophic factors, such as NGF, that have a limited supply (Hamburger, 1992). Only those neurons that have success in establishing correct connections with target tissues or organs can obtain trophic factor support to allow for their survival. NGF functions as a survival signal and suppresses the cellular suicide program of apoptosis; deprivation of those factors activates cell death (Kristiansen and Ham, 2014; Yuan and Yankner, 2000). During development, target-derived NGF sends retrograde signals to the cell body and supports the neuronal survival, matching the number and properties of the innervating neurons to the needs of the target tissues or organs (Bibel and Barde, 2000; Glebova and Ginty, 2005; Huang and Reichardt, 2001; Snider, 1994). NGF also signals locally at axon terminals to promote sprouting and target innervation, ensureing appropriate innervation even if the size of the animal changes (Miller and Kaplan, 2001). Thus, NGF plays pivotal roles in the survival and maintenance of NGF-dependent neurons, including NGF-dependent primary afferents and sympathetic postganglionic neurons, during development.

In addition to these developmental roles, NGF, binding to TrkA (and/or the other low affinity p75 neurotrophin receptor: p75NTR), also regulates the phenotype of peripheral neurons, such as cell body and dendrite size and the expression of neurotransmitters, channels, receptors and sensors in adult life. NGF especially influences on the pain mechanisms, having various biological effects on nociceptive processing (Denk et al., 2017).

3. NGF and its receptor tyrosine kinase, TrkA

NGF binds TrkA, a receptor tyrosine kinase, and generates signals for the survival and maintenance of NGF-dependent neurons (Barbacid, 1995; Bothwell, 1995). The binding of NGF to TrkA stimulates homodimer formation and activates its tyrosine kinase activity, resulting in phosphorylation of specific tyrosine residues in intracellular domain (Chao, 2003; Huang and Reichardt, 2001; Kaplan and Miller, 2000; Reichardt, 2006; Segal, 2003). TrkA has specific intracellular tyrosine residues for autophosphorylation sites (Stephens et al., 1994) and controls three major signaling pathways for the neuronal differentiation, including neurite outgrowth, and the survival and growth of neurons, as well as for the synaptic plasticity (Reichardt, 2006). NGF has not only developmental role, but also sensitizing effects to heat and mechanical stimulation on nociceptors that results in hyperalgesia (Denk et al., 2017).

Target-derived NGF binds to and activates TrkA receptor at nerve terminals and mediates the retrograde biological effects. Retrograde transport of NGF and its receptor may allow a neuron to send cues received at its terminus to its cell body and nucleus (Barker et al., 2002; Campenot and MacInnis, 2004; Miller and Kaplan, 2001; Segal, 2003). Retrograde signals mainly required for the survival and gene expression are considered to be activated TrkA itself (Howe et al., 2001; Miller and Kaplan, 2001). NGF signaling via the TrkA receptor requires the formation of a signaling endosome containing both NGF and activated TrkA, as well as substrates of TrkA, which regulate the survival, growth and gene expression (Howe et al., 2001). Thus, endocytosis of the NGF–TrkA complex is essential for the generation of intracellular signaling and compartmentalization of signaling events.

4. NGF-dependent neurons

NGF-dependent neurons in the PNS are NGF-dependent primary afferents and sympathetic postganglionic neurons. Pain is transmitted by small-diameter (Aδ and C) primary afferent fibers, which are polymodal and innervate all tissues of the body (Kumazawa, 1996). NGF-dependent primary afferents are dependent on the NGF–TrkA system during development and probably include most primary afferent neurons with small-diameter (Aδ- and C-) fibers. In contrast, the autonomic sympathetic nervous system conveys efferent signals from the brain to various internal tissues or organs and maintains homeostasis of the body. Most of the sympathetic postganglionic neurons are unmyelinated (Brodal, 2010b) and innervate and regulate functions of various tissues or internal organs, including skin appendages (such as sweat glands and errector pili muscles).

'Sympathetic visceral sensory afferents' are sometimes referred to as sensory afferents from the internal organs (Saper, 2002). These afferent neurons enter the central nervous system (CNS) via the spinal nerves and convey mainly sensations related to temperature and impending or ongoing tissue injury of either mechanical, chemical or thermal origin (Saper, 2002). The term 'spinal visceral afferent system' has been proposed, as 'sympathetic visceral sensory afferents' seemed confusing (Saper, 2002). The 'spinal visceral afferent system' also includes pelvic sensory afferents important for the regulation of the sacral parasympathetic outflow (Saper, 2002). In contrast, visceral sensory information mainly related to mechanoreceptors and chemoreceptors enters the brain via four cranial nerves (the trigeminal nerve, the facial nerve, the glossopharyngeal nerve and the vagus nerve). These visceral afferents provided by the cranial nerves are sometimes called the 'parasympathetic afferent system' (Saper, 2002).

NGF-dependent primary afferents probably include most of the neurons in the 'spinal visceral afferent system'. However, whether or not neurons in the 'parasympathetic afferent system' include NGF-dependent primary afferents remains unclear. NGF-dependent primary afferents not only detect noxious stimuli but also transmit sensation from the body's interior; this is known as 'interoceptive sense' (Craig, 2002), as described below. NGF-dependent primary afferents, i.e. 'interoceptive polymodal receptors', transmit interoception (Indo, 2009).

NGF-dependent neurons probably exist in the CNS, since the expression of TrkA mRNA has been observed in various brain regions of rodents (Gibbs and Pfaff, 1994; Holtzman et al., 1995; Sobreviela et al., 1994) and humans (Indo, 2014), and gene knockout mice for *Ntrk1* encoding TrkA lack some neurons in the brain (Fagan et al., 1997; Smeyne et al., 1994). However, in contrast to those of the PNS, most NGF-dependent neurons in the brain remain uncharacterized.

4.1. NGF-dependent primary afferents

A nociceptor is a primary sensory neuron that is activated by stimuli capable of causing tissue damage (Julius and Basbaum, 2001; Woolf and Ma, 2007). NGF-dependent primary afferents include various nociceptors. Nociceptors are divided into two classes: C fibers and Aδ-fibers, having unmyelinated and lightly myelinated axons, respectively. They both mediate pain evoked by noxious stimuli but differ in conduction velocity and physiological characteristics (Caterina and Julius, 1999). They also respond to innocuous stimuli and play an important role as reflex afferents and as effector organs (Kumazawa, 1998), acting at both innocuous and noxious levels. For this reason, they are also referred to as 'polymodal receptors' (Kumazawa, 1998). Pain or nociceptive sensations and visceral sensation probably have a close relationship. Pain is considered to be 'a visceral sensory modality': the sensation arises from mechanical or thermal stress that threatens integrity of both deep and superficial tissues (Saper, 2002). Nociceptive sensations (or pain) are concerned with the internal state of the body itself. In contrast, the neural system representing position sense and fine cutaneous discrimination are externally directed (Saper, 2002). NGF-dependent primary afferents thus monitor tissue integrity and are internally directed and concerned with the state of the body. In contrast, touch and proprioception (position sense) are considered to be externally directed and concerned with exploring the external world and discerning the relationship of the body with external space (Saper, 2002).

Two categories of unmyelinated primary afferent nociceptor are

subdivided on the basis of histological markers (Snider and McMahon, 1998). One group (peptidergic) expresses neuropeptides, such as substance P and calcitonin gene-related peptide (CGRP). The second group (nonpeptidergic) does not express such neuropeptides but can be identified by the presence of specific tissue markers, IB4 (isolectin B4)-binding protein versican. Nonpeptidergic primary afferents are firstly depending on NGF and later depending on GDNF (glial cell-derived neurotrophic factor) (Bennett et al., 1996; Bogen et al., 2005; Priestley et al., 2002). These two categories of nociceptors express distinct repertoires of ion channels and receptors and innervate distinct peripheral and central targets (Woolf and Ma, 2007). They may relay different aspects of noxious stimuli, although little is known about the functional consequences of this dichotomy. NGF controls the survival, differentiation and target innervation of both peptidergic and nonpeptidergic sensory neurons in DRG (Snider and McMahon, 1998). Both types of neurons require NGF during early development, since they are lost in animals lacking NGF (Crowley et al., 1994) or TrkA (Smeyne et al., 1994). Thus, NGF-dependent primary afferents include these two types of peripheral neurons.

4.2. Sympathetic postganglionic neurons

The sympathetic nervous system, a part of the autonomic nervous system, plays essential roles in maintaining homeostasis under changing physiological demands (Ernsberger, 2001; Glebova and Ginty, 2005; Sato et al., 1997). Pain activates the sympathetic nervous system and often leads to hypertension in humans. In animals, the activation of peripheral nociceptors evokes an excitation of the vasoconstrictor sympathetic outflow (Morrison, 2001). Painful stimuli to the body also cause increases in the sympathetic outflow to the heart and adrenal glands, as well as vasoconstriction of cutaneous, renal and mesenteric vascular beds (Saper, 2002). Vasoconstriction of the skin has also been demonstrated during surgical incision in anesthetized humans (Mashimo et al., 1997; Shimoda et al., 1998).

Sympathetic postganglionic neurons innervate various internal organs or tissues throughout the body, such as endocrine and exocrine glands, cardiac muscle, and smooth muscle. They regulate secretomotor, vasomotor, pilomotor, sudomotor and pupilodilator functions (Ernsberger, 2001; Glebova and Ginty, 2005). Tissue-specific populations of sympathetic premotor neurons probably exist in the CNS and generate autonomic responses at selective sites in the body (Morrison, 2001). They orchestrate complex autonomic patterns related to the sympathetic outflows to relevant targets. Thus, autonomic networks involving the sympathetic premotor neurons in the CNS selectively control the sympathetic outflow to individual tissues and aid in expressing patterned autonomic responses (Morrison, 2001).

The sympathetic nervous system activates the ‘fight-or-flight’ response in coping with life-threatening challenges (Cannon, 1927). However, this system also plays crucial roles in maintaining homeostasis of the core body temperature in daily life (Morrison, 2001). Homeostasis of the core or deep-body temperature is considered to be an important physiological process that the sympathetic nervous system regulates. Previous studies have indicated that an animal can survive without a sympathetic nervous system but only under conditions of constant ambient temperature and in the absence of stress (Glebova and Ginty, 2005). In humans, changes in the environmental temperature activate the sympathetic nervous system and affect the functions of skin blood vessels and sweat glands as well as pilomotor muscles. Sympathetic postganglionic fibers related to thermoregulation of the body include sudomotor, cutaneous vasoconstrictor and muscle vasoconstrictor (Saper, 2002). Thermoregulation of the body requires differential control of sympathetic outflows to these effector tissues (Morrison, 2001; Saper, 2002). A hot environment stimulates sudomotor sympathetic activity while suppressing cutaneous vasoconstrictor activity. Conversely, exposure to a cold environment activates the sympathetic outflow to vasoconstrictor nerves and brown fat tissue (for heat production in infant and rodents) while inhibiting sudomotor nerves. Thus, sweating is essential for humans in hot environments. In contrast, a reduction in the cutaneous blood flow and dilation of deeper vascular beds are required in order to increase heat retention in cold environments. Some animals also increase the heat retention of fur by piloerection.

In addition to these efferent pathways from the brain via the sympathetic nervous system, afferent input from the body is essential for thermoregulation. Intriguingly, a neurobiological study in rats has revealed a thermosensory pathway that mediates physiological heat-defense responses to elevated environmental temperature (Nakamura and Morrison, 2010).

Sympathetic ganglia are composed of two neuronal populations that innervate various target organs: noradrenergic and cholinergic. Sympathetic postganglionic neurons are distinguished based on the neurotransmitter molecules they employ to convey information to target tissues or organs (Ernsberger, 2001). These neurotransmitters, noradrenaline and acetylcholine, are allocated to different populations of postganglionic sympathetic neurons. The great majority of sympathetic postganglionic fibers are noradrenergic, although eccrine sweat glands are exceptionally innervated by sympathetic cholinergic fibers originating from the paravertebral ganglia (Gabella, 1976). The noradrenergic fibers innervate blood vessels (vasoconstriction), smooth muscles and nerve plexi of internal organs, while the cholinergic fibers innervate eccrine sweat gland (sudomotor function) and the periosteum (Apostolova and Dechant, 2009; Francis and Landis, 1999). Interestingly, it is also known that autonomic postganglionic neurons in some species project into blood vessels in the skeletal muscle (Apostolova and Dechant, 2009) and in the orofacial region (Izumi, 1999) and exert a vasodilation function.

Sympathetic neurons originate from the neural crest (Gilbert, 2006) and are formed, depending on numerous signaling pathways and transcription factors (Apostolova and Dechant, 2009; Francis and Landis, 1999; Kameda, 2014). The generation of noradrenergic and cholinergic neurons in the sympathetic postganglionic neurons probably requires environmental cues and/or target-derived signals during development (Ernsberger, 2001; Francis and Landis, 1999). Cholinergic neurons are detectable later during sympathetic development in certain groups of postganglionic neurons, but only after target innervation. A model for the differentiation of sympathetic neurons is as follows: the noradrenergic and cholinergic phenotypes of sympathetic postganglionic neurons are concurrently induced and transiently co-expressed during early development (Apostolova and Dechant, 2009). In addition, each mature phenotype probably develops by positive and negative selection of cellular properties in initially bimodal neurons, depending on extracellular signals during migration and after target contact (Apostolova and Dechant, 2009). Some sympathetic neurons that have acquired a noradrenergic phenotype under negative selection may still be instructed to switch their phenotype under the influence of target-related factors (Apostolova and Dechant, 2009).

Of note, individuals with CIPA lack both noradrenergic and cholinergic sympathetic postganglionic neurons, due to defects in TrkA. Thus, one central hub of sympathetic development appears to be the neurotrophic factor NGF and its receptor tyrosine kinase TrkA. The NGF–TrkA system, regarded as a survival system for sympathetic neurons, also steers neurotransmitter synthesis and additional processes of neuronal maturation.

4.3. Neurons in brain regions that express TrkA mRNA

NGF-dependent neurons probably exist in various human brain regions, considering pathological changes observed in several neurological disorders and gene-knockout animals. Basal forebrain cholinergic neurons (BFCNs) in Alzheimer disease show a decrease in TrkA mRNA (Boissiere et al., 1997; Mufson et al., 2003). Significant down-regulation of TrkA expression is also observed during the development of

Alzheimer's disease (Ginsberg et al., 2006), and an imbalance in the expression of NGF and TrkA may be a critical factor underlying BFCN dysfunction in Alzheimer's disease (Mufson et al., 2008). These findings suggest that the dysfunction of TrkA-expressing neurons in the brain may underlie the deterioration of some cognitive or other functions observed in patients with Alzheimer's disease. In addition, the NGF–TrkA signaling might be involved in other neurological and/or neuropsychiatric disorders (Berry et al., 2012; Tirassa et al., 2015; Iannitelli et al., 2017).

Mice lacking TrkA show a decrease in the number of BFCNs projecting to the hippocampus and cortex (Smeyne et al., 1994), and these neurons do not mature fully in the absence of NGF–TrkA signaling (Fagan et al., 1997). Individuals with CIPA also show mental retardation and other characteristic behaviors and are probably neuron-deficient within the brain. A recent study has indicated that various brain regions of normal human brains show a relatively high expression of TrkA mRNA, based on data from the Allen Human Brain Atlas (Indo, 2014). These brain regions or structures include the basal forebrain, the striatum, the hypothalamus, the cerebellar nuclei, the basal part of the pons, the pontine tegmentum and the myelencephalon. Given these findings and those from studies in animal models lacking TrkA, it is likely that NGF-dependent neurons exist in the brain, although the functions of those neurons remain to be clarified.

5. Congenital insensitivity to pain

Several genetic disorders are known to be associated with congenital insensitivity to pain (CIP), a term often used to describe an impaired ability to perceive the type, intensity and quality of noxious (or painful) stimuli. Children with CIP often injure themselves severely, and the injury may go unnoticed, resulting in permanent damage (Indo, 2004). CIPA is the first human genetic disorder for which the molecular basis of CIP has been identified and is caused by loss-of-function mutations in the *NTRK1* gene-encoding TrkA (Indo et al., 1996).

Subsequent studies have identified the genetic bases of other forms of CIP, including CIP due to defects in NGF itself (Capsoni, 2014; Carvalho et al., 2011; Einarsdottir et al., 2004; Minde et al., 2004). Further genetic studies on individuals with CIP have also revealed channelopathy due to loss-of-function mutations in the *SCN9A* gene (Ahmad et al., 2007; Cox et al., 2006; Goldberg et al., 2007) or to gain-of-function mutations in *SCN11A* (Leipold et al., 2013)[see also Cox and Wood. (Cox and Wood, 2013)]. Intriguingly, a recent study has identified loss-of-function mutations in *PRDM12* (encoding a transcriptional regulator, PRDI-BF1 and RIZ homology domain-containing protein 12) as a genetic basis of CIP (Chen et al., 2015). The protein product of intact *PRDM12* is probably an epigenetic regulator involved in the sensory neurogenesis essential for pain perception.

6. Congenital insensitivity to pain with anhidrosis

This review focuses on CIPA as a characteristic human genetic disorder, since individuals with CIPA lack NGF-dependent neurons, providing rare opportunities to explore the unique function these neurons serve in our species.

6.1. Historical aspects

CIPA has prominent features of dysfunction of autonomic and sensory neurons in the PNS and probably some neurons in the CNS. Swanson described two male siblings with CIPA (Swanson, 1963; Swanson et al., 1965). He considered that the anatomic changes observed in CIPA were due to an abnormality in the differentiation of the small sensory afferent and sympathetic efferent neurons in embryogenesis, citing the pioneering work of Hamburger and Levi-Montalcini in the developmental biology of the neural crest in chicks (Hamburger and Levi-Montalcini, 1949). Pinsky and DiGeorge reported three mentally retarded children with CIPA (Pinsky and DiGeorge, 1966). These five patients presented with a history of recurrent febrile episodes, repeated traumatic and thermal injuries, self-mutilating behavior and mental retardation. Sweating was not able to be elicited by thermal, painful, emotional or chemical stimuli. Brown et al. also reported an additional case and proposed a defect in neural crest differentiation during the embryonic period to explain the phenotypes observed in CIPA (Brown and Podosin, 1966). Vassella et al. added a similar case report (Vassella et al., 1968). Intriguingly, two cases previously reported as 'generalized anhidrosis' (Nishida et al., 1951) or 'congenital generalized indifference to pain (congenital analgesia)' (Gillespie and Perucca, 1960), seem to share many features associated with CIPA, including insensitivity to pain and anhidrosis.

The absence of pain and temperature sensation and the presence of anhidrosis in CIPA are due to a loss of NGF-dependent neurons in the PNS, including NGF-dependent primary afferents and sympathetic postganglionic neurons. NGF-dependent primary afferents have been referred as 'afferent neurons activated by tissue-damaging stimuli' in previous articles (Goebel et al., 1980; Langer et al., 1981; Rafel et al., 1980; Swanson et al., 1965). A lack of pain leads to an inability to protect oneself from external or self-inflicted-damage. Therefore, children with CIPA can sustain severe and unrecognized injury, which is often slow to heal. Anhidrosis disturbs the homeostasis of the core body temperature and increases susceptibility to recurrent febrile episodes, since sweating is essential for maintaining normothermia in hot environments.

The findings derived from gene knockout mice lacking NGF (Crowley et al., 1994) or its receptors (Lee et al., 1992; Smeyne et al., 1994) provide a clue to the cause of CIPA. On testing the hypothesis that NGF signaling might be involved in individuals with CIPA, Indo et al. identified mutations in *NTRK1(or TRKA)* as the genetic basis of CIPA (Indo et al., 1996) [see also Wood 1996 (Wood, 1996)]. Loss-of-function mutations in *NTRK1* cause the lack of NGF-dependent neurons in individuals with CIPA.

6.2. Clinical features

CIPA is rare in most populations, although it has been reported worldwide. In Japan, the number of CIPA patients was estimated at between 130 and 210 in 2009 (Haga et al., 2015).

Recurrent episodic fevers due to anhidrosis are usually the first clinical sign and can begin in infancy or early childhood (Indo, 2008 Aug 5 [Updated 2014 Apr 17]). However, children with CIPA can develop hyperthermia or hypothermia, depending on the environmental temperature (Ismail et al., 1998; Loewenthal et al., 2005; Matsuo et al., 1981; Swanson, 1963). Recurrent febrile convulsions can also be induced by high environmental temperature in some individuals (Brown and Podosin, 1966; Ismail et al., 1998; Iwanaga et al., 1996; Pinsky and DiGeorge, 1966). The surface of the palms and soles gradually becomes thickening with cracks (Brown and Podosin, 1966). Palmoplantar hyperkeratosis is common with significant fissuring of the plantar skin (Bonkowsky et al., 2003; Mardy et al., 1999); however, these skin lesions are not obvious in early infancy. The hair on the scalp and body is distributed normally.

Self-mutilation, such as biting of the tongue, lips, and fingertips, frequently starts after the first teeth erupt and can lead to a bifid or absent tongue and missing fingertips (Amano et al., 1998; Ishii et al., 1988; Matsuo et al., 1981; Pinsky and DiGeorge, 1966; Vassella et al., 1968). The tip of the tongue, lip edges, and the distal ends of fingers are often missing due to self-biting. Physical trauma, such as bruises, cuts, burns and even fractures, do not provoke normal reactions and may often go unnoticed. Impaired pain perception is not recognized initially, but parents may recall that their children did not cry during immunization shots or venipuncture. Scars and abrasions in their skin increase as children get older.

When children with CIPA start to crawl and walk alone, they often

experience accidental injuries such as falls or burns. These injuries are not recognized and can lead to multiple scars and bone or joint fractures. Infections of deep tissues, such as osteomyelitis, occur commonly as a complication of bone or joint fractures and are slow to heal. Some children with CIPA may sustain painless deep heel ulcers that are slow to heal (Mardy et al., 1999).

Orthopedic deformities may be prominent at the elbow, knee, and ankle joints (Rafel et al., 1980). Recurring trauma to large weight-bearing joints, such as the ankles, knees and femoral joints, causes joint deformity and frequently induces neurogenic arthropathy (Charcot joints). Fingers or limbs may be missing as a result of self-mutilation or accidental injuries.

Blinking and lacrimation are normal (Rosemberg et al., 1994; Yagev et al., 1999). When emotionally upset or when deprived of some special privilege, individuals with CIPA cry and produce tears (Lee et al., 1976; Swanson, 1963). Chronic conjunctivitis and corneal ulcerations may occur as a result of some corneal hypoesthesia and can develop into corneal opacities or active corneal ulcers (Yagev et al., 1999). These corneal ulcers are characterized by very poor healing.

Various clinical complications associated with CIPA involve orthopedic (Bar-On et al., 2002; Ismail et al., 1998; Kim et al., 2013; Pinsky and DiGeorge, 1966; Szoke et al., 1996), dental (Amano et al., 1998), ophthalmological (Amano et al., 2006; Mimura et al., 2008; Yagev et al., 1999) and dermatological (Bonkowsky et al., 2003; Ismail et al., 1998; Pinsky and DiGeorge, 1966) problems [(see also (Indo, 2008 Aug 5 [Updated 2014 Apr 17]) and (Haga et al., 2015) for recent reviews). For surgical operations of various injuries or complications, anesthetic management is necessary in order to regulate the body temperature and accidental movements (Tomioka et al., 2002b).

Regarding the prognosis of CIPA, a previous study indicated that approximately 20% of affected children succumbed to hyperpyrexia within the first 3 years of life (Rosemberg et al., 1994). In a recent study, death from hyperpyrexia was relatively rare, but local and systemic infections were found to carry risks of death from sepsis (Shorer et al., 2001). High rates of mortality (22%) and severe morbidity (30%) were found in 31 Israeli Bedouin individuals with an average age of 5.2 years (Loewenthal et al., 2005); the cause of death included infectious diseases, cardiac arrest or unknown causes, with the age of death ranging between 40 days and 7 years.

6.3. Neurological examination

Individuals with CIPA show characteristic neurological findings. Painful stimuli fail to evoke either withdrawal responses or emotional changes (Swanson, 1963). Whole body areas, including cranial and visceral tissues, lack pain sensation. Temperature perception is also impaired, since consistent errors are made in a test to distinguish between hot and cold substances (Rafel et al., 1980; Swanson, 1963). Extreme cold or heat does not elicit the usual withdrawal response. Even passive or active movements of injured or broken joints fail to elicit pain sensation.

Touch, vibration and position senses are normal. The motor functions are usually normal, but repeated injuries to the motor neurons or joints can cause secondary dysfunctions. Deep tendon reflexes as well as superficial abdominal and cremasteric reflexes are normal; there are no pathological reflexes (Pinsky and DiGeorge, 1966). The sense of smell is probably normal, and there is no clinical evidence suggestive of any salivary gland dysfunction (Shorer et al., 2001). Corneal reflexes are inconsistently present (Yagev et al., 1999). Swanson's surviving patient was said to show a normal corneal reflex and probably perceived the corneal stimulus as a light touch without discomfort (Chatrian et al., 1975; Swanson, 1963). Puffs of air blown to the cornea of either eye elicit a direct and consensual blinking response consistently (Chatrian et al., 1975).

6.4. Mental aspects

Children with CIPA show mental retardation to variable degrees and characteristic behaviors. They have learning problems and show defects in conceptual thinking, abstract reasoning and social behavior (Pinsky and DiGeorge, 1966; Swanson, 1963). They may also show moderate to severe emotional disturbance and have a low frustration tolerance, resorting to tantrums in an effort to gratify impulsive wishes. Some may have difficulty establishing interpersonal relationships.

The developmental milestones are usually normal or mildly delayed in infancy. Toilet training may be delayed, and some remain incontinent of urine and feces (Brown and Podosin, 1966; Pinsky and DiGeorge, 1966). Mental development tests show that most children with CIPA are retarded, although results of such tests can vary (Rosemberg et al., 1994). Their behaviors are characterized as labile, hyperactive and erratic. Irritability, hyperactivity, impulsivity and acting-out behaviors observed in these children may improve with age.

A formal assessment of cognitive and adaptive behavior also suggests that many children with CIPA have intellectual disability (or learning disabilities) and severe attention-deficit-hyperactivity disorder (ADHD) (Levy Erez et al., 2010). Interestingly, that study identified an inverse relationship between age and the intelligence quotient (IQ) among children: the older the child with CIPA, the lower the IQ score. This decline in the cognitive function in older children may be due to various complications that children with CIPA suffer but remains to be clarified. Thus, children with CIPA have cognitive/behavioral problems, including hyperactivity, impulsivity and learning difficulties.

6.5. Laboratory examinations

Some laboratory examinations may reveal specific findings in indivuals with CIPA, although routine clinical studies of the blood, urine and cerebrospinal fluid are usually normal. Radiographic studies of the skeletal system may reveal fractures of bones, deformities and dislocations of joints, osteomyelitis, avascular necrosis and acro-osteolysis (Rafel et al., 1980; Rosemberg et al., 1994). Neurogenic arthropathy (Charcot joint) is often observed in the knees and ankles, as well as in other joints. Bone fractures are slow to heal, and prolonged inflammation may induce systemic amyloidosis (Toscano et al., 2000). Some individuals may show multisystem involvement, including putative immunological abnormalities, as described below.

Neurological studies such as electroencephalogram (EEG) and computed tomography (CT) usually show normal findings in the majority of individuals (Goebel et al., 1980; Matsuo et al., 1981), although nonspecific dilatation of the third or the lateral cerebral ventricle has been reported in some individuals (Schulman et al., 2001; Swanson, 1963; Vassella et al., 1968). The findings on magnetic resonance imaging (MRI) of the brain are normal (Ohto et al., 2004; Sztriha et al., 2001). However, a series of MRI studies in an individual with CIPA suggested that a recurrent high fever associated with generalized convulsions can lead to brain damage (Iwanaga et al., 1996).

Conduction velocities of motor and sensory neurons are usually normal (Goebel et al., 1980; Lee et al., 1976; Rafel et al., 1980). Somatosensory, visual, and brainstem-evoked potentials are also normal. However, recurring injuries related to severe neurogenic arthropathy can cause abnormalities of the evoked sensory potential in the lower extremities (Rafel et al., 1980).

6.6. Special studies

The evaluation of the sensory and autonomic functions in individuals with CIPA is useful for a clinical diagnosis as well as for the elucidation of pathophysiology.

6.6.1. Pain tests

(CAUTION: These tests should not be conducted routinely for

ethical reasons.)

Individuals with CIPA lack pain and temperature sensations and show abnormal patterns in pain-mediated reflexes (Swanson, 1963). Extreme cold or heat can be endured without discomfort. They do not move away from an ice cube applied to the back without notice, nor get goose bumps (piloerection). Corporal punishment holds little significance.

Painful stimuli usually provoke either withdrawal or emotional changes in healthy individuals but fail to do so in individuals with CIPA. Tried-and-tested painful stimuli were as follows: pin prick; vigorous pressure on the Achilles tendons, the testes, the stylomastoid processes, and the superior orbital rim; burning heat; immersion of the limbs in ice water; galvanic electrical stimulation of the skin; prolonged ischemia of the limbs (Swanson, 1963); testicular compression; periosteal irritation with a sterile needle; the application of a glass tube containing boiling water to the trunk or extremities (Pinsky and DiGeorge, 1966); strong electrical shocks; intramuscular injection of potassium chloride and urinary catheterization (Brown and Podosin, 1966). Interestingly, ultra-violet light did not provoke erythema or tanning after prolonged exposure (Brown and Podosin, 1966).

Visceral or intracranial pain perception is also impaired. No discomfort is elicited when a balloon is inflated in the lower esophagus or when pneumoencephalogram is performed (Swanson, 1963). The latter is a procedure previously used in neurosurgery, that often induces headaches during or after the procedure (Swanson, 1963). Electrical stimulation of the tooth pulp elicits pain and cerebral responses in healthy individuals, but did not generate cortical sensory potentials in Swanson's surviving patient, in whom the dentine of the occlusal surfaces of the teeth was exposed (Chatrian et al., 1975). The patient clearly perceived the sensation of touch and pressure on the teeth tested but experienced no pain and failed to recognize either cold or heat. This finding indicates that primary afferents innervating tooth pulp consist exclusively of Aδ- and C-fibers in healthy individuals (Chatrian et al., 1975).

6.6.2. Histamine test

Histamine test is used as a positive control in the skin prick test for diagnosis of allergic disorders. It is also useful for clinical diagnosis of CIPA. NGF-dependent primary afferents not only transmit afferent messages to the spinal cord dorsal horn (and from there to the brain), but their activation also initiate the process of 'neurogenic inflammation' in healthy individuals (Fig. 1). The 'neurogenic inflammation' means that well-known signs of inflammation (tumor, rubor, calor and dolor) develop upon activation of afferent neurons and the consecutive release of neuronal mediators (e.g. substance P and CGRP) from these neurons (Holzer, 1998; Sauerstein et al., 2000). The release of neuronal mediators from the peripheral nerve fibers not only induces vasodilation and plasma extravasation (leakage of proteins and fluid from postcapillary venules), but also activates many non-neuronal cells, including mast cells and neutrophils (Fig. 1). This is an efferent function of NGF-dependent primary afferents and also known as the 'axon reflex' in human skin (Izumi and Karita, 1988). A noxious stimulus to one branch of NGF-dependent primary afferents subsequently induces an impulse that moves centrally to the point of division of that afferent. The impulse is then reflected down the other branch reaching the arterioles at the point of division. Thus, afferent (orthodromic) impulses pass antidromatically to the arterioles and cause reflex vasodilation.

Histamine is a major product of mast-cell degranulation and a well-recognized mediator of acute inflammation and allergic reactions. The axon reflex is evaluated using an intradermal injection of histamine (Ishii et al., 1988; Lee et al., 1976; Pinsky and DiGeorge, 1966; Swanson, 1963). Histamine produces a wheal and a flare response (diffuse erythema surrounding the wheal) in healthy individuals. Afferents for axon reflex in humans (which is different from afferents responsible for axon reflex in rats) have been identified, and extravasation does not occur in humans (Schmelz et al., 1997; Schmelz et al., 2000; Lynn et al., 1996). In CIPA individuals, histamine causes a wheal but no flare response, and the injection and post-injection period are not perceived as painful, in contrast to healthy individuals who complain of burning pain or pruritus in the axon flare area.

6.6.3. Sweating tests

Sweating tests are useful for clinical diagnosis of CIPA, too. Warming in a heat chamber increases the rectal temperature in individuals with CIPA, but no definite sweating is noted (Swanson, 1963). However, slight moisture of the intertriginous areas of the skin of the neck, axillae and groin can occur and probably reflects delayed evaporation of insensible water (Swanson, 1963). The sympathetic skin response measures the electrical resistance of the palmar surfaces and evaluates emotional sweating responses. Pin prick, deep pain and startling sounds fail to produce a change in skin resistance in individuals with CIPA (Swanson, 1963). Thus, emotional sweating is completely absent.

The sweat glands can be directly stimulated by the intradermal injection of a cholinergic reagent (Indo, 2002), and the axon reflex mechanism probably mediates the sweat response to such compounds (Riedl et al., 1998; Wada et al., 1952). In individuals with CIPA, neither pilocarpine nor methacholine (mecholyl) stimulate local sweating (Pinsky and DiGeorge, 1966; Rafel et al., 1980). Electrical stimulation and intradermal injection of noradrenaline also fail to evoke local sweating (Swanson, 1963). Intriguingly, the intradermal injection of adrenaline induces no piloerection (Rafel et al., 1980).

6.6.4. Autonomic nervous system

Several studies to evaluate various functions of the autonomic nervous system have been reported in CIPA. In the cold pressor test, the submersion of the forearm in ice-cold water increases the blood pressure in healthy individuals but not in CIPA individuals (Goebel et al., 1980; Lee et al., 1976; Pinsky and DiGeorge, 1966; Swanson, 1963; Vassella et al., 1968). A paradoxical response of a slight decrease in the blood pressure has been reported during the cold pressor test (Swanson, 1963). This finding suggests a defect in either the cold-sensitive afferent neurons or sympathetic efferent neurons (Indo, 2009).

Ophthalmologic evaluations often reveal mild bilateral ptosis (Brown and Podosin, 1966), and the pupils are mildly miotic and equal in diameter. Painful stimuli applied to the neck cause a dilation of the ipsilateral pupil in healthy individuals, but this ciliospinal (skin-pupillary) reflex is absent in CIPA individuals. The combination of bilateral mild ptosis, bilateral anhidrosis and mid-position pupils is consistent with 'congenital bilateral Horner's syndrome'. The pupils fail to dilate in darkness but are briskly reactive to light, convergence and accommodation (Brown and Podosin, 1966). Adrenaline instilled into the conjunctival sac induced dilatation of the pupils, but cocaine produced no response. Methacholine (Mecholyl) produced miosis in a dark room, but this response was not seen in a well-lit room. These findings indicate sympathetic denervation of the eyes in individuals with CIPA (Brown and Podosin, 1966).

Carotid sinus massage, ocular pressure and mechanical stimulation of the external auditory meatus induce bradycardia in healthy individuals via the parasympathetic afferent pathway but do not alter the heart rate in CIPA individuals (Brown and Podosin, 1966). The lack of a response to these stimuli might suggest either a defect in afferent neurons, such as the glossopharyngeal, trigeminal and vagal nerves, or a defect in parasympathetic efferent neurons. Another study, however, reported that carotid sinus massage and the application of pressure to the eye slowed the pulse from 80 to 60/min and that intravenous injection of atropine induced tachycardia at 150/min (Rafel et al., 1980). This latter observation suggest that parasympathetic afferent and efferent neurons are both intact in individuals with CIPA.

In a study of sympathetic vasomotor control, the Valsalva maneuver produced a drop in blood pressure followed by a normal overshoot (Swanson, 1963). However, a recent study reported that two

individuals with CIPA who were able to perform the Valsalva maneuver adequately showed no overshoot in blood pressure after the strain (i.e. no phase IV) (Norcliffe-Kaufmann et al., 2015). This is a finding consistent with sympathetic noradrenergic impairment, but it may also suggest a defect in the baroreceptor neurons.

Individuals with CIPA have normal variability of the heart rate during spontaneous breathing, supporting the notion that the parasympathetic control of the heart rate is intact and the parasympathetic innervation of the heart is preserved (Norcliffe-Kaufmann et al., 2015). The ratio between low- and high-frequency values derived from spectrum measurements of the heart rate variability suggests a possible shift in the sympathovagal balance toward parasympathetic modulation in individuals with CIPA (Norcliffe-Kaufmann et al., 2015; Ohto et al., 2004).

Most sympathetic postganglionic neurons (except for sudomotor) release noradrenaline and are noradrenergic (Brodal, 2010b). In contrast, adrenaline is released from the chromaffin cells of the adrenal medulla by sympathetic stimulation. A study of catecholamine metabolites in the urine of an individual with CIPA showed a decrease in the levels of metabolites from noradrenaline and normal levels of metabolites from adrenaline (Shekim et al., 1980). That study also showed a decrease in the levels of the main metabolite from noradrenaline in the CNS. In the same individual, polygraph recording and the evaluation of some orienting response components revealed no obvious signs of autonomic perturbation (Daniel et al., 1980). These findings suggest decreased noradrenergic activity in the PNS as well as in the CNS. However, noradrenergic neurons and their function in the CNS of individuals with CIPA remain to be characterized.

Intriguingly, no postural hypotension is observed in individuals with CIPA, as tilting does not cause a decrease in the blood pressure (Pinsky and DiGeorge, 1966; Swanson, 1963). This finding is counterintuitive, as individuals with CIPA lack sympathetic postganglionic neurons. Indeed, plasma noradrenaline levels in individuals with CIPA are lower than in healthy individuals (Loewenthal et al., 2005). In an individual with CIPA under anesthetic management by propofol infusion, the plasma catecholamine levels did not change before or during surgery, indicating the lack of a sympathetic reaction during surgical stimulation (Uemura et al., 2010).

A recent study has confirmed these findings and shown that plasma noradrenaline levels are very low or undetectable and fail to increase when individuals with CIPA are upright; nevertheless, the upright blood pressure is well maintained (Norcliffe-Kaufmann et al., 2015). In contrast, plasma adrenaline levels are normal and increase when individuals with CIPA are upright. These results indicate that individuals with CIPA lack sympathetic postganglionic neurons, but chromaffin cells of the adrenal medulla are spared (Norcliffe-Kaufmann et al., 2015). The authors suggest that adrenaline release from the adrenal medulla and plasma renin release from the kidney are maintained in CIPA, compensating for the lack of noradrenaline release from sympathetic postganglionic neurons. A previous study also reported that the infusion of noradrenaline increased the systolic pressure, associated with erythematous blotching of the face and forehead (Pinsky and DiGeorge, 1966). This suggests that autonomic receptor sites on the vascular muscle become sensitive to exogenous vasopressor substances (Pinsky and DiGeorge, 1966). In addition, individuals with CIPA have a more pronounced initial increase in the heart rate upon head-up tilt than healthy individuals, indicating 'parasympathetic withdrawal' (Norcliffe-Kaufmann et al., 2015). However, in contrast to healthy individuals, the heart rate fails to increase further during prolonged orthostatic stress, suggesting a lack of sympathetic innervation of the sinoatrial node (Norcliffe-Kaufmann et al., 2015).

The phenomenon 'sensitization' can occur when the sympathetic postganglionic neurons to an organ are interrupted (Brodal, 2010b). The sensitivity of the organ to a neurotransmitter (which is no longer released) is increased. Thus, adrenaline and noradrenaline in the bloodstream may have a more powerful action after an organ has lost its sympathetic innervation than before (Brodal, 2010b). Taken together, these findings indicate that the development of sympathetic postganglionic neurons is affected while that of chromaffin cells in the adrenal medulla and parasympathetic efferent neurons is probably spared in individuals with CIPA.

6.6.5. Microneurography

Microneurography is a special laboratory method used to detect activities of sensory or sympathetic C fibers. It reveals no activity from either sensory or cutaneous sympathetic C fibers, while neural activity from Aβ sensory fibers linked to low-threshold mechanoreceptors can be detected in individuals with CIPA (Nolano et al., 2000). Consistent with this finding, the sympathetic skin response is also lacking. Intraneural electrical stimulation induces unbearable pain in healthy individuals but does not provoke any painful sensation in CIPA individuals. However, orthodromic sensory nerve conduction is conventionally induced by electrical and mechanical stimuli, and its velocity is normal. Visual and brainstem-evoked potentials are also normal. In a test of pure motor bundle, stretching of the muscle evokes intraneural activity from mechanoreceptor units (Nolano et al., 2000). These observations strongly suggest that individuals with CIPA lack unmyelinated (C) and small myelinated (Aδ) fibers in the PNS.

6.6.6. Control of physical activities

The function of the neuromuscular system is not impaired directly in individuals with CIPA, but sensory deficits may affect the motor control. A recent study examined the capacity for motor control in CIPA individuals and measured the grip force and acceleration of a held object in order to evaluate the grasping behavior (Kawashima et al., 2012). Temporal coupling between grip force and load is important for the grasping behavior. The grip force is significantly larger during the object grasp-lift-holding task in individuals with CIPA than in healthy individuals, albeit with less reproducibility and larger fluctuation in the acceleration of the object. Some individuals with CIPA indicate a lack of temporal coupling between the grip and load force. In the 'learning-based internal model', sensory feedback relays information on the object properties and mechanical events to modify motor commands and update internal representations automatically (Kawashima et al., 2012). Thus, anticipatory modulation and updating of the 'learning-based internal model' may be impaired in individuals with CIPA (Kawashima et al., 2012).

In another study, the features of gait were monitored and characterized by a video-recording method (Zhang et al., 2013). Young individuals with CIPA were found to walk faster, with a longer step length and higher heel contact angular velocity, than healthy individuals. The authors hypothesized that these characteristics might lead to a higher frequency of lower extremity injuries in CIPA individuals.

6.6.7. Herpes zoster in individuals with CIPA

Herpes zoster is considered to be due to the reactivation of latent virus that has remained in primary sensory neurons after varicella or chickenpox. Two individuals with CIPA suffered from herpes zoster, the reactivation of latent varicella-zoster virus (Ogata et al., 2007; Tomioka et al., 2002a). Both individuals complained of no pain, even though one suffered from severe skin eruptions on the face (Ogata et al., 2007). Curiously, the other complained of 'itching', although he had never done so even when bitten by mosquitos (Tomioka et al., 2002a). His 'itching' was probably different from ours and may have actually been some form of discomfort provoked by stimuli to sensory neurons other than NGF-dependent primary afferents, as individuals with CIPA lack the latter.

In primary infectious disease (varicella or chickenpox), varicella-zoster virus is considered to ascend sensory neurons from nerve endings in the skin to the dorsal or trigeminal ganglia, wherein it usually remains latent for the individual's lifetime (Ogata et al., 2007).

Intriguingly, a histopathological study on herpes zoster in individuals (without CIPA) indicates that sensory neurons with large fibers undergo degeneration, but those with small fibers are preserved in the early stage of the disease (Zacks et al., 1964). Further, an autopsy study of an individual (without CIPA) suffering from post-herpetic neuralgia suggested that neurons with myelinated fibers, but not those with unmyelinated fibers, are lost in the DRG (Watson et al., 1988).

Taken together, these findings suggest that varicella-zoster virus probably remains in the dorsal or trigeminal ganglia of primary sensory (afferent) neurons with large fibers rather than NGF-dependent primary afferents. When the latent virus is reactivated for some reasons, it descends these primary sensory neurons and reaches the skin to cause herpes zoster. Individuals with CIPA suffer from characteristic skin eruption associated with herpes zoster, but they probably do not develop herpetic or postherpetic neuralgia since they lack NGF-dependent primary afferents.

6.6.8. Putative disturbances of immunological functions

The immune system, including lymphocytes, expresses *NTRK1* [for a review, see Vega JA et al. (Vega et al., 2003)]. Peripheral blood mononuclear cells derived from individuals with CIPA show a reduced response to proliferative stimuli, including phytohemagglutinin (PHA) (Toscano et al., 2000). This may suggest a putative interaction between the immune system and NGF–TrkA system (Levi-Montalcini et al., 1996). Indeed, a defect in lymphocyte-signaling (Melamed et al., 2004), abnormal neutrophil activity (Beigelman et al., 2009) and humoral immunodeficiency (Kilic et al., 2009) have been described in individuals with CIPA. However, all but one of these individuals (Kilic et al., 2009) have shown normal immunoglobulin levels, a normal T-cell lymphocyte count and function, and the production of specific antibodies. The role the NGF–TrkA system plays in the immunological system remains to be elucidated.

Intriguingly, a recent study suggested that the NGF–TrkA system plays critical roles in pathogen-specific host immunity, particularly innate immunity to *Staphylococcus aureus* infection (Hepburn et al., 2014). With respect to this, the neutrophil chemotactic activity is impaired in individuals with CIPA (Beigelman et al., 2009), and this chemotactic defect may account for the high prevalence of severe skin and bone infections due to *Staphylococcus aureus* in CIPA. In addition to lack of NGF-dependent neurons, putative defects in the innate immunity may lead to a high rate of infection and persistent wound infections, with prolonged healing, osteomyelitis and septic arthritis often observed in individuals with CIPA (Indo, 2008 Aug 5 [Updated 2014 Apr 17]).

6.7. Histopathological studies

Histopathological studies on CIPA include nerve biopsies, skin biopsies and autopsy study.

6.7.1. Nerve biopsies

Nerve biopsy studies on CIPA have revealed characteristic findings. Electron microscopy studies on the cutaneous branch of the radial nerve in individuals with CIPA reveal the complete absence of small myelinated and unmyelinated fibers, lacking degenerative or regenerative changes (Rafel et al., 1980). This may suggest abnormal development of the nervous system as the pathogenesis of CIPA. Subsequent studies also indicate a reduction in the number of unmyelinated and small myelinated fibers of the sural nerve (Goebel et al., 1980; Matsuo et al., 1981) and the median nerve (Itoh et al., 1986) in individuals with CIPA. Morphometric analyses confirm these findings. An analysis of the cross-sectional area of the primary sensory neurons from healthy individuals showed a bimodal distribution, i.e. two morphological groups of neurons with a small or large diameter. In contrast, the same analysis of the neurons from individuals with CIPA showed a unimodal distribution, i.e. only a group of neurons with a large diameter. Taken together, the findings from these studies indicate the almost complete absence of primary afferent neurons with unmyelinated fibers and reduced numbers of primary afferent neurons with small myelinated fibers in individuals with CIPA.

6.7.2. Skin biopsies

Skin biopsies have also revealed characteristic findings in CIPA. The sweat glands, (Pinsky and DiGeorge, 1966; Swanson, 1963; Vassella et al., 1968), as well as sebaceous glands and hair follicles (Brown and Podosin, 1966), appear normal on a skin biopsy. Sensory receptors, such as Pacinian and Meissner's corpuscles, are observed normally (Vassella et al., 1968). However, nonspecific changes considered secondary to repeated trauma are occasionally observed in the epidermis (Rafel et al., 1980). Dermal nerves are normal in number and appearance on silver stain light microscopy (Itoh et al., 1986; Rafel et al., 1980).

Electron microscopic studies on the eccrine sweat glands reveal a lack of innervation by unmyelinated nerve fibers in individuals with CIPA (Ismail et al., 1998; Langer et al., 1981; Rafel et al., 1980). Sweat glands are not atrophic but intensively PAS-positive, while most glands are PAS-negative or weakly positive in healthy individuals (Itoh et al., 1986). Many dense exocrine secretory granules are also observed in the epithelia. Desmosomes, microvilli and other intracytoplasmic organelles of sweat glands appear to have a normal distribution (Itoh et al., 1986).

An immunohistochemical study of the skin from an individual with CIPA demonstrated the complete absence of epidermal fibers (all unmyelinated) and an almost complete absence of dermal fibers to blood vessels and erector pilomotor muscles (mostly unmyelinated fibers and small myelinated fibers) (Nolano et al., 2000). These findings in the skin are consistent with the observations on a nerve biopsy, with a loss of unmyelinated and small myelinated fibers.

6.7.3. Autopsy

An autopsy was performed in only one case with CIPA (Swanson et al., 1965), and a previous neuroanatomical study examined another individual with congenital universal insensitivity to pain (Baxter and Olszewski, 1960). The latter individual first reported by Dr. McMurray is probably the best-documented of all cases of congenital insensitivity to pain (Melzack and Wall, 1996). Given that anhidrosis and mental retardation were not apparent in this well-known individual, the genetic basis in this case seems to be different from that of individuals with CIPA. Indeed, neuroanatomical studies on this individual with congenital universal insensitivity to pain demonstrated no abnormalities of the central or peripheral nervous systems (Baxter and Olszewski, 1960).

In contrast, the autopsy of the above individual with CIPA showed characteristic defects in the sensory pathways (Swanson et al., 1965). Swanson reported two boys with CIPA (Swanson, 1963), and the younger died suddenly at 12 years of age after a 24-h febrile illness during which his body temperature exceeded 43 °C (Swanson et al., 1965). In the autopsy, hemorrhaging was noted in many tissues and attributed to the high fever. No obvious gross abnormalities were recognized in the brain or brainstem. The post-mortem examination revealed a normal ventricular system (Swanson et al., 1965), although the lateral ventricles had been mildly dilated on pneumoencephalography (Swanson, 1963).

The spinal tract of the trigeminal nerve in the brainstem was about one third of the normal size. A distinct decrease in the number of fine, lightly myelinated axons was observed in this tract, and the majority of fibers were of large diameter (Swanson et al., 1965). Sections of the posterior ventral lateral nucleus of the thalamus and the somatosensory cortex were normal.

In the spinal cord, the absence of Lissauer's tract (dorsolateral fasciculus) was remarkable and this tract could not be identified in myelin or axon-stained sections at any level (Swanson et al., 1965). The dorsal

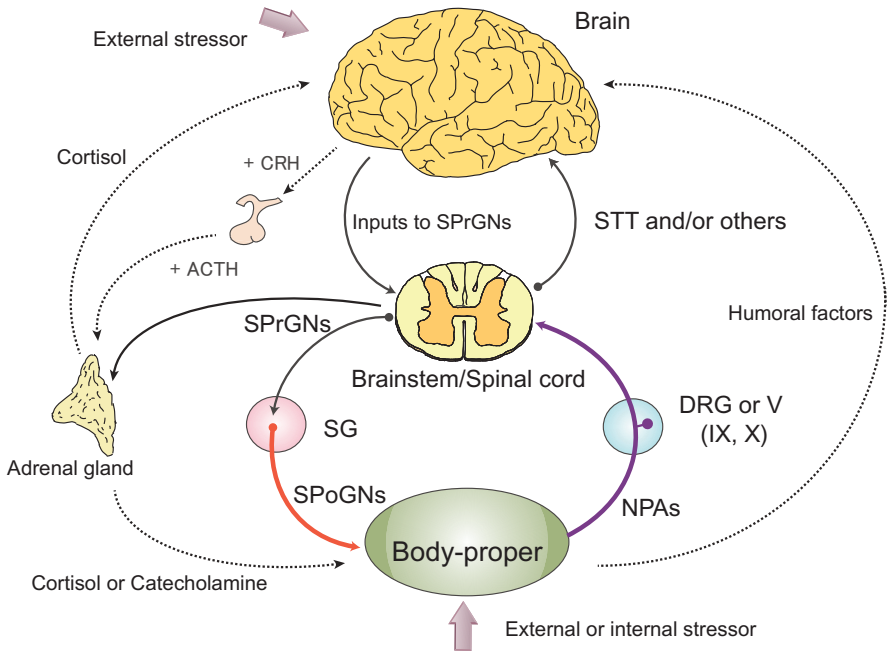

Fig. 2. NGF-dependent neurons in the peripheral nervous system and the stress system.

NGF-dependent neurons mediate reciprocal communication between the brain and the 'body-proper'. This diagram is a schematic presentation of the transmission signals that occur between the body-proper and the brain via NGF-dependent neurons, including NGF-dependent primary afferents (NPAs) and sympathetic postganglionic neurons (SPoGNs). The 'body-proper' refers to the organism minus the neural tissues (the central and peripheral components of the nervous system). NPAs and SPoGNs also form an interface between the nervous system and the body-proper and play critical roles in mediating cross-talk between the three 'super-systems': the brain and the immune and endocrine systems (Indo, 2012). The immune system here is included in the body-proper. NPAs report the physiological or pathological status of various tissues in the body to the brain via the spinal cord and brainstem, and the brain maintains homeostasis in the body via sympathetic neurons and other autonomic, neuroendocrine and behavioral mechanisms. External or internal stressors (shown by bold arrows) to the body-proper are triggering factor that may directly or indirectly stimulate NPAs. External stressors include temperature and mechanical stimuli, and internal stressors include a change in the local metabolism, cell rupture, a parasite penetrating the skin, the activation of mast cells and the activation of the immune and endocrine systems. External stressors to the brain specifically include triggering factors that may stimulate the 'stress system' (e.g. threats to life, mental conflicts that arise in human relationships, receiving bad news). The endocrine 'hypothalamic-pituitary-adrenal (HPA) axis' and the efferent 'sympathetic/adrenomedullary systems' are the peripheral limbs of the 'stress system' (Chrousos, 1995). NGF-dependent neurons in the peripheral nervous system are probably included in the peripheral limbs of the 'stress system', as indicated previously (Chrousos, 1995). The central components of this system are located in the hypothalamus and the brain stem (not shown). The systemic response of the stress system to dangerous signals is known as the 'fight-or-flight' response (Cannon, 1927). Humoral factors include cytokines. The immune system can affect the brain directly via cytokines in the blood flow during inflammatory responses (Chrousos, 1995; Paus et al., 2006; Roosterman et al., 2006; Sternberg, 2006). In response to these humoral factors, the brain affects the immune system via SPoGNs and the 'stress system'. The parasympathetic portion of the autonomic nervous system also plays an important role in the control of immunity and inflammation (not shown). The 'stress system' is engaged in coordinating and controlling complex responses of the brain and the immune system. Thus, NGF-dependent neurons in the peripheral nervous system constitute part of the neural network for interoception and homeostasis and play important roles in the 'stress response'. ACTH: adrenocorticotropic hormone; CRH: corticotropin-releasing hormone; DRG: dorsal root ganglia; SG: sympathetic ganglion; SPrGNs: sympathetic preganglionic neurons; STT: spinothalamic tract.

roots entered the spinal cord and turned medially into the posterior columns; the lateral portion usually continuing into the superficial dorsal gray horn was missing. The spinothalamic tracts could not be specifically identified (Swanson et al., 1965). The cells of the substantia gelatinosa and the anterior and posterior commissures were normal in number and morphology, and the lateral and ventral columns of the spinal cord appeared normal. The spinal dura mater was thickened, and many thin, traslucent, fibrous adhesions ran from the dura mater to the pia-arachoid around the spinal cord. Intriguingly, a transverse section through the cord and dura showed two slit-like cavities: one dorsal and one ventral (Swanson et al., 1965).

Cross sections of the dorsal roots revealed a nearly uniform large nerve fiber population with only a few small fibers scattered in the individual with CIPA, although large and small myelinated fibers were intermingled in healthy individuals (Swanson et al., 1965). In the dorsal root ganglia, an almost uniform population of large neurons replaced the normal pattern of large and small ganglion cells. No abnormalities were noted in the sympathetic ganglia or in the intermediolateral cell column of the spinal cord (Swanson et al., 1965). The autonomic ganglia appeared normal, although quantitative studies were not performed. The ganglion cells in the wall of the intestinal tract were normal.

7. Lessons from the pathophysiology and pathology of CIPA

The revelation that *NTRK1* is responsible for CIPA, together with the findings from animal studies, has greatly enhanced our understanding of the critical role that the NGF–TrkA system plays in the survival and maintenance of NGF-dependent neurons in humans. The pathophysiology of CIPA also provides unique opportunities to explore the critical functions of NGF-dependent neurons in human physiology. (According to the current nomenclature system, *Ngf* and *Ntrk1* in mice encode NGF and TrkA, respectively.) Neither *Ngf* nor *Ntrk1* knockout mice survive longer than one month (Crowley et al., 1994; Smeyne et al., 1994), hampering behavioral and physiological studies, whereas individuals with CIPA often survive into adulthood if they receive careful medical treatment. Thus, CIPA can serve as a valuable model in humans for determining the mechanisms of the survival and maintenance of NGF-dependent neurons in sensory, autonomic and central nervous systems, as well as their contribution to the physiology and neurobiology in our species.

Recent advances in the various fields of neuroscience have provided the tools for rethinking the conventional concept of neurophysiology and facilitated the proposal of conceptual changes in the somatosensory and autonomic systems (Craig, 2002) and their contribution to mental processes, such as 'emotions and feelings' (Damasio and Carvalho, 2013; Damasio, 1994). I will next discuss some critical roles that NGF-dependent neurons play in human physiology and neurobiology.

7.1. NGF-dependent neurons in interoception, inflammation, and homeostasis

NGF-dependent neurons probably contribute to the process of interoception, inflammation and homeostasis in individuals without CIPA. NGF-dependent neurons in the PNS include NGF-dependent primary afferents and sympathetic postganglionic neurons. Sympathetic postganglionic neurons form a well-defined efferent and direct pathway to target organs or tissues for maintaining homeostasis of the body. However, thus far, the afferent complement of the efferent sympathetic (or more broadly autonomic) nervous system has been somewhat confusing. Two words—the 'parasympathetic afferent system' and the 'sympathetic afferent system'—are conventionally used to classify afferent systems for visceral sensory information (Saper, 2002). A new word, the 'spinal visceral afferent system', has been proposed, considering the information that the two former systems carry. The 'spinal visceral afferent system' is sensory afferents from the internal organs as

a whole (Saper, 2002). This system, including the nociceptive sensations for monitoring tissue integrity, is considered to be internally directed and probably concerned with the state of the body itself (Saper, 2002). NGF-dependent primary afferents probably include most primary afferent neurons in the 'spinal visceral afferent system', as individuals with CIPA lack visceral pain.

The 'interoception' is a afferent system internally directed to the body itself and considered to be 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, muscles, joints, teeth and viscera (Craig, 2002). NGF-dependent primary afferents transmitting sensations from the body's interior are responsible for interoception (Indo, 2009, 2010) and form an afferent interface between the 'body-proper' and the nervous system (Indo, 2012) (Fig. 2). Thus, NGF-dependent primary afferents are also referred to as 'interoceptive polymodal receptors' (Indo, 2009, 2010). In contrast, sympathetic postganglionic neurons form an efferent interface between the nervous system and the body-proper and act as a neuronal network for maintaining homeostasis of the body (Indo, 2012, 2014) (Fig. 2). Together, NGF-dependent neurons in the PNS constitute homeostatic afferent and efferent pathways for homeostasis of the body and provide the basis for somato-autonomic reflex arcs.

NGF was discovered as a neurotrophic factor for the survival and maintenance of NGF-dependent neurons during embryonic development (Levi-Montalcini, 1987), but it also acts as an inflammatory mediator in adult animals (Dawes et al., 2013; McMahon, 1996; Pezet and McMahon, 2006; Denk et al., 2017). NGF changes the response properties of NGF-dependent primary afferents, as well as sympathetic postganglionic neurons, and plays a significant role as a mediator and modulator of pain, itching and inflammation. Thus, NGF itself can act as an active stimulator of 'interoceptive polymodal receptors', provoking various neurobiological processes.

Homeostasis is the process of maintaining the internal milieu physiological parameters (such as temperature, pH and nutrient levels) of a biological system within the range that facilitates the survival and optimal function (Shizgal and Hyman, 2013). NGF-dependent neurons in the PNS contribute to homeostasis of the body (Fig. 2), and here the physiological regulation of the core body temperature is cited as an example of the role played by NGF-dependent neurons in homeostasis. The brain receives information from internal sensors and acts on that information to regulate the body temperature. The internal temperature sensors of the PNS are NGF-dependent primary afferents (Indo, 2014). NGF-dependent primary afferents terminate in lamina I of the spinal dorsal horns and trigeminal nucleus, conducting information on the temperature via intervening pathways (such as the spinothalamic tract) to the brain. With regard to this, the parabrachial nucleus, the main brainstem homeostatic integration site, is considered to be very important relay nucleus for autonomic and somatosensory afferent transmission for the control of autonomic function (Craig, 2002; Saper, 2002).

In response to the body temperature sensed by NGF-dependent primary afferents, the brain, including the hypothalamus (the main autonomic control center) (Craig, 2002; Saper, 2002), maintain a constant core body temperature, regulating various tissues via efferent neurons, such as sympathetic postganglionic neurons (Fig. 2). These neurons then act on the sweat glands, piloerector muscles, blood vessels and striated muscles in humans. A fall in temperature induces vasoconstriction and piloerection (goose bumps) in the skin and involuntary shivering of the muscles. The organism may also voluntarily seek warmth in response to cold. A rise in temperature causes vasodilation of the skin to shunt blood toward the skin to dissipate heat, and the organism may voluntarily seek shade or some other way of cooling itself. In humans, sweating plays a critical role in maintaining body temperature in a hot environment, whereas panting is essential for dissipating heat in some other mammals, like dogs. A species-dependent mechanism for evaporative heat loss for the control of body temperature, such as sweating in humans, explains the characteristic phenotype of CIPA: anhidrosis associated with repeated episodes of a fever.

Hypothermia in a cold environment as well as hyperthermia in a hot environment are observed in individuals with CIPA. The dysfunction of NGF-dependent neurons, including NGF-dependent primary afferents and sympathetic postganglionic neurons, whether by preventing afferent information from reaching the brain or disrupting effector functions, leads to a labile regulation of body temperature observed in individuals with CIPA. In healthy individuals, the brain regulates the core body temperature via NGF-dependent neurons despite continual thermal changes. For homeostasis of the core body temperature, NGF-dependent primary afferents and sympathetic postganglionic neurons act as thermal receptors and effectors, respectively.

Thus, NGF-dependent neurons in the PNS constitute a part of the neural network for interoception and homeostasis and contribute to the survival of organisms by mediating the reciprocal communication between the brain and the body-proper.

7.2. Stress system and allostasis

The stress system regulates various functions of our body. NGF-dependent neurons in the PNS play critical roles in the stress system and probably in the biological process underlining 'allostasis'.

For our ancestors, predatory attacks were probably one of the most stressful challenges to homeostasis of the body. The sympathetic nervous system has evolved and adapted to evolutionary pressure to cope with these stressful challenges. This system induces the so-called 'fight-or-flight' response during extreme emotional or physical states, regulating a broad range of body functions (Cannon, 1927). The activation of both the cardiovascular and adrenal catecholamine systems is a typical physical change associated with the fight-or-flight response (Jansen et al., 1995). Modern lifestyles have almost eradicated the danger of predatory attack. Instead, we are faced with the increased awareness and prevalence of diseases such as hypertension, obesity and cardiac arrhythmia (Guyenet, 2006; Morrison, 2001).

The key concepts related to stress are homeostasis, stressors and adaptive response, which are defined as follows (Chrousos, 1998): 'Life exists by maintaining a complex dynamic equilibrium, or *homeostasis*, that is consistently challenged by intrinsic or extrinsic adverse forces or *stressors*. *Stress* is thus defined as a state of threatened homeostasis, which is reestablished by a complex repertoire of *physiologic and behavioral adaptive responses* of the organism' (Chrousos, 1998).

Extremely high- or low-temperature environments are stressors for organisms and are harmful to their survival (Fig. 2). Hyper- or hypothermia is a state of threatened homeostasis and should be reestablished by a set of physiologic and behavioral adaptive responses to regulate the body temperature. In this case, a sensed discrepancy between afferent information and a set point for response leads to the activation of effectors in order to reduce the discrepancy (Goldstein, 2008). The brain receives information from internal sensors and activates effectors based on that information to regulate the inner condition. NGF-dependent primary afferents and sympathetic postganglionic neurons work in the PNS as thermal receptors and effectors, respectively. Behavioral adaptive responses, such as seeking a cool place or warmth, supplement physiologic responses. We are motivated or driven to interact with our environment to keep our bodies within a narrow range of temperature.

The nervous, immune and endocrine 'super-systems' engage in multiple interactions in response to acute and chronic stress (Elenkov et al., 2000; Paus et al., 2006), and NGF-dependent neurons in the PNS play critical roles in mediating cross-talk among these 'super-systems' (Indo, 2012). The 'stress system' mainly functions to maintain basal and stress-related homeostasis (Chrousos, 1995). The 'hypothalamic–pituitary–adrenal (HPA) axis' and the 'systemic sympathetic and adrenomedullary (sympathetic) systems' are the peripheral components of the

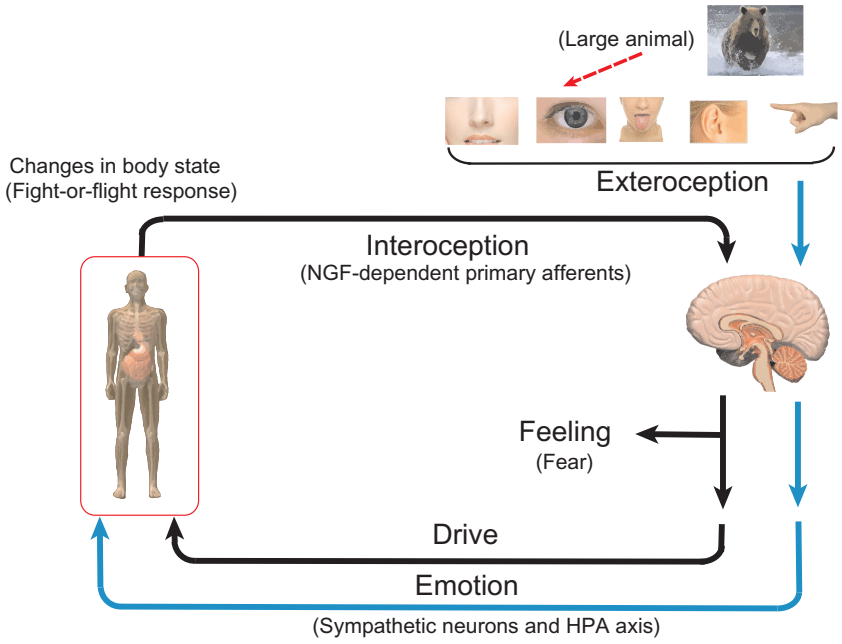

Fig. 3. NGF-dependent neurons in the peripheral nervous system and their contribution to neurobiological processes of 'emotions and feelings'.
The relationship between the brain and body-proper are illustrated in fear responses, according to the definition of 'emotion' and 'feeling' by Damasio and Carvalho (Damasio and Carvalho, 2013). The exteroceptive detection and mapping of an external threat (e.g. a large animal) triggers 'action programs' (the so-called 'fight-or-flight' response): a systemic response of the sympathetic nervous system to dangerous signals and activation of the 'stress system' in the brain. Changes in the body state caused by 'action programs' are in turn sensed by NGF-dependent primary afferents, signaled to the brain, and displayed as neural maps of the body ('interoceptive maps') (Damasio, 2010). Changes in the body state mapped in interoceptive neural maps may be experienced consciously as 'feelings' (or may remain unconscious in some instances) (Damasio and Carvalho, 2013). Damasio and Carvalho note that 'fear can refer to either an emotion (the set of programmed physiological actions triggered by a fear-inducing stimulus) or a feeling (the conscious experience of fear)' (Damasio and Carvalho, 2013). In these responses, NGF-dependent neurons in the peripheral nervous system mediate the reciprocal communication between the brain and the body-proper. Taken together, these findings indicate that these neurons play critical roles in the neurobiological processes of both 'emotion and feeling'.

stress system (Fig. 2), while the central components of this system are located in the hypothalamus and the brain stem (Chrousos, 1995). NGF-dependent primary afferents and sympathetic postganglionic neurons are considered components of the peripheral limbs of the stress system in immune-mediated inflammation (Indo, 2010).Thus, NGF-dependent primary afferents are directly involved in various inflammatory processes, including acute, chronic and allergic inflammation.

Further, these immune-mediated inflammatory reactions exert influence on the HPA axis via signal transduction to the brain through NGF-dependent primary afferents, as well as humoral factors (e.g. inflammatory cytokines) (Fig. 2). Sympathetic postganglionic neurons also secrete pro- and anti-inflammatory substances locally (Chrousos, 1995). Thus, NGF-dependent neurons in the PNS constitute neuronal components of the stress system and play pivotal roles in various inflammation reactions.

The physiologic systems stimulated by stress not only protect and restore the body, but can also harm it. If a complex repertoire of physiologic and behavioral adaptive responses is inadequate to maintain homeostasis or if it takes too long for the reestablishment of homeostasis, then the healthy steady state of the organism is not maintained, and pathology may ensue (Chrousos, 1998).

The sensitivity to stress is probably influenced by genetics, personal experience and behaviors. The term 'allostasis' is defined as the adaptive process of the organism for actively maintaining stability through change (Korte et al., 2005; McEwen, 1998). The physiologic and behavioral responses to acute stressors is adaptive (allostasis), whereas those to chronic stressors can lead to the dysregulation of various mediators and worsen the pathophysiology (allostatic load or overload) (McEwen, 2008). Some changes in behavior (poor sleep, eating or drinking too much, smoking, a lack of physical activity) are included in the concept of 'allostatic load' (McEwen, 2008).

NGF-dependent neurons in the PNS constitute the neuronal components of the stress system and probably contribute to the neurobiological process of allostasis (Fig. 2). Mediators of the stress system (and allostasis) include adrenal hormones (e.g. adrenaline and cortisol), neurotransmitters of sympathetic postganglionic neurons such as noradrenaline, neuropeptides released from NGF-dependent primary afferent neurons and various inflammatory mediators, such as immunocytokines. If these mediators are released too often or are inefficiently managed as a result of allostatic load/overload, suffering can ensue.

The brain is the central organ of stress. NGF-dependent neurons in the PNS form an interface between the nervous system and the body-proper (the organism minus the neural tissues) and play critical roles in mediating cross-talk between the three super-systems (Indo, 2012). NGF-dependent primary afferents report the physiological or pathological status of various tissues in the body-proper to the brain, and the brain maintains homeostasis in the body via sympathetic neurons and other autonomic, neuroendocrine and behavioral mechanisms. NGF-dependent neurons mediate part of the physiologic and behavioral responses to acute stressors. These responses are considered 'allostasis' if they are adaptive. NGF-dependent neurons are also involved in such responses of chronic stress. If these responses are prolonged and insufficiently managed under chronic stress, hyper-activity of NGF-dependent neurons persists over a long time. The dysregulation of various mediators released from NGF-dependent neurons probably exacerbates the pathophysiology (allostatic load or overload) and consequently can lead to suffering of the organism.

Thus, NGF-dependent neurons in the PNS, constituting a neuronal component of the stress system, play critical roles in allostasis, and their prolonged overactivity in daily life may lead to allostatic load or overload. Such maladaptive patterns of NGF-dependent neurons may occur during psychogenically elicited cardiac arrhythmias or mental disorders (e.g. posttraumatic stress disorders). Further analyses of NGF-dependent neurons in the stress system may provide a unique approach to understanding and controlling or even reversing the maladaptive patterns observed in stress-related disorders in our modern lifestyles.

7.3. Emotions and feelings

Recent advances in various fields of neuroscience are revealing neurobiological processes of emotions and feelings. Here described is the relationship between NGF-dependent neurons and neurobiology of emotions and feelings.

Pain is not only a personal and subjective sensation in a part or parts of the physical body, but also an unpleasant and therefore an emotional experience. 'Individuals with an intact ability to sense pain learn the application of the word through experiences related to injury in early life' (Merskey and Bogduk et al., 1994)(IASP Taxonomy). Individuals with CIPA lack pain sensation and therefore have difficulty learning the application of the word to suitable situations. They also are unable to accumulate the various emotional experiences associated with pain in daily life.

The brain always monitors our internal and external environments (Fig. 3). Changes in the external environment are perceived via the exteroceptive senses (smell, sight, taste, hearing and touch) (Kandel et al., 2013). In contrast, changes in the internal environment of our body are sensed and monitored by the 'interoceptive system' (Craig, 2002). Pain occurs in the body, i.e. our interior environment and is sensed by the interoceptive system. The 'interoceptive system', a collection of nerve pathways and CNS nuclei dedicated to detecting and mapping homeostatic signals, comprises the nociceptive system for pain. The main pathways for the 'interoceptive system' are the lamina I (spinothalamocortical) pathway and the vagus nerve (Craig, 2002).

There has long been a 'missing link' in autonomic research: 'the gap between understanding visceral sensory systems and their role in emotion versus the ways in which emotional and cognitive responses impact autonomic function' (Saper, 2002). Advances in the various fields of neuroscience have narrowed this gap. NGF-dependent neurons in the PNS described here may provide some anchor points for future investigation of the 'missing link' (Fig. 3). These neurons constitute a part of the neural network for interoception and homeostasis and mediate reciprocal communication between the brain and the body-proper (Indo, 2012). These neurons probably play important roles in emotions and adaptive behaviors.

More than 20 years ago, Damasio proposed a neurobiological definition of 'emotion and feeling', emphasizing the role of reciprocal communication between the brain and body-proper (Damasio, 1994). According to this definition, 'emotion is a collection of changes occurring in both brain and body, usually prompted by a particular mental content and feeling is the perception of those changes' (Damasio, 1994) (Damasio, 1994 p270 in Penguin Books 2005). Intriguingly, the sympathetic skin response, which evaluates emotional or mental sweating, is used to demonstrate such a change occurring in emotion. Intact sympathetic postganglionic neurons are absolutely imperative for this response. Damasio also later indicated that the 'interoceptive system' plays critical roles in 'feelings', conveying visceral signals and signals from the body's milieu to the brain (Damasio, 2003). Intact NGF-dependent primary afferents are essential for interoception, as described above. Taken together, these findings indicate that NGF-dependent neurons in the PNS contribute to the neurobiological processes of both 'emotion' and 'feeling' (Fig. 3).

Recently, Damasio and Carvalho also stated that 'feelings are mental experiences of body states' and introduced the concept 'action programs', including 'drives' and 'emotions' (Fig. 3) (Damasio and Carvalho, 2013). The 'action programs' are aimed at maintaining or restoring homeostatic balance and defined as 'a set of innate, physiological actions triggered by changes in the internal or external environments' (Damasio and Carvalho, 2013). 'Drive' is aimed at satisfying a basic, instinctual physiological need (e.g. hunger and thirst), while 'emotions' are largely triggered by external stimuli (perceived or recalled) (e.g. fear and anger), although 'drive and emotions' are together referred to as emotions by some authors (Damasio and Carvalho, 2013). Actions induced by 'action programs' include changes in the viscera and internal milieu (e.g. alterations in heart rate, breathing and hormonal secretion), striated muscle (e.g. facial expressions and running) and cognition (e.g. focusing attention and favoring certain ideas and modes of thinking (Damasio and Carvalho, 2013).

In the case of fear, the exteroceptive detection and mapping of an external threat (for example, a large animal) triggers 'action programs' (so-called 'fight-or-flight' response) (Fig. 3): the systemic response of the sympathetic nervous system to dangerous signals and the activation of the stress system in the brain (Cannon, 1927). These include increased heart and respiratory rates, the secretion of cortisol and adrenaline, the redistribution of the blood flow, analgesia, specific facial expressions, and attention focused on the perceived threat. Changes of the body state caused by 'action programs' are in turn sensed by the 'interoceptive system' (Craig, 2002), signaled to sensory regions of the brain committed to body functions and displayed as 'neural maps of the body' ('interoceptive maps') (Damasio, 2010). Changes in the body state mapped in interoceptive neural maps may be experienced consciously as 'feelings' (or may remain unconscious in some instances) (Damasio and Carvalho, 2013). Thus, changes occurring in the external environment are displayed in the exteroceptive maps of visions or hearing and may cause 'feelings' by triggering 'action programs' indirectly. Damasio and Carvalho note that an action program and the corresponding feeling are often referenced using the same name, although they are distinct phenomena (Damasio and Carvalho, 2013). For instance, these authors mention that 'fear can refer to either an emotion (the set of programmed physiological actions triggered by a fear-inducing stimulus) or a feeling (the conscious experience of fear)'.

When humans are exposed to danger or trauma, the stimuli or contexts associated with the danger or trauma become learned triggers that unleash emotional responses (LeDoux, 2000). The triggers for fear can be external (such as a threat) or internal (such as an evolving myocardial infarction) (Damasio and Carvalho, 2013). Thus, 'fear conditioning' is established by pairing the stimuli or contexts with danger or trauma (LeDoux, 2000). Subsequently, these learning or cognitive processes coupled with action programs contribute to the prevention of danger or trauma. Pain is an alarming signal provoked by tissue damage and is essential for the survival of organisms. Indeed, an animal species would become extinct in the course of evolution if it were unable to sense pain. NGF-dependent primary afferents are an essential component for the 'interoceptive system', thereby contributing to the protection of the body. Interestingly, a subset of C-fibers also mediates the affective aspects of touch and likely operates as an additional component of the 'interoceptive system' (Olausson et al., 2002). The processing of bodily signals therefore largely relies on unmyelinated structures, i.e. NGF-dependent primary afferents. Changes at the cellular level in unmyelinated structures temporally synchronize across individual neurons via 'ephaptic communication' and probably contribute to the experience of feelings (Damasio and Carvalho, 2013). Sympathetic postganglionic neurons are also essential for the survival, playing critical roles in the homeostasis of the body and emotions. Since sympathetic postganglionic fibers are also unmyelinated, they may temporally synchronize across individual neurons via ephaptic communication and contribute to the emotional responses.

Individuals with CIPA teach us how these biological processes performed by NGF-dependent neurons are important, as they are always in danger of dying. This is probably why NGF-dependent neurons in the PNS are conserved in the course of evolution. 'Emotions' are action programs that are largely triggered by external stimuli (perceived or recalled) and are essential for the survival of an organism. 'Feelings' constitute a crucial component of the mechanisms of life regulation (Damasio and Carvalho, 2013). The 'interoceptive system' monitors the state of the body, orchestrates responses thereto, and has a central role in generating feelings. Neural substrates of emotions and feelings can be found at all levels of the nervous system, as pointed out by Damasio and Carvalho (Damasio and Carvalho, 2013). The crucial neurons in the PNS essential for 'emotions and feelings' are sympathetic postganglionic neurons and NGF-dependent primary afferents, respectively. These NGF-dependent neurons therefore play a critical role in 'emotions and feelings' and probably contribute to the neurobiological basis of the mind-body relationship

8. Concluding remarks

The NGF–TrkA system is important for establishing the peripheral neuronal network to mediate reciprocal communications between the brain and the body-proper in embryonic development. This system also contributes to the regulation of those networks in adults, which in turn are involved in various biological processes, including pain, interoception, homeostasis and inflammation, as well as emotions and feelings. Individuals with CIPA have various symptoms related to the CNS, such as mental retardation and hyperactivity. However, the

neurological mechanisms underlying those symptoms remain to be elucidated. *NTRK1* is expressed in the brains of non-affected individuals, suggesting the existence of NGF-dependent neurons in the human brain (Indo, 2014), perhaps like the cholinergic neurons of the basal forebrain. The elucidation of putative neuronal networks consisting of NGF-dependent neurons in the brain and their functions will provide insight into the neurobiological basis for intractable pain, interoception, homeostasis, the stress system and allostasis, as well as emotions and feelings in our species.

Conflict of interest

The author reports no conflict of interest.

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