Title: Congenital Insensitivity to Pain with Anhidrosis *GeneReview* - Neurophysiology of CIPA
Author: Indo Y
Date: April 2014

Note: The following information is provided by the author listed above and has not been reviewed by *GeneReviews* staff.

Neurophysiology of CIPA

Neurophysiology. Nerve growth factor (NGF) is a neurotropic 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 neurons in the PNS form an interface between the nervous system and the body-proper (the organism minus the neural tissues) [Indo 2012].

NGF-dependent primary afferents are defined as primary afferent neurons with small-diameter, thinly myelinated Aδ–fibers, or unmyelinated C-fibers that dependent on the NGF—TrkA system during development. NGF-dependent primary afferents not only detect noxious stimuli but also transmit sensation from the body's interior; this is known as interoceptive sense. NGF-dependent primary afferents are also referred to as 'interoceptive polymodal receptors' [Indo 2009]. The interoceptive system is 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 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.

Neurophysiologic examinations. Individuals with CIPA show various abnormalities in neurophysiologic examinations, due to the absence of NGF-dependent neurons.

Individuals with CIPA lack sympathetic regulation of various target tissues, including internal organs, and therefore exhibit defects in sympathetic regulation [Indo 2009].

The cold pressor test, submersion of the forearm in ice-cold water, usually causes an increase in blood pressure, but not in individual with CIPA. In addition, piloerection, or goose bumps, in response to cold stimuli does not occur in these individuals. 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 [Indo 2009]. 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 does not function properly in CIPA.

Individuals with CIPA have very low levels of norepinephrine [Loewenthal et al 2005], but do not have orthostatic hypotension [Indo 2002]. Individuals with CIPA have very

low levels of norepinephrine supine and upright, but do not have orthostatic hypotension [Norcliffe-Kaufmann et al 2011]. Other vasoactive peptides involved in orthostatic blood pressure maintenance are not increased. The mechanism by which patients with CIPA maintain their blood pressure is unknown.

Traditional electrophysiologic studies such as motor and sensory conduction velocities by electrical and mechanical stimuli are usually normal as are somatosensory, visual, and brain stem evoked potentials [Shatzky et al 2000, Shorer et al 2001].

Microneurography shows neural activity from A-beta sensory fibers connected to low-threshold mechanoreceptors; however, nociceptive and skin sympathetic C fiber nerve activity is absent [Nolano et al 2000]. Intraneural electrical stimulation that produces unbearable pain in normal controls does not evoke any painful sensation. In a pure motor bundle, stretching of the muscle evokes intraneural acitivity from mechanoreceptor units. The sympathetic skin response is absent.

NGF-dependent primary afferents also mediate an axon reflex responsible for neurogenic inflammation in adults [Indo 2012]. The axon reflex is an efferent function of the NGF-dependent primary afferents, in which release of neuropeptides from the peripheral terminal induces vasodilation and extravasation of plasma. The term ‘neurogenic inflammation’ means that signs of inflammation (e.g., tumor, rubor, calor and dolor) develop upon activations of neurons and the consecutive release of neuronal mediator. NGF-dependent primary afferents thus play critical roles in pain, itch and inflammation. Individual with CIPA lack axon reflex that contributes to inflammation.

The axon reflex sweating is mediated through sympathetic postganglionic neurons [Indo 2002]. Intradermal injection of a cholinergic agent, such as acetylcholine or pilocarpine, can stimulate the sympathetic postganglionic fibers and induce the axon reflex sweating in a surrounding skin area. The axon reflex sweating is also quantified by a method, such as quantitative sudomotor axon reflex testing (QSART). Individuals with CIPA lack the axon reflex sweating.

Emotional sweating responses are also not observed in individuals with CIPA by studying the electrical resistance of the palmar surface, i.e. sympathetic skin response [Shorer et al 2001]. Pinprick, deep pain and starling sound fail to produce a change in skin resistance. Electrical stimulation and intradermal injection of norepinephrine also fail to evoke local sweating [Swanson 1963].

Abnormal circadian rhythm of cardiovascular autonomic nervous system is observed [Ohto et al 2004].

The grip force during the object grasp-lift-holding task is significantly greater in individuals with CIPA than in control subjects [Kawashima et al 2012]. This suggests that anticipatory modulation of the grip force may be partly impaired. Young individuals with CIPA walk faster, with a longer step length and higher heel contact angular velocity, than young control participants [Zhang et al 2013], suggesting higher frequency of lower extremity injuries observed.

Other. In some individuals, endocrinological or immunological abnormalities have been reported [Toscano et al 2000]. Subnormal adrenal function and abnormalities in the first-phase insulin response to glucose challenge may emphasize the importance of the

NGF-TrkA pathway in the physiology of the neuroendocrine system and its response to stress [Loewenthal et al 2005, Schreiber et al 2005]. Presence of a *TrkA* mutation in B cells can result in defects in a lymphocyte signaling or a humoral immune function [Melamed et al 2004, Kilic et al 2009]. Abnormal neutrophil chemotactic activity in individuals with this genetic disorder may contribute to a high rate of infection [Beigelman et al 2009]. These may explain some of the delayed healing observed in this disorder.

Autopsy. Swanson reported two brothers with CIPA [Swanson 1963]. Autopsy was performed in younger boy who had died suddenly at the age of 12 years after a 24-hr febrile illness during which his body temperature exceeded 43 degrees centigrade [Swanson et al 1965]. Hemorrhages were noted in many tissues and attributed to the high fever. Detailed electrophysiological analysis of the sibling's lack of response to tooth pulp pain has been reported [Chatrian et al 1975].

- Normal autonomic ganglion cells were found in the intestinal tract and the skin had abundant sweat glands [Swanson et al 1965]. No obvious gross abnormalities were recognized in the brain or brainstem.
- On microscopic examination of the brainstem, the spinal tract of the trigeminal nerve was about one third of normal. The majority of fibers in this tract were of large diameter, and there was a marked decrease in number of fine, lightly myelinated axons.
- Sections of the posterior ventral lateral nucleus of the thalamus and the somatosensory cortex were normal.
- No abnormalities were identified in the sympathetic ganglia or in the intermediolateral cell column of the spinal cord. The autonomic ganglia also appeared normal, but quantitative counts were not performed.
- The spinal dura mater was thickened with a unique and unexplained abnormality consisting of two slit-like cavities, one dorsal and one ventral. Lissauer's tract (dorsolateral fasciculus) could not be identified in myelin or axon-stained sections at any level of the spinal cord. The dorsal roots entered the cord and turned medially into the posterior columns; the usual lateral portion continuing into the superficial dorsal gray horn was missing.
- Cross sections of dorsal roots demonstrated a nearly uniform large fiber population with only a few scattered small fibers, in contrast to the normal picture of intermingled large and small myelinated fibers. In dorsal ganglia, an almost uniform population of large neurons replaced the normal pattern of large and small ganglion cells.
- The cells of the substantia gelatinosa and the anterior and posterior white commissures were normal in number and morphology. The spinothalamic tracts could not be specifically identified, but the lateral and ventral columns of the spinal cord appeared normal.
- In summary, the abnormalities were absence of small neurons in the dorsal ganglia, lack of small fibers in the dorsal roots, absence of Lissauer's tract, and

reduction in size of the spinal tract of the trigeminal nerve with paucity of small fibers. These findings represent almost complete absence of the first order afferent system generally considered responsible for pain and temperature sensation [Swanson 1963, Swanson et al 1965].

References

Beigelman A, Levy J, Hadad N, Pinsk V, Haim A, Fruchtman Y, Levy R (2009) Abnormal neutrophil chemotactic activity in children with congenital insensitivity to pain with anhidrosis (CIPA): the role of nerve growth factor. *Clin Immunol* 130:365-72

Chatrian GE, Farrell DF, Canfield RC, Lettich E (1975) Congenital insensitivity to noxious stimuli. Arch Neurol 32(3):141-5.

Craig AD (2002) How do you feel ? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 3: 655-66

Indo Y (2002) Genetics of congenital insensitivity to pain with anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV. Clinical, biologicial and molecular aspects of mutations in TRKA (*NTRK1*) gene encoding the receptor tyrosine kinase for nerve growth factor*. Clin Auton Res* 12 Suppl 1:120-30

Indo Y (2009) Nerve growth factor, interoception, and sympathetic neuron: lesson from congenital insensitivity to pain with anhidrosis. *Auton Neurosci* 147: 3-8

Indo Y (2012) Nerve growth factor and the physiology of pain: lessons from congenital inseisitivity to pain with anhidrosis. *Clin Genet* 82: 341-50

Kawashima N, Abe MO, Iwaya T, Haga, N (2012) Abnormal capacity for grip force control in patients with congenital insensitivity to pain. Exp Brain Res 218: 579-88

Kilic SS, Ozturk R, Sarisozen B, Rotthier A, Baets J, Timmerman V (2009) Humoral immunodeficiency in congenital insensitivity to pain with anhidrosis. Neurogenetics 10:161-5

Loewenthal N, Levy J, Schreiber R, Pinsk V, Perry Z, Shorer Z, Hershkovitz E (2005) Nerve growth factor-tyrosine kinase A pathway is involved in thermoregulation and adaptation to stress:studies on patients with hereditary sensory and autonomic neuropathy type IV. *Pediatr Res* 57:587-90

Melamed I, Levy J, Parvari R, Gelfand EW (2004) A novel lymphocyte signaling defect: trk A mutation in the syndrome of congenital insensitivity to pain and anhidrosis (CIPA). *J Clin Immunol* 24:441-8

Nolano M, Crisci C, Santoro L, Barbieri F, Casale R, Kennedy WR, Wendelschafer-Crabb G, Provitera V, Di Lorenzo N, Caruso G (2000) Absent innervation of skin and sweat glands in congenital insensitivity to pain with anhidrosis. Clin Neurophysiol 111:1596-601

Norcliffe-Kaufmann L.J. Axelrod F.B. Kaufmann H (2011) The norepinephrine paradox in hereditary sensory and autonomic neuropathy type IV. *Clin Auton Res* 21: 286

Ohto T, Iwasaki N, Fujiwara J, Ohkoshi N, Kimura S, Kawade K, Tanaka R, Matsui A (2004) The Evaluation of Autonomic Nervous Function in a Patient with Hereditary Sensory and Autonomic Neuropathy Type IV with Novel Mutations of the TRKA Gene. *Neuropediatrics* 35:274–8

Schreiber R, Levy J, Loewenthal N, Pinsk V, Hershkovitz E (2005) Decreased first phase insulin response in children with congenital insensitivity to pain with anhidrosis. *J Pediatr Endocrinol Metab* 18:873-7

Shatzky S, Moses S, Levy J, Pinsk V, Hershkovitz E, Herzog L, Shorer Z, Luder A, Parvari R (2000) Congenital insensitivity to pain with anhidrosis (CIPA) in Israeli-Bedouins: genetic heterogeneity, novel mutations in the *TRKA/NGF* receptor gene, clinical findings, and results of nerve conduction studies*. Am J Med Genet* 92:353-60

Shorer Z, Moses SW, Hershkovitz E, Pinsk V, Levy J (2001) Neurophysioloic studies in congenital insensitivity to pain with anhidrosis. *Pediatr Neurol* 25:397-400

Swanson AG (1963) Congenital insensitivity to pain with anhidrosis. *Arch Neurol* 8:299-306

Swanson AG, Buchan GC, Alvord EC (1965) Anatomic changes in congenital insensitivity to pain. *Arch Neurol* 12:12-18

Toscano E, della Casa R, Mardy S, Gaetaniello L, Sadile F, Indo Y, Pignata C, Andria G (2000) Multisystem involvement in congenital insensitivity to pain with anhidrosis (CIPA), a nerve growth factor receptor(TrkA)-related disorder. *Neuropediatrics* 31:39-41

Zhang Y, Ogata N, Yozu A, Haga N (2013) Two-dimensional video gait analyses in patients with congenital insensitivity to pain. *Dev Neurorehabil* 16: 266-70