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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.

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Contents

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;

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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 et al., 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,b,c; 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 et al., 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 et al., 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

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