Review

Nerve growth factor, interoception, and sympathetic neuron: Lesson from congenital insensitivity to pain with anhidrosis

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Abstract

Nerve growth factor (NGF) is a well-known neurotrophic factor essential for the survival and maintenance of sensory and sympathetic neurons. Congenital insensitivity to pain with anhidrosis (CIPA) is a genetic disorder due to loss-of-function mutations in the *NTRK1 (*also known as *TRKA)* gene encoding TrkA, a receptor tyrosine kinase for NGF. Patients with CIPA provide us a rare opportunity to explore the developmental and physiological function of the NGF-dependent neurons in behavior, cognitive, and mental activities that are not available in animal studies. Here, I discuss the significance of findings that patients with CIPA lack NGF-dependent neurons, including interoceptive polymodal receptors, sympathetic postganglionic neurons, and probably several types of neurons in the brain. They also exhibit characteristic emotional behavior or problems. Together, the NGF-TrkA system is essential for the establishment of a neural network for interoception and homeostasis that may underlie 'gut feelings'. Thus, NGF-dependent neurons play a crucial role in emotional experiences and decision-making processes. Prospective studies focused on these neurons might provide further insights into the neural basis of human emotion and feeling.

Keywords:
Nerve growth factor (NGF); Receptor tyrosine kinase for NGF; TrkA protein; *NTRK1* gene; *TRKA* gene; Congenital insensitivity to pain with anhidrosis; Interoception; Polymodal receptor; Sympathetic neuron; Basal forebrain cholinergic neuron; Emotion; Pain; Homeostasis; Hereditary sensory and autonomic neuropathy type IV

NGF is a neurotrophic factor essential for the survival and maintenance of various types of neurons, including the nociceptive neurons, sympathetic neurons, and some neurons of the central nervous system (Levi-Montalcini, 1987; Pezet and McMahon, 2006; Reichardt, 2006). CIPA or hereditary sensory and autonomic neuropathy type IV is a rare autosomal recessive genetic disorder due to loss-of-function mutations in the *NTRK1* (also known as *TRKA*) gene (Indo et al., 1996, 2001; Indo, 2001, 2002, 2004; Mardy et al., 1999, 2001; Miura et al., 2000). Defects in NGF-TrkA signal transduction lead to failure of survival of various NGF-dependent neurons, since these neurons are not maintained due to apoptosis during development. CIPA is the first human genetic disorder in which the molecular basis of congenital insensitivity to pain has been identified. The clinical phenotype of CIPA is characterized by insensitivity to noxious stimuli, anhidrosis (inability to sweat), and mental retardation (Axelrod, 2006; Freeman, 2005; Indo, 2001, 2002, 2004; Swanson, 1963; Swanson et al., 1965). Pain is an unpleasant sensory and emotional experience, but offers one of the best protective mechanisms favoring survival. Individuals attend to pain signals and act to avert their source or correct their consequences. Pain is also essential for the proper development drives and instincts, and probably for the development of related decision-making strategies. Alterations in pain perception often lead to behavioral impairment. Sweating is regulated by the autonomic nervous system and is important in maintaining body temperature, especially in humans. Anhidrosis therefore causes hyperthermia in patients with CIPA in hot environmental conditions. Thus, patients with CIPA provide a rare opportunity to explore the developmental and physiological functions of the NGF-TrkA system in behavior, cognitive, and mental activities in humans.

Primary afferent fibers of small diameter (Aδ and C fibers) mediate pain and temperature sensation. However, recent studies have uncovered important evidence that these small-diameter afferent fibers also transmit a sense of the body's interior, an interoceptive sense (Craig, 2002). These fibers innervate all tissues of the body and terminate in lamina I of the spinal dorsal horns and trigeminal nucleus, conducting information regarding all manner of physiological conditions via various intervening pathways into the brain. Accordingly, the primates including humans have a distinct cortical image of afferent activity that reflects all aspects of the physiological condition of all tissues of the body, the interoceptive system (Craig, 2002, 2003a, 2003b, 2003c; Craig et al., 2000). The interoceptive system is considered a homeostatic afferent pathway that represents the physiological status of all tissues of the body, including the mechanical, thermal, chemical, metabolic, and hormonal status of the skin, muscle, joints, teeth, and viscera. In response to physiological changes in the body, the autonomic nervous system plays an important role as a system involved in feedback

regulation. Thus, the interoceptive system and the autonomic nervous system provide the substrate for the somato-autonomic adjustments that are continually being made by homeostatic processes. Intriguingly, patients with CIPA lack not only the interoceptive polymodal primary afferent fibers, but also autonomic sympathetic efferent neurons (Axelrod, 2006; Freeman, 2005; Swanson, 1963; Swanson et al., 1965; Indo, 2002 , 2004).

Emotions are considered a part of homeostatic regulation devoted to an organism's survival (Iversen et al., 2000). Recent advances in neural science have elucidated intriguing mechanisms of emotion or emotional behaviors with the use of multidisciplinary approaches (Adolphs, 2002; Buchel et al., 1998; Craig, 2002; Damasio, 1994, 1999, 2003; Damasio et al., 2000; LeDoux, 1996, 2000, 2002). Neuroimaging studies in humans have identified cortical and subcortical brain regions involved in the neural basis of emotion and feeling (Adolphs, 2002; Buchel et al., 1998; Damasio et al., 2000). Findings from experimental animals have contributed to progress in understanding the cellular and molecular mechanisms of emotions, especially fear conditioning (LeDoux, 2000). Both human and animal studies have clearly contributed to understanding of specific brain regions and associated neural networks involved in emotion. On the basis of neurological analyses of patients with brain lesions, the 'somatic marker' hypothesis has been advanced (Damasio, 1994, 1996). The hypothesis includes the entire pattern of somatic and visceral feedback from the body. Such information may underlie 'gut feelings' and play a crucial role in our emotional experiences and decision-making processes. This challenging hypothesis proposes that the subjective process of feeling emotions requires the participation of brain regions that are involved in the mapping and /or regulation of changing internal states – that is, in homeostasis. CIPA may provide insights useful for testing the 'somatic marker' hypothesis, since patients with CIPA lack both afferent and efferent pathways essential for homeostatic regulation.

Here, I discuss the significance of findings that patients with CIPA lack interoceptive polymodal receptors, sympathetic postganglionic neurons, and probably several types of neurons in the brain, including basal forebrain cholinergic neurons (BFCNs). Accordingly, it is likely that these patients fail to exhibit emergency or 'fight-or-flight' reactions. They also exhibit certain emotional problems, and fail to exhibit characteristic protective behaviors in response to various harmful conditions. The NGF-TrkA system thus contributes to establishment of a neural framework for homeostatic regulation and emotion that leads to proper behavioral drive. These findings serve as a helpful guide to future studies in identifying specific brain regions and neural networks involved in human emotion and feeling.

1. Congenital Insensitivity to Pain with Anhidrosis

Patients with CIPA lack Aδ and C primary afferent fibers. They are therefore unable to respond to changes in the physiological condition of all tissues of the body. Patients exhibit insensitivity to both superficial and deep painful stimuli (Axelrod, 2006; Freeman, 2005; Indo, 2002, 2004; Swanson, 1963; Swanson et al., 1965). Visceral pain perception is also impaired. Touch, vibration, and position senses are normal. Motor functions are normal, although repeated trauma can result in secondary dysfunction of the motor system. Patients with CIPA specifically lack interoceptive polymodal receptors, and, accordingly, interoception.

Patients with CIPA also lack the sympathetic postganglionic neurons. Sweating is controlled by the sympathetic nervous system and is important in maintaining body temperature, especially in humans. Because patients with CIPA do not sweat, they tend to develop hyperthermia when they are in a hot environment. Patients with CIPA also lack sympathetic innervation of various target tissues, and therefore exhibit defects in sympathetic regulation. Thus, patients with CIPA cannot properly maintain a variety of neural processes, including those related to autonomic, neuroendocrine, and behavioral responses in the body.

Patients with CIPA probably lack some neurons in the brain as well. Children with CIPA are mentally retarded and exhibit severe learning deficits. Affected children demonstrate defects in conceptual thinking, abstract reasoning, and social behavior, and exhibit symptoms of moderate to severe emotional disturbance (Pinsky and DiGeorge, 1966; Swanson, 1963). Hyperactivity and emotional lability are common. Their behavior is characterized as labile, hyperactive, and erratic. They have a low frustration tolerance, resort to tantrums in an effort to gratify impulsive wishes, and avoid attempts to establish interpersonal relationships. These emotional or learning problems suggest defects of NGF-dependent neurons in the brain.

Neuroanatomical studies of the forebrain in CIPA would be intriguing, though no obvious gross abnormalities were recognized in one patient examined more than four decades ago (Swanson et al., 1965). However, the corresponding gene-knockout mice lack BFCNs and striatal cholinergic neurons (Smeyne et al., 1994). BFCNs include those of the nucleus basalis of Meynert, medial septal nucleus, and the vertical and horizontal nuclei of the diagonal band (Broca) (Mesulam et al., 1983). BFCNs are projection neurons, the axons of which extend throughout the hippocampus and neocortex and are important for learning, memory, and more specifically processes of attention (Blokland, 1996). Striatal cholinergic neurons are large interneurons involved in the control of movement. Recent studies of rodents and humans suggest that striatum is critical for the procedural memory involved in forming behavioral habits (Bear et al., 2007). Neither BFCNs nor striatal cholinergic neurons in the knockout mice mature fully in the absence of NGF/TrkA signaling (Fagan et al., 1997). It is thus likely

that patients with CIPA lack the corresponding neurons in humans.

2. Animal Studies Suggest the Existence of Other NGF-Dependent Neurons in the Brain

Neuroanatomical studies on the brains of rats and mice suggest that specific neurons express the TrkA receptor (Gibbs and Pfaff, 1994; Holtzman et al., 1995; Sobreviela et al., 1994). TrkA mRNA is detected within cells located in BFCNs as well as in the caudate, raphe nuclei, interpeduncular nucleus (IPN), prepositus hypoglossal nucleus, vestibular nuclei, cochlear nucleus, gigantocellular as well as perigigantocellular neurons in the medullary reticular formation, paraventricular and reuniens nuclei of the thalamus, the area postrema, sensory trigeminal nuclei, and scattered neurons in the ventrolateral and paramedian medulla. In addition, TrkA-immunoreactive neurons are observed among BFCNs, in the striatum, raphe nuclei, IPN, prepositus hypoglossal nucleus, medial vestibular nucleus, ventral cochlear nucleus, paraventricular and reuniens nuclei of the thalamus, periventricular hypothalamus, mesencephalic and oralis portions of the spinal trigeminal nucleus of the fifth nerve, nucleus accumbens, dorsal nucleus of the lateral lemniscus, ventral lateral tegmentum, solitarius tract nucleus, and olfactory tubercle (Sobreviela et al., 1994).

The ‘modular’ neurons, such as BFCNs and serotonergic neurons in raphe nuclei, exert powerful effects on virtually the entire set of neural circuits that can be modified by experience (Coull and Thiele, 2004). Both acetylcholine and serotonin are principal neurotransmitters whose actions contribute to virtually all aspects of behavior and cognition. These chemicals are released in widespread regions and can influence processing by other neural circuits. Intriguingly, neurons of the raphe nuclear complex contain the protein and mRNA for TrkA (Gibbs and Pfaff, 1994; Sobreviela et al., 1994). The raphe nuclei of the brainstem provide the major source of serotonergic neurons in the central nervous system and are systemically organized so as to differentially innervate discrete regions of the brain. Serotonergic afferents from the raphe nucleus also innervate the striatum in rat and may have a potent excitory effect on striatal cholinergic interneurons (Bonsi et al., 2007). Thus, the NGF-TrkA system might specify at least some ‘modular’ neurons that distribute neurotransmitters to widespread regions of the cerebral cortex and subcortical nuclei.

It is also interesting to note that the IPN contains TrkA protein and mRNA (Gibbs and Pfaff, 1994; Holtzman et al., 1995; Sobreviela et al., 1994). The IPN receives the retroflex fasciculus from the habenula, and projects to the raphe nuclei and periaqueductal central gray (PAG) of the midbrain. This axial anatomy of the habenula-IPN is shared by numerous brain circuits that subserve diverse functions and might be involved in a variety of brain functions and behaviors, including nociception, learning and memory, motor activity, sexual and

maternal behavior, stress, affective states (anxiety, depression, and reward phenomena), sleep, and eating and drinking behavior (Klemm, 2004). Intriguingly, the IPN also receives inputs from the BFCNs and has widespread projections, both ascending to limbic structures and descending to the midbrain raphe nuclei, PAG, and tegmental nuclei. PAG is known to be involved in well-coordinated production of emotion, producing different types of fear reaction - the type that ends in fight-or-flight behavior or, instead, in freezing behavior (Damasio, 2003). The NGF-TrkA system might thus be involved in various brain functions and behaviors via establishment of the habenula-IPN axis, although further studies are needed to confirm this.

Brainstem neurons in the perihypoglossal area relay information from the inner ear and vestibular apparatus to the cerebellum and tectum. Some of these neurons are responsive to NGF and express the TrkA receptor. These neurons, located in the prepositus hypoglossal nucleus, spinal vestibular nucleus, cochlear complex, and gigantocellular and paragigantocellular nuclei of the reticular formation, are believed to be involved in vestibular-auditory gaze control function (Sukhov et al., 1997). With regard to gaze control, it is interesting to note that expression of anger often involves direct gaze in both humans and other animals (LeDoux, 1996). In addition, both humans and other animals tend to respond immediately to an unexpected loud noise or sudden movement, orienting toward the stimulus (LeDoux, 1996). In connection with this finding, a neurophysiological study has suggested that both the prepositus hypoglossal nucleus and medial vestibular nucleus might participate in central cardiovascular regulation (Talman and Robertson, 1991). In either case, these neurons together appear to be related to some types of emotional expression. Elucidation of the functional significance of these brainstem neurons awaits further study.

Furthermore, retrograde transport of NGF from the hippocampus and amygdala to TrkA messenger RNA-expressing neurons in the paraventricular and reuniens nuclei of the thalamus has been demonstrated in rat, suggesting a physiological role of this trophic factor in the function of these cells (Venero et al., 1995). The thalamic paraventricular anterior and reuniens nuclei are considered parts of the reticular formation that play a role in general cortical activation, behavioral arousal, and control of awareness. Again, these neural structures might be related to emotional expression.

In parallel to these neural pathways, chemical signals such as hormones and peptides released in the body can reach the brain via the bloodstream. Chemicals flowing in the bloodstream are sensed by nuclei of neurons in some regions of the brain (Damasio, 1999). Examples of such regions are the area postrema and the subfornical organs. The chemically excited neurons in these areas pass information to other neurons. It is interesting to note that

the area postrema, a region expressing TrkA mRNA, lacks a blood-brain barrier, allowing chemical signals to penetrate the brain directly. Thus, some NGF-dependent neurons in the brain might function as interoceptive receptors for chemical signals released in the body and brought to the brain via the bloodstream.

Further studies are needed to determine the functional significance of various nuclei or neurons expressing TrkA.

3. Patients with CIPA Exhibit Phenotypic Characteristics Not Observable in Mutant Animals

Although CIPA patients and TrkA gene knockout mice share some characteristic behaviors and features (Indo, 2002, 2004; Smeyne et al., 1994), some behaviors and clinical features in human CIPA are not apparent or not recognized in the mutant mice. The reason for this might involve species differences or, alternatively, technical difficulties in the analysis of mice. Indeed, gene knockout mice die within a month, hampering extended behavioral and neurophysiological studies.

Patients with CIPA probably lack a subset of NGF-dependent neurons for transmission of visceral afferent information. Much of the information from the thoracic and abdominal cavities reaches the brain via the vagus nerve (cranial nerve X). The glossopharyngeal nerve (cranial nerve IX) also conveys visceral sensory information from the head and neck. Both of these nerves relay special visceral sensory information (a visceral chemosensory function) from the oral cavity. Interestingly, patients with CIPA are unable to discriminate between hot and cold material ingested orally, leading to repeated burns without discomfort. In addition, they are probably unable to perceive the pungent flavor of chili pepper when it is orally applied as a gustatory stimulus. Anecdotal observations on patients with CIPA support this speculation in Japan. Infants with CIPA often do not exhibit aversive reactions to wasabi, a root vegetable with a strong taste like horseradish, used in Japanese cooking, especially with raw fish. However, they enjoy sweet flavors such as chocolate, suggesting sparing of their gustatory sense. They seem, at least, to be able to distinguish several types of taste such as, sweet, bitter, and sour in their diet. Children with CIPA usually prefer sweet rather than bitter foods, and they often exhibit aversive reactions to sour foods such as lemon. However, further specific studies are needed to confirm these various types of taste (salt, sour, sweet, bitter, umami) in CIPA patients. These findings reflect defects of specific nerve fibers in detecting pungent chemical substance such as capsaicin. Oropharyngeal perception of noxious, thermal, and chemical stimuli is also impaired in these patients, in addition to visceral pain perception. Nevertheless, some gustatory function seems to be preserved. Thus, patients with CIPA are

probably unable to transmit visceral afferent information that enters the brain through cranial nerves IX and X. With respect to these findings, it is interesting to note that survival of a subset of nodose ganglion neurons (inferior ganglion of vagus nerve) requires NGF in mice (Forgie et al., 2000). The nodose ganglion neurons provide sensory innervation to the thoracic and abdominal viscera.

Patients with CIPA also lack a neural pathway for itch, as demonstrated by a defect in histamine-mediated axonal reflexes (Indo, 2002). Histamine is a well-recognized mediator of acute inflammation and a potent pruritic agent. The axon reflex is an efferent function of the interoceptive polymodal fibers in which release of neuropeptides, such as substance P and calcitonin-gene related peptide (CGRP), from the peripheral terminal induces vasodilation and extravasation of plasma (Julius and Basbaum, 2001). Patients with CIPA lack the axon reflexes that reflect the phenomenon known as neurogenic inflammation. Interestingly, CGRP-containing nerve fibers are also known to be intimately associated with immune modulatory cells, such as Langerhans cells, suggesting a locus of interaction between the nervous system and immunological function (Hosoi et al., 1993; Vega et al., 2003). Thus, patients with CIPA might lack a protective inflammatory reaction due to a defect in axon reflexes.

Anhidrosis is one of the most remarkable features in CIPA, although it is not observed in the mutant mice. Thermal sweating is essential for maintaining body temperature under hot environmental conditions, especially in humans. Rodents probably maintain body temperature by different mechanisms. They cool through evaporation of self-applied spittle as well as through their tail. These considerations suggest that different neural mechanisms may work to maintain homeostasis and determine related behaviors in humans and other animals, indicating the importance of human studies of CIPA. In addition to lacking thermal sweating, patients also lack emotional sweating responses observed on the palmar and plantar surfaces.

The sympathetic responses in patients with CIPA are intriguing. The cold pressor test, submersion of the forearm in ice-cold water, usually causes an increase in blood pressure, but not in patients with CIPA (Swanson, 1963). In addition, piloerection, or goose bumps, in response to cold stimuli does not occur in these patients. These autonomic reactions often accompany emotional responses in humans. Lack of innervation of the sweat glands, blood vessels, and erector pilomotor muscles by the sympathetic neurons is a principal cause of these autonomic defects. Another possibility is that afferent transmission of temperature sensation is disturbed due to a loss of specific neurons. In either case, the neural mechanism controlling body temperature homeostasis and emotional response does not function properly in CIPA. Together, these findings suggest that patients lack the so-called ‘fight-or-flight’

reaction. At least some components of this homeostatic mechanism are mediated by NGF-dependent neurons such as the interoceptive and sympathetic neurons. Thus, patients with CIPA cannot maintain appropriate homeostatic control of the body and emotional responses, due to lack of NGF-dependent neurons. They are always at a disadvantage because of this, with threatened survival.

4. NGF-Dependent Neurons Constitute a Neural Network to Maintain Homeostasis

Primates have a distinct cortical image of interoceptive input (Craig, 2002, 2003a, 2003b, 2003c). The interoceptive polymodal receptors convey various types of information from the body to the brain via the lamina I spinothalamocortical pathway (Figure 1), forming an interface between the nervous system and the body proper, and provide the basis for somato-autonomic reflex arcs together with the sympathetic neurons (Craig, 2002). Here, the 'body proper' means the organism minus its neural tissues (the central and peripheral components of the nervous system). Such information is further brought to the insula via the thalamus or brainstem sites of homeostatic integration. The same information is also conveyed to the amygdala and hypothalamus. Subsequently, the insula signals region such as the ventral (or ventromedial) prefrontal cortex and the medial prefrontal cortex (or anterior cingulate cortex).

The amygdala receives inputs from a wide range of levels of cognitive processing and sends outputs towards various regions of the brain (Aggleton, 2000; LeDoux, 1996, 2000). The hypothalamus, with closely linked structures in the brainstem and the amygdala, acts directly on the internal environment through its control of the endocrine system and autonomic nervous system. To evaluate autonomic function in humans, neurologists often perform the so-called cold pressor test, in which submersion of the forearm in ice-cold water usually causes an increase in blood pressure as an autonomic response. The neural input and output in this autonomic reflex are the interoceptive polymodal receptors in the skin and the sympathetic postganglionic neurons, respectively (Figure 1). Intriguingly, functional magnetic resonance studies in healthy subjects have demonstrated signal changes in multiple brain sites during pressor challenges (Harper et al., 2000). Pressor challenges elicit regional signal intensity changes in medial and orbital prefrontal cortex; anterior cingulate cortex; midline and medial thalamus, especially caudally; hypothalamus; midbrain; ventral and dorsal pons; the temporal lobe, including amygdala, hippocampal formation, and adjacent perirhinal and entorhinal cortical regions; insular cortex; and cerebellum. These findings suggest that these neural regions are indeed involved in the neural circuit or network depicted in Figure 1.

BFCNs receive various cortical inputs from medial temporal cortex (amygdala), insula,

and ventral prefrontal cortex as well as subcortical inputs from septal nuclei, nucleus accumbens-ventral pallidum complex, and hypothalamus (Mesulam and Mufson, 1984). In turn, BFCNs send widespread projections to the amygdala, hippocampus, hypothalamus, olfactory bulb, and widespread areas of cortex (Figure 1). BFCNs are also NGF-dependent neurons and have extensive connections with various cortical and subcortical regions in the brain, playing a critical role in homeostasis and emotional responses. Animal studies have indicated that several types of brain neurons other than BFCNs express TrkA receptors, as described above. For instance, the raphe nuclei of the brainstem express TrkA receptors and are the major source of serotonergic neurons in the central nervous system.

Together, these findings indicate that the NGF-TrkA system functions to establish at least some parts of neural networks involved in homeostasis and emotional experience.

5. NGF-Dependent Neurons Play an Important Role in Emotion

Emotions provide a natural means for the brain and mind to evaluate the environment within and around the organism, and respond accordingly and adaptively (Damasio, 2003). Emotional reactions are typically accompanied by intense cortical arousal. Arousal contributes significantly to attention, perception, memory, and problem solving. The interactions between the amygdala and BFCNs are particularly important for arousal in the presence of stimuli that are dangerous or that warn of danger (LeDoux, 1996). Emotion systems learn by association – when an emotionally arousing stimulus is present, other stimuli that are also present acquire emotion-arousing qualities (classical conditioning), and actions that bring an individual in contact with emotionally desirable stimuli or protect it from harmful or unpleasant ones are learned (instrumental conditioning) (LeDoux, 2002). Emotion can be defined as the process by which the brain determines or computes the value of a stimulus. BFCNs have been proposed to be members of the neuromodulatory systems in the brain and have been suggested to be candidates for neurons in ‘neural value systems’ (Friston et al., 1994). BFCNs are well suited to carry out this determination or computation process, since they respond to evolutionarily important cues (innate values), broadcast their responses to widely distributed areas of the brain through diffuse projections, and release acetylcholine that can modulate changes in synaptic strength (Friston et al., 1994). The amygdala and the hypothalamus, projecting directly or indirectly to BFCNs, might act as a gateway through which salient events, both innate and learned, or homeostatic changes in the body gain access to BFCNs (Figure 1). In addition, raphe nuclei in the brainstem have connections with the amygdala, hypothalamus, and the habenula-IPN axis, and send connections to widespread brain regions, releasing serotonin during significant events. Thus, both BFCNs and the raphe

nuclei participate in neural networks relevant to both homeostasis and emotional responses. These modulatory systems probably facilitate the induction of neural plasticity and its maintenance in emotions.

Some aspects of emotional problems and learning difficulties in CIPA are similar to behavioral problems of animals with lesions of the neural circuit in the brain responsible for 'emotional processing'. When humans are exposed to danger or trauma, the stimuli or contexts associated with the danger or trauma become learned triggers that unleash emotional reactions (LeDoux, 1996). Patients with CIPA do not experience fear in the same way normal individuals would in situations that would normally induce it. In addition, they are probably unable to exhibit the so-called 'fear conditioning' induced by pairing a context with noxious (painful) stimuli in daily life. As a result, they are not able to learn the contexts announcing possible dangers and potentially averse consequences.

The interoceptive neurons, sympathetic neurons, and modulatory systems probably play important roles in the structure and behaviors underlying the 'somatic marker' hypothesis (Damasio, 1994, Damasio, 2003). Normal individuals are born with a genetically controlled neural network, modifiable by experience, which supports the feelings of the body. Patients with CIPA probably cannot experience 'gut feelings' in the body in the same way that normal individuals do. In addition, they are probably unable to maintain homeostasis because they lack NGF-dependent neurons responsible for interoception and autonomic sympathetic regulation. Thus, patients with CIPA are unable to exhibit emotional responses to various interoceptive stimuli. Accordingly, they cannot learn to modify their behaviors to protect their bodies and maintain homeostasis.

6. Other human disorders

There are other human disorders characterized by congenital insensitivity to pain. One well-documented case is of a young Canadian girl who was a student at a university (McMurray, 1950; Melzack and Wall, 1996). This girl was highly intelligent and appeared normal in every way except that she had never felt pain. She exhibited characteristic behaviors similar but not identical to those observed in CIPA. However, the molecular basis for the findings in this individual remains unclear. Recently, a channelopathy-associated insensitivity to pain has been reported, and the genetic basis of this disorder has been shown to involve loss-of-function mutations in the gene encoding a subunit of the voltage-gated sodium channel (Cox et al., 2006). People who are born with insensitivity to pain provide convincing testimony to the value of pain. In addition to this type of congenital insensitivity to pain, there is another syndrome termed 'asymbolia for pain', featuring acquired (not

genetic) lesions of the insular cortex (Berthier et al., 1988; Ramachandran, 1998). Intriguingly, patients with the latter condition perceive noxious stimuli as painful and can distinguish sharp from dull pain but do not display appropriate emotional responses to the pain.

In addition, some other genetic disorders are characterized by decreased pain perception. For instance, familial dysautonomia (or hereditary sensory and autonomic neuropathy type III) also leads to incomplete neuronal development and central functional abnormalities (Axelrod, 2006). Psychological profiles, levels of intelligence, and neuroendocrine abnormalities are described in patients with this disorder. There is another disorder of neurotrophin signal transduction in which a mutation of the *NTRK2 (TRKB)* gene impaired TrkB kinase signaling, resulting in severe hyperphagic obesity and severe impairment of nociception, learning and memory in a patient (Yeo et al., 2004).

Studies of these various neurological disorders permit exploration of neural mechanisms that might underlie the nociceptive system, pain perception, and emotional responses to sensory stimuli.

7. Conclusion

Patients with CIPA lack both interoceptive polymodal receptors and sympathetic postganglionic neurons that are important for homeostasis and emotional responses, and form an interface between the nervous system and the body proper. They probably lack BFCNs and certain other types of neurons in the brain. Together, these findings indicate that the NGF-TrkA system plays an important role in establishing at least some parts of neural networks involved in homeostasis, arousal, and emotion. Potential links between the NGF-dependent neurons and emotion might serve as helpful guides to future research. Prospective studies focused on these neurons may provide further insights into the neural basis of human emotion and feeling.

Acknowledgments

This work was supported by the Japan Society for the Promotion of Science: (KAKENHI) Grant -in-Aid for Scientific Research (C) (18613012).

Figure

Figure 1. A putative neural network for interoception, homeostasis, and emotion.

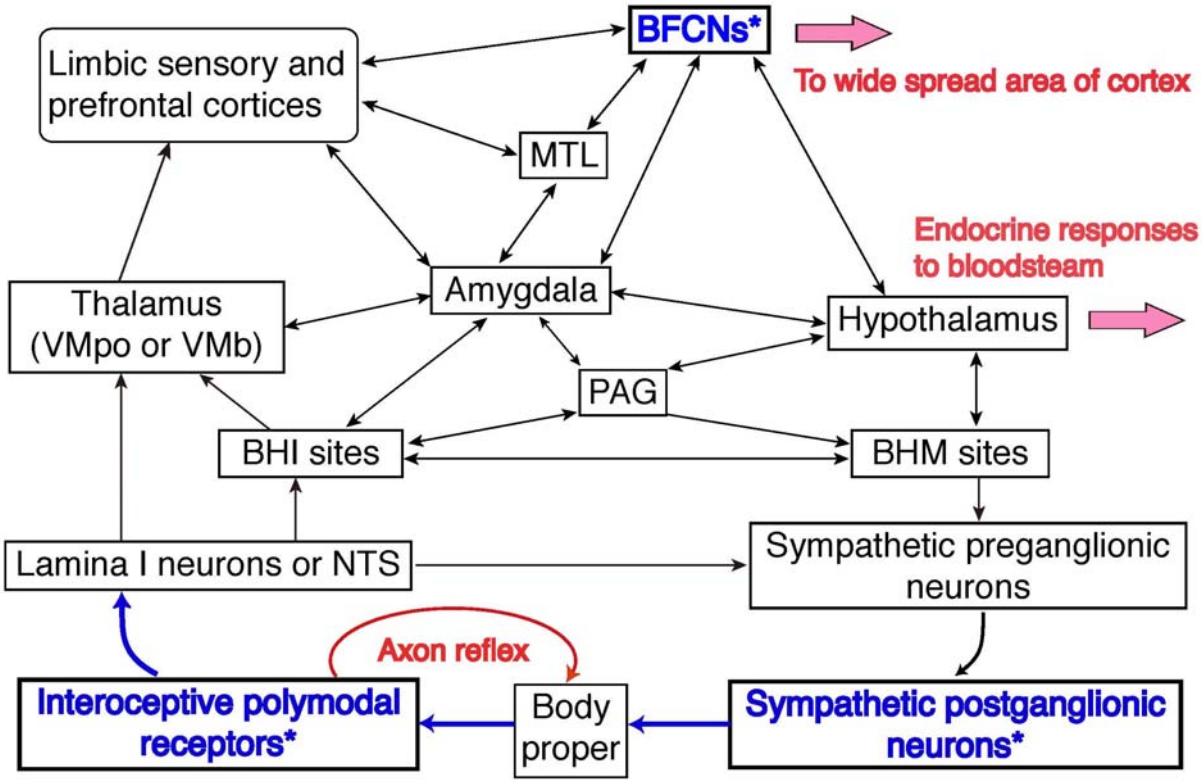

Figure 1. A putative neural network for interoception, homeostasis, and emotion.

The diagram is a schematic presentation of the transmission signals between the body proper and the brain via NGF-dependent neurons, including the interoceptive polymodal receptors, sympathetic postganglionic neurons, and the basal forebrain cholinergic neurons (BFCNs). The body proper means the organism minus the neural tissues (the central and peripheral components of the nervous system). Asterisks indicate neurons or neural structures expressing the TrkA protein, a receptor tyrosine kinase for NGF. Putative NGF-dependent neurons not shown here include those of the striatal cholinergic interneurons, interpeduncular nucleus, raphe nuclei, area postrema, prepositus hypoglossal nucleus, and others (see text). Bidirectional arrows indicate interconnected regions. Some connections have been omitted for clarity. The axon reflex is an efferent function of the interoceptive polymodal receptors, contributing to local defensive reactions in the body. Limbic sensory and prefrontal cortices include insula/somatosensory cortices and ventral and medial prefrontal cortices, respectively.

They have interconnections with one another and connections with various other neural structures (Damasio, 1994, 2003; LeDoux, 1996, 2002). BFCNs send widespread projections to widespread areas of cortex and subcortical nuclei. The hypothalamus also controls endocrine responses. Together, these NGF-dependent neurons constitute a part of a neural network for interoception and homeostasis, and probably play important roles in emotion and adaptive behavior.

NTS: nucleus tractus solitarius, VMpo: posterior portion of ventral medial nucleus (Blomqvist et al., 2000), VMb: basal portion of ventral medial nucleus (Blomqvist et al., 2000), MTL: medial temporal lobe memory system (LeDoux, 2002), PAG: periaqueductal central gray, BHI: brainstem homeostatic integration; BHM: brainstem homeostatic motor

References

Adolphs, R., 2002. Neural systems for recognizing emotion. Curr Opin Neurobiol *12*, 169-177.

Aggleton, J. P., 2000. The Amygdala. A Functional Analysis, second ed. Oxford University Press, Oxford.

Axelrod, F. B., Chelimsky, G. G., Weese-Mayer, D. E., 2006. Pediatric autonomic disorders. Pediatrics *118*, 309-321.

Bear, M. F., Connors, B. W., Paradiso, M. A., 2007. Neuroscience. Exploring the Brain, third ed. Lippincott Williams & Wilkins, Baltimore.

Berthier, M., Starkstein, S., Leiguarda, R., 1988. Asymbolia for pain: a sensory-limbic disconnection syndrome. Ann Neurol *24*, 41-49.

Blokland, A., 1996. Acetylcholine: a neurotransmitter for learning and memory? Brain Res Rev *21*, 285-300.

Blomqvist, A., Zhang, E. T., Craig, A. D., 2000. Cytoarchitectonic and immunohistochemical characterization of a specific pain and temperature relay, the posterior portion of the ventral medial nucleus, in the human thalamus. Brain *123*, 601-619.

Bonsi, P., Cuomo, D., Ding, J., Sciamanna, G., Ulrich, S., Tscherter, A., Bernardi, G., Surmeier, D. J., Pisani, A., 2007. Endogenous serotonin excites striatal cholinergic interneurons via the activation of 5-HT 2C, 5-HT6, and 5-HT7 serotonin receptors: implications for extrapyramidal side effects of serotonin reuptake inhibitors. Neuropsychopharmacology *32*, 1840-1854.

Buchel, C., Morris, J., Dolan, R. J., Friston, K. J., 1998. Brain systems mediating aversive conditioning: an event-related fMRI study. Neuron *20*, 947-957.

Coull, J., Thiele, C., 2004. Functional imaging of cognitive psychopharmacology. In: Frackowiak, R. S. J., Friston, K. J., Frith, C. D., Dolan, R. J., Price, C. J., Zeki, S., Ashburner, J., Penny, W. (Eds.), Human Brain Function, second ed. Elsevier, Amsterdam, pp. 303-327.

Cox, J. J., Reimann, F., Nicholas, A. K., Thornton, G., Roberts, E., Springell, K., Karbani, G., Jafri, H., Mannan, J., Raashid, Y., Al-Gazali, L., Hamamy, H., Valente, E. M., Gorman, S., Williams, R., McHale, D. P., Wood, J. N., Gribble, F. M., Woods, C. G., 2006. An SCN9A channelopathy causes congenital inability to experience pain. Nature *444*, 894-898.

Craig, A. D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci *3*, 655-666.

Craig, A. D., 2003a. Interoception: the sense of the physiological condition of the body. Curr

Opin Neurobiol *13*, 500-505.

Craig, A. D., 2003b. A new view of pain as a homeostatic emotion. Trends Neurosci *26*, 303-307.

Craig, A. D., 2003c. Pain mechanisms: labeled lines versus convergence in central processing. Annu Rev Neurosci *26*, 1-30.

Craig, A. D., Chen, K., Bandy, D., Reiman, E. M., 2000. Thermosensory activation of insular cortex. Nat Neurosci *3*, 184-190.

Damasio, A. R., 1994. Descartes' Error: Emotion, Reason, and the Human Brain. Penguin Books, New York.

Damasio, A. R.,1996. The somatic marker hypothesis and the possible functions of the prefrontal cortex. Philos Trans R Soc Lond B Biol Sci *351*, 1413-1420.

Damasio, A. R.,1999. The Feeling of What Happens: Body and Emotion in the Making of Consciousness. Harcourt, New York.

Damasio, A. R., 2003. Looking for Spinoza. Harcourt, Orlando.

Damasio, A. R., Grabowski, T. J., Bechara, A., Damasio, H., Ponto, L. L., Parvizi, J., Hichwa, R. D., 2000. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nat Neurosci *3*, 1049-1056.

Fagan, A. M., Garber, M., Barbacid, M., Silos-Santiago, I., Holtzman, D. M., 1997. A role for TrkA during maturation of striatal and basal forebrain cholinergic neurons in vivo. J Neurosci *17*, 7644-7654.

Forgie, A., Kuehnel, F., Wyatt, S., Davies, A. M., 2000. In vivo survival requirement of a subset of nodose ganglion neurons for nerve growth factor. Eur J Neurosci *12*, 670-676.

Freeman, R., 2005. Autonomic peripheral neuropathy. Lancet *365*, 1259-1270.

Friston, K. J., Tononi, G., Reeke Jr., G. N., Sporns, O., Edelman, G. M., 1994. Value-dependent selection in the brain: simulation in a synthetic neural model. Neuroscience *59*, 229-243.

Gibbs, R. B., Pfaff, D. W., 1994. In situ hybridization detection of trkA mRNA in brain: distribution, colocalization with p75NGFR and up-regulation by nerve growth factor. J Comp Neurol *341*, 324-339.

Harper, R. M., Bandler, R., Spriggs, D., Alger, J. R., 2000. Lateralized and widespread brain activation during transient blood pressure elevation revealed by magnetic resonance imaging. J Comp Neurol *417*, 195-204.

Holtzman, D. M., Kilbridge, J., Li, Y., Cunningham Jr., E. T., Lenn, N. J., Clary, D. O., Reichardt, L. F., Mobley, W. C., 1995. TrkA expression in the CNS: evidence for the existence of several novel NGF-responsive CNS neurons. J Neurosci *15*, 1567-1576.

Hosoi, J., Murphy, G. F., Egan, C. L., Lerner, E. A., Grabbe, S., Asahina, A., Granstein, R. D., 1993. Regulation of Langerhans cell function by nerves containing calcitonin gene-related peptide. Nature *363*, 159-163.

Indo, Y., 2001. Molecular basis of congenital insensitivity to pain with anhidrosis (CIPA): mutations and polymorphisms in TRKA (NTRK1) gene encoding the receptor tyrosine kinase for nerve growth factor. Hum Mutat *18*, 462-471.

Indo, Y., 2002. Genetics of congenital insensitivity to pain with anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV. Clinical, biological and molecular aspects of mutations in TRKA(NTRK1) gene encoding the receptor tyrosine kinase for nerve growth factor. Clin Auton Res *12 Suppl 1*, 20-32.

Indo, Y., 2004. Congenital insensitivity to pain. In: Mogil, J. S. (Ed.), The Genetics of Pain. IASP Press, Seattle, pp. 171-191.

Indo, Y., Mardy, S., Miura, Y., Moosa, A., Ismail, E. A., Toscano, E., Andria, G., Pavone, V., Brown, D. L., Brooks, A., Endo, F., Matsuda, I., 2001. Congenital insensitivity to pain with anhidrosis (CIPA): novel mutations of the TRKA (NTRK1) gene, a putative uniparental disomy, and a linkage of the mutant TRKA and PKLR genes in a family with CIPA and pyruvate kinase deficiency. Hum Mutat *18*, 308-318.

Indo, Y., Tsuruta, M., Hayashida, Y., Karim, M. A., Ohta, K., Kawano, T., Mitsubuchi, H., Tonoki, H., Awaya, Y., Matsuda, I., 1996. Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat Genet *13*, 485-488.

Iversen, S., Kupfermann, I., Kandel, E. R., 2000. Emotional states and feelings. In: Kandel, E. R., Schwartz, J. H., Jessell T. M. (Eds.), Principles of Neural Science, fourth ed. McGraw-Hill, New York, pp. 982-997.

Julius, D., Basbaum, A. I., 2001. Molecular mechanisms of nociception. Nature *413*, 203-210.

Klemm, W. R., 2004. Habenular and interpeduncularis nuclei: shared components in multiple-function networks. Med Sci Monit *10*, RA261-273.

LeDoux, J. E., 1996. The Emotional Brain. Simon & Schuster, New York.

LeDoux, J. E., 2000. Emotion circuits in the brain. Annu Rev Neurosci *23*, 155-184.

LeDoux, J. E., 2002. Synaptic Self: How Our Brains Become Who We Are. Penguin Books, New York.

Levi-Montalcini, R., 1987. The nerve growth factor: thirty-five years later. EMBO J *6*, 1145-1154.

Mardy, S., Miura, Y., Endo, F., Matsuda, I., Indo, Y., 2001. Congenital insensitivity to pain with anhidrosis (CIPA): effect of TRKA (NTRK1) missense mutations on autophosphorylation of the receptor tyrosine kinase for nerve growth factor. Hum Mol

Genet *10*, 179-188.

Mardy, S., Miura, Y., Endo, F., Matsuda, I., Sztriha, L., Frossard, P., Moosa, A., Ismail, E. A. R., Macaya, A., Andria, G., Toscano, E., Gibson, W., Graham, G. E., Indo, Y., 1999. Congenital insensitivity to pain with anhidrosis: novel mutations in the *TRKA (NTRK1)* gene encoding a high-affinity receptor for nerve growth factor. Am J Hum Genet *64*, 1570-1579.

McMurray, G. A., 1950. Experimental study of a case of insensitivity to pain. AMA Arch Neurol Psychiatry *64*, 650-667.

Melzack, R., Wall, P. D., 1996. The Challenge of Pain. Penguin Books, London. Updated Second Edition.

Mesulam, M. M., Mufson, E. J., Levey, A. I., Wainer, B. H., 1983. Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. J Comp Neurol *214*, 170-197.

Mesulam, M. M., Mufson, E. J., 1984. Neural inputs into the nucleus basalis of the substantia innominata (Ch4) in the rhesus monkey. Brain *107*, 253-274.

Miura, Y., Mardy, S., Awaya, Y., Nihei, K., Endo, F., Matsuda, I., Indo, Y., 2000. Mutation and polymorphism analysis of the TRKA (NTRK1) gene encoding a high-affinity receptor for nerve growth factor in congenital insensitivity to pain with anhidrosis (CIPA) families. Hum Genet *106*, 116-124.

Pezet, S., McMahon, S. B., 2006. Neurotrophins: mediators and modulators of pain. Annu Rev Neurosci *29*, 507-538.

Pinsky, L., DiGeorge, A. M., 1966. Congenital familial sensory neuropathy with anhidrosis. J Pediatr *68*, 1-13.

Ramachandran, V. S., 1998. Consciousness and body image: lessons from phantom limbs, Capgras syndrome and pain asymbolia. Philos Trans R Soc Lond B Biol Sci *353*, 1851-1859.

Reichardt, L. F., 2006. Neurotrophin-regulated signalling pathways. Philos Trans R Soc Lond B Biol Sci *361*, 1545-1564.

Smeyne, R. J., Klein, R., Schnapp, A., Long, L. K., Bryant, S., Lewin, A., Lira, S. A., Barbacid, M., 1994. Severe sensory and sympathetic neuropathies in mice carrying a disrupted Trk/NGF receptor gene. Nature *368*, 246-249.

Sobreviela, T., Clary, D. O., Reichardt, L. F., Brandabur, M. M., Kordower, J. H., Mufson, E. J., 1994. TrkA-immunoreactive profiles in the central nervous system: colocalization with neurons containing p75 nerve growth factor receptor, choline acetyltransferase, and

serotonin. J Comp Neurol *350*, 587-611.

Sukhov, R. R., Cayouette, M. H., Radeke, M. J., Feinstein, S. C., Blumberg, D., Rosenthal, A., Price, D. L., Koliatsos, V. E., 1997. Evidence that perihypoglossal neurons involved in vestibular-auditory and gaze control functions respond to nerve growth factor. J Comp Neurol *383*, 123-134.

Swanson, A. G.,1963. Congenital insensitivity to pain with anhydrosis. A unique syndrome in two male siblings. Arch Neurol *8*, 299-306.

Swanson, A. G., Buchan, G. C., Alvord, E. C., 1965. Anatomic changes in congenital insensitivity to pain. Arch Neurol *12*, 12-18.

Talman, W. T., Robertson, S. C., 1991. Nucleus prepositus hypoglossi. A medullary pressor region. Hypertension *17*, 1173-1176.

Vega, J. A., Garcia-Suarez, O., Hannestad, J., Perez-Perez, M., Germana, A., 2003. Neurotrophins and the immune system. J Anat *203*, 1-19.

Venero, J. L., Hefti, F., Beck, K. D., 1995. Retrograde transport of nerve growth factor from hippocampus and amygdala to trkA messenger RNA expressing neurons in paraventricular and reuniens nuclei of the thalamus. Neuroscience *64*, 855-860.

Yeo, G. S. H., Hung C-C. C., Rochford, J., Keogh, J., Gray, J., Sivaramakrishnan, S., O'Rahilly, S., Farooqi, I. S., 2004. A *de novo* mutation affecting human TrkB associated with severe obesity and developmental delay. Nat Neurosci *7*, 1187-1189.