Neurocutaneous disease

Cutaneous neuroanatomy and mechanisms of itch and pain

Miguel Chuquilin, MD,[a] Yazan Alghalith, BA,[b] and Kristen Heins Fernandez, MD[c]
Columbia, Missouri

Learning objectives
After participating in this learning activity, participants should be able to describe the nervous innervation of the skin, describe current knowledge of the mechanisms of pain and itch and their similarities and differences, and correlate innervations with possible mechanisms of action of drugs used in treatment of pain and itch.

Disclosures
Editors
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Authors
The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Planners
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Few sources of information exist regarding cutaneous innervation and how to apply this basic neurologic science to the clinical treatment of itch, as often performed on a daily basis by dermatologists. We address the types of nerve fibers that innervate the skin and their different components and discuss the similarities and differences between itch and pain. We hope that increased knowledge of this topic will improve the recognition and treatment of neuropathic itch. (J Am Acad Dermatol 2016;74:197-212.)

Key words: cutaneous innervation; itch; nerve fibers; neuroanatomy; pain; pruritogens.

SKIN INNERVATION

The skin contains different types of nerve fiber endings, each with a different function. These nerve fibers are the axons from projecting neurons whose cell bodies are located in the dorsal root ganglia (DRG) or trigeminal ganglia (TG) and can be classified according to both diameter and myelination (Table I). Large fibers (Aβ) are thickly myelinated and carry light touch and mechanical information. Small, thinly myelinated (Aδ) or unmyelinated (C) fibers are responsible for pain and temperature sensation. The nerve fibers that receive and transmit painful stimulus are called nociceptors; neurons that respond to pruritogenic stimulus (pruriceptors) are a subset of nociceptors. Aδ fibers constitute ~80% of the primary sensory nerve fibers; C fibers comprise ~20% of the primary afferents. Only about 5% of C fibers transmit itch.[1-3]

Thinly myelinated or unmyelinated nerve fibers in the skin form what is called the "subepidermal neural plexus" or "subpapillary plexus" that consists of a mesh of nerve fibers that run parallel to the epidermis just below the tips of the dermal papillae. From this plexus, Aδ and C fiber branches come out and enter the epidermis to course between keratinocytes as unmyelinated fibers. Nerves also divide to innervate sweat glands, erector pili muscles, hair follicles, and arterioles. Nerve bundles and single

From the Department of Neurology,[a] School of Medicine,[b] and Department of Dermatology,[c] University of Missouri, Columbia.
Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication April 22, 2015.
Correspondence to: Kristen Heins Fernandez, MD, Department of Dermatology, 1 Hospital Dr, MA 111, Columbia, MO 65212. E-mail: fernandezk@health.missouri.edu.

0190-9622/$36.00
Published by Elsevier on behalf of the American Academy of Dermatology, Inc.
http://dx.doi.org/10.1016/j.jaad.2015.04.060
Date of release: February 2016
Expiration date: February 2019

Table I. Classification of nerve fibers

Sensory nerves	Myelin	Diameter (μm)	CV (m/s)	Location/function
Aα	Thick	12-22	70-120	Muscular spindles, tendon organs
Aβ	Moderate	6-12		Touch receptors
Aδ	Thin	1-5	4-30	Polymodal, "first pain"
C	Unmyelinated	0.2-1.5	0.5-2	Polymodal, "second pain"

nerve fibers in the dermis are usually associated with capillaries. The papillary dermis also contains unmyelinated nerve fibers that form the dermal microvascular unit where axons often terminate in close proximity to mast cells. These are important in itch and allergic reactions. Thickly myelinated Aβ fibers are located in the reticular and papillary dermis.[4-10]

The skin also contains encapsulated nerve organs. Meissner corpuscles (MC) are cylindrical or pear-shaped tactile mechanoreceptors located high in the dermal papillae of the palms, soles, digits, nipples, and lips. MCs are innervated by intrapapillary myelinated endings (IMEs). One IME typically furnishes between 1 and 3 MCs per dermal papilla. Each MC contains a zigzag arrangement of unmyelinated terminal afferent nerve fibers.[5,7,11-13] Pacinian corpuscles, in contrast, are ovoid pressure mechanoreceptors in the reticular dermis.[14] The axons entering MCs and Pacinian corpuscles represent the specialized endings of Aα and Aβ fibers.[5,13] Studies in animals have also found unmyelinated axons.[15]

Mucocutaneous end organs are located in the papillary dermis of modified hairless skin at the mucocutaneous junctions (eg, the glans, prepuce, clitoris, labia minora, perianal region, and vermilion border of the lip). Two to 6 myelinated nerve fibers enter each mucocutaneous end organ and form many loops of nerve fibers resembling an irregularly round ball of yarn.[4]

Merkel cells are neuroendocrine cutaneous cells that are located in the basal layer of the epidermis and are concentrated in touch-sensitive areas of glabrous and hairy skin and in some mucosa. They are innervated by slowly adapting type 1 mechanoreceptor nerve fibers, a subset of Aβ touch receptors, forming "touch domes." A Merkel cell–neurite complex or Merkel disk consists of the Merkel cell and the nerve fibers in close apposition to it. Other sensory fibers, including Aδ and C fibers, also come into contact with Merkel cells.[11,16,17]

ITCH

Itch can be classified by etiology. Pruriceptive itch originates from the activation of primary afferent nerve terminals (eg, insect bites). Neuropathic itch is a chronic condition related to nerve injury that is sometimes associated with burning and stinging pain. Neurogenic itch is caused by central nervous system injury or activation without the activation of sensory nerve terminals (eg, renal disease and kidney failure). Psychogenic itch results from a pure central psychic processing disorder in the absence of skin pathology or underlying medical disease.[18,19]

Itch mediators and receptors

Numerous itch mediators (pruritogens) and receptors (pruriceptors) have been identified (Table II), of which the best understood are histamine, proteases, opioids, substance P, the Mas-related G protein–coupled receptor (Mrgpr) family, and calcitonin gene–related peptide (CGRP).

Histamine. Histamine is the best known pruritogen. It is released from mast cells and keratinocytes and acts on neurons that express histamine receptors. H1 and H4 receptors are involved in itch signaling, whereas H3 receptor activation in mice is associated with a decrease in scratching behavior.[20] Once histamine binds to its receptor, it leads to the activation of transient receptor potential vanilloid 1 (TRPV1) ion channels.[21] These are heat- and capsaicin-gated ion channels necessary for the histamine transmission of itch. Once TRPV1 channels are indirectly activated by histamine, the cell depolarizes, leading to the opening of sodium channels along the nerve and subsequent itch sensation. TRPV1 channels are expressed on primary afferent neurons, keratinocytes, dendritic cells, and mast cells. Their activation generates action potential and neuropeptide release. However, prolonged activation with resultant calcium influx can cause desensitization of the primary afferents and leaves the nociceptive and pruriceptive neurons inactive. Blocking or genetic silencing of TRPV1 receptors also reduces the scratch response induced by pruritogenic agents other than histamine, which suggests that TRPV1-positive neurons also express other itch receptors.[21]

The site of histamine release also changes the clinical manifestations of itch. The release of