CONGENITAL INSENSITIVITY TO PAIN

Pathoprofile

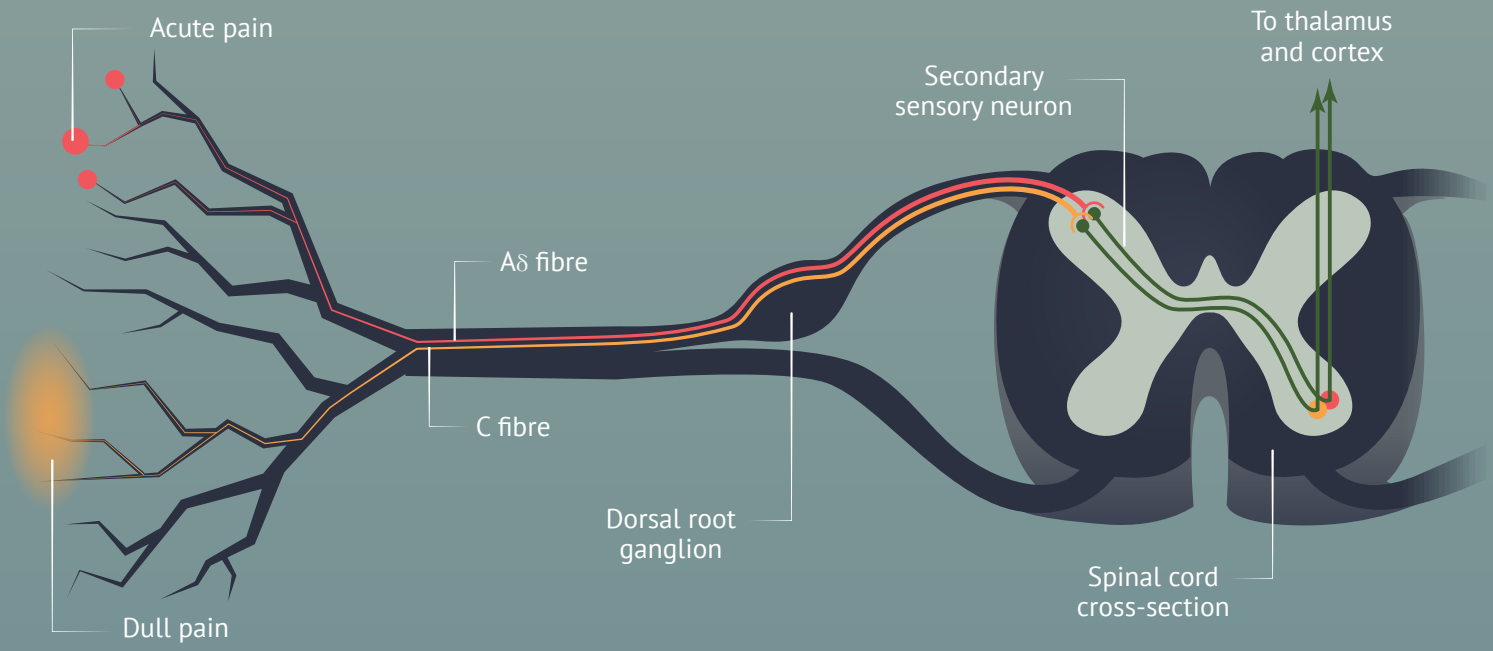
AUTHORS: Deeksha Kundapur & Sheila Yu
ARTIST: Sylvia Mohanraj

INTRODUCTION

Pain is an essential sensation that has developed in complex organisms as an evolutionary mechanism to signal impending danger. Without pain, day-to-day functions become incredibly compromised. Pain is responsible for triggering the adoption of protective behaviours, such as physical withdrawal from painful stimuli to for tissue protection.[1] Hereditary sensory and autonomic neuropathy type V (HSAN V), generally known as congenital insensitivity to pain (CIP), is a rare autosomal recessive sensory neuropathy. It is caused by defective nociceptive mechanisms, which result in an inability to experience pain.[2,3] HSANs range from type I to type V, encompassing varying degrees of sensory impairment at each level. Only a handful of individuals experience the clinical symptoms associated with HSAN V, as it is the rarest of the HSAN disorders.[2]

GENERAL NOCICEPTION

Pain is perceived through nociception: central and peripheral neurological events that encode information regarding noxious stimuli. When the intensity of a stimulus reaches the noxious threshold, primary nociceptive peripheral nerve endings located in the skin, muscles, visceral tissue, corneas, and mucosa depolarize to send signals to their cell bodies in the dorsal root ganglia. There, primary nociceptive neurons synapse with interneurons, which transmit the neural impulse to the thalamus and cortex for pain perception. A spinal nerve contains different types of pain fibres, which are categorized based on anatomical and functional criteria. Of particular interest are the thinly myelinated C fibres, which conduct rapid, sharp and acute pain, and the thicker, unmyelinated Aδ fibres, which facilitate delayed, diffused, and dull pain.[1,4]



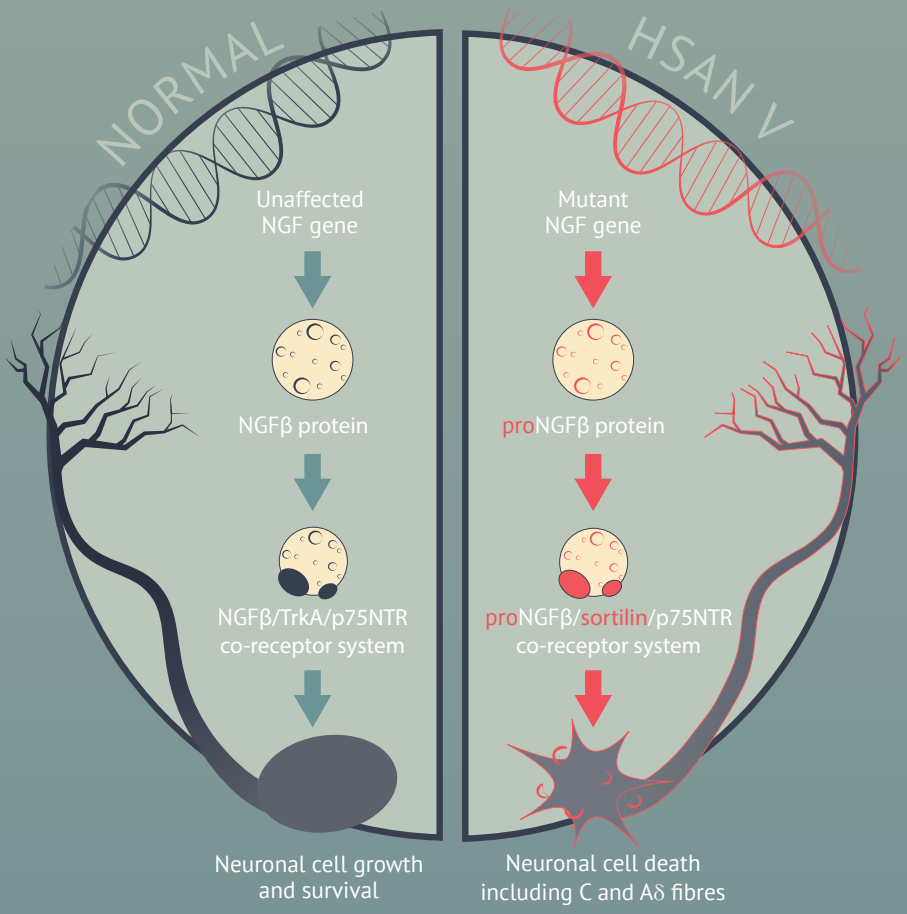
MOLECULAR MECHANISMS

Neuron growth, including that of Aδ and C fibres, is stimulated by NGFβ, a protein encoded by the NGF gene (1p13.2).[2,5] NGFβ regulates the transduction of anti-apoptotic and differentiative signals by binding to the high affinity TrkA receptor and the low-affinity p75NTR receptor; these form a co-receptor system that positively modulates neuronal growth.[6] More specifically, the binding of NGFβ to TrkA triggers the phosphorylation of PLC-γ1 and RAS/ERK, initiating signalling pathways necessary for cell growth, survival, proliferation, and differentiation. Additionally, the binding of NGFβ to p75NTR activates JNK/C-jun, resulting in a cascade that transmits noxious stimuli.[6-8] In contrast to the normal nociceptive mechanism described above, HSAN V is characterized by mutations in the NGF gene, producing mutant NGFβ that does not undergo normal post-translational processing events.[2,9] As a result, it remains as immature proNGFβ that binds to a related, but different co-receptor system: p75NTR and sortilin.[9] The activation of this system triggers a signal cascade responsible for apoptosis, which, in the absence of cell survival and growth factors, results in neurodegeneration. Nerve biopsies demonstrate that the resulting loss of the aforementioned Aδ and C fibres leads to a significant loss in pain perception.[10]

CLINICAL IMPLICATIONS

With their inability to experience pain, patients with HSAN V are more vulnerable to wounds, injuries, and self-mutilating behaviour, which may result in autoamputation in extreme cases.[6] Additionally, the absence of deep pain perception—the feeling of pain from injuries to bones, ligaments, or muscles—can lead to fractures, bone necrosis, osteochondritis, and osteomyelitis, ultimately necessitating neuropathic arthroplasty.[10] Less common symptoms include anhidrosis (the inability to sweat), fevers, and mental retardation. This latter group of symptoms occurs primarily in cases that symptomatically overlap with HSAN IV, otherwise known as CIP with anhidrosis.[11]

Current treatments for CIP are largely supportive and oriented to prevent self-mutilation or to manage orthopedic problems. Examples may include continual monitoring for injuries, special footwear for orthopedic complications, and surgery. However, many difficulties arise when treating CIP patients. For instance, due to their absence of pain awareness, they lack incentive to wear braces or other orthoses.[12] Despite the severity of the disease, there is no effective standard for CIP treatment, in part due to the limited amount of research that has been conducted regarding the condition. Additionally, the poor delineation between HSAN IV and HSAN V has further complicated the diagnosis and treatment of each condition.[3]



FUTURE RESEARCH

In order to achieve a more thorough understanding of NGF/proNGF receptor distribution and function, a more accurate model for HSAN V is needed, as existing mouse models lack validity. Compared to humans, current NGF knockout mice exhibit more severe phenotypes, as demonstrated by the massive loss of sensory fibres and the higher risk of death within a few weeks of birth.[13,14] A more accurate model for testing NGF function is crucial to a better understanding of CIP and its consequences.[6]

Despite our general aversion to pain, the sensation of pain is a basic physiological necessity. Those with CIP are deprived of the sensory input necessary to navigating the dangers of their environment, leaving them unable to identify—let alone avoid—these threats. With an improved *in vivo* model, research may further inform the development of pharmacological treatments or genetic therapies as early interventions for CIP, ultimately helping to prevent or better manage its harmful and long-lasting effects.

REVIEWED BY DR. ERIC SEIDLITZ

Dr. Seidlitz is both a researcher and educator, with specific interest in the fields of pain, novel cancer therapeutics, and drug development. He completed his Doctorate in Physiology and Pharmacology at McMaster University, where he is now a faculty member.

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