Title: *NTRK1* Congenital Insensitivity to Pain with Anhidrosis *GeneReview* – Neuroscience of NGF-Dependent Neurons
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Nerve growth factor (NGF), a prototype neurotrophin and the first growth factor to be identified [Levi-Montalcini 1987], plays pivotal roles in controlling the survival and differentiation of the nervous system during embryonic and early postnatal stages [Reichardt 2006]. NGF is a neurotrophic factor essential for the survival and maintenance of NGF-dependent neurons. NGF-dependent neurons include NGF-dependent primary afferents and sympathetic postganglionic neurons in the peripheral nervous system (PNS). NGF-dependent primary afferents are defined as primary afferent neurons with small-diameter, thinly myelinated Aδ (delta) fibers, or unmyelinated C-fibers that depend on the NGF-TrkA system during development [Indo 2012]. NGF-dependent neurons also exist in the central nervous system [Indo 2014].

NGF-dependent primary afferents not only detect noxious (painful) stimuli but also transmit sensation from the body's interior; this is known as interoceptive sense [Craig 2002]. NGF-dependent primary afferents are also referred to as "interoceptive polymodal receptors" [Indo 2009]. The interoceptive system is considered to be a homeostatic afferent pathway representing the physiologic 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 are thus responsible for both nociceptive and homeostatic afferent pathways.

Sympathetic postganglionic neurons innervate blood vessels, piloerector muscles, and sweat glands as well as other target organs or tissues in the body. These neurons contribute to homeostasis in the body, together with NGF-dependent primary afferents [Indo 2012, Indo 2018]. In response to the interoceptive polymodal inputs through NGF-dependent primary afferents, the brain regulates various functions of target organs and tissues through autonomic sympathetic postganglionic neurons. This is well illustrated by (unconscious) homeostatic control of the body temperature. NGF-dependent primary afferents and sympathetic postganglionic neurons are also considered to be thermal receptors and thermal effectors, respectively. Evaporative heat loss for the control of body temperature is a species-dependent mechanism. Sweating is essential for body temperature control in humans. Therefore, recurrent febrile episodes in hot environments are characteristic features observed in individuals with *NTRK1* congenital insensitivity to pain with anhidrosis (*NTRK1*-CIPA). These individuals can also develop hypothermia in cold environments. Thus, NGF-dependent neurons in the PNS contribute to the homeostasis of the core body temperature. NGF-dependent neurons in the PNS also play critical roles in inflammatory processes [Indo 2010].

The sympathetic nervous system also plays pivotal roles in the "fight or flight" response in coping with life-threatening challenges. The "fight or flight" response is a well-known physical and emotional state associated with an extreme excitation of the sympathetic nervous system. When animals are exposed to danger or trauma, stimuli or contexts associated with the danger or trauma become learned triggers that unleash emotional responses [LeDoux 1996, LeDoux 2000]. The "fight or flight" response is considered to be essential for the survival of animals, including humans. From birth, normal individuals experience emotions such as fear whenever they are exposed to danger or trauma in daily life. These emotional experiences then induce so-called fear conditioning by pairing the stimuli or contexts with danger or trauma. Therefore, emotional responses serve a protective role by producing aversion to contexts associated with danger.

Individuals with *NTRK1*-CIPA cannot detect various noxious stimuli nor trigger emotional responses to noxious stimuli in the same way as normal individuals because they lack NGF-dependent neurons [Indo 2012, Indo 2018]. Accordingly, they may be impaired in their ability to modify their behaviors in order to protect their bodies and maintain homeostasis. Because of this they are always at a disadvantage, with threatened survival. With respect to the survival and emotional responses, a new concept of "survival circuits" has been proposed as sensory-motor integrative neuronal devices to serve specific adaptive purposes [LeDoux 2012]. The activity in "survival circuits" detect threats and generate automatic defense reactions. The pathophysiology of *NTRK1*-CIPA suggests that NGF-dependent neurons in the PNS constitute a neuronal component of the "survival circuits" in humans.

Pain is an unpleasant sensory and emotional experience. Emotion, such as fear, is characterized by various complex reactions with both mental and physical manifestations closely related to activities of the sympathetic nervous system. Damasio proposes a neurobiologic definition of "emotions and feelings" and emphasizes the role of reciprocal communication between the brain and body-proper (the organism minus the neural tissues) [Damasio 1994, Damasio & Carvalho 2013]. According to this definition, "emotions are a set of innate, physiologic actions triggered by changes in the internal or external environments" and "feelings are mental experiences of the body states" [Damasio & Carvalho 2013]. Thus, the sympathetic nervous system and the interoceptive system probably mediate neuronal processes for emotions and feelings, respectively.

The pathophysiology of *NTRK1*-CIPA provides intriguing findings to elucidate the unique functions that NGF-dependent neurons serve in humans. NGF-dependent neurons in the PNS form an interface between the brain and body-proper and play essential roles in the interoception and homeostasis of our body [Indo 2018]. Furthermore, these neurons are likely requisite for the stress response, as well as neurobiologic processes of "emotions and feelings" in our species.

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