Sensory Function of the Skin

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Keywords

Aδ fibers • Mechanoreceptors • Nociceptors • Pruriceptors • Silent C fibers • Skin sensory function • Anatomical classifications • Emotional experience • Gate control • Itch • Merkel cells • Nociceptors • Pain • Pruriceptors • Rapid accommodation • Thermoreceptors

Sensory function (touch) is one of the most important functions of the skin-nervous system but is not the only one (Misery 1997). Autonomic nervous system controls vasodilatation (and thus thermoregulation), pilo-arrection, sebaceous excretion, and sweat secretion and excretion. Sensory nerve fibers are also able to strongly modulate skin immunity, skin trophicity, hair growth, cutaneous effects of ultraviolet light (photoprotection and immunosuppression), keratinocyte differentiation or proliferation, and all other functions of the skin, thanks to an antidromic secretion of neuropeptides and neural growth factors. Hence, they also modulate wound healing and inflammation and exert effects on the time course of skin diseases.

1 The Cutaneous Sensitivity

Following an external stimulus, the signal generated in the skin is conveyed by activated C and Aδ fibers of the neurosensory system to the neuron cell (Reznik 1996; Boulais and Misery 2007). At this level the information is received through a

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receptor, and then the electric potential of the cell membrane is altered and neurotransmitters are produced. The nervous impulse is conveyed to sensitive ganglions then to the spinal cord. A second neuron, via the spinothalamic funiculus, transmits the information to the thalamus, at the brain basis. A third neuron conducts the impulse to the temporal cortex. At all levels, the "gate control," exerted by intermediary neurons, regulates the system.

In the epidermis, Merkel cells (Boulais and Misery 2007) have a specific sensory function, especially in mechanoreception, in a close interaction with Aβ fibers. Other epidermal cells (mainly keratinocytes) could also have sensory functions because they express sensor proteins (Boulais and Misery 2008), and the epidermis can be considered as the forefront of the sensory system (Denda et al. 2007).

Anatomical and functional classifications of cutaneous neuroreceptors are not superimposable. Indeed, a same anatomical type of nerve endings is able to receive and transmit different types of information. Four functional types of receptors are defined: mechanoreceptors, thermoreceptors, nociceptors, and pruriceptors (Table 1).

1.1 Mechanoreceptors

There could have a slow accommodation (response over the whole duration of stimulus) or a rapid accommodation (response at the beginning and the end of the stimulus).

In non-hairy skin, type I receptors (Merkel cells and Meissner corpuscles) have small and well-limited receptive fields and the conduction velocity is 55–60 m/s. Type II receptors (Ruffini and Pacini corpuscles) have broader and less limited receptive fields and the conduction velocity is 45–50 m/s. In hairy skin, mechanoreceptors are perifollicular free nerve endings, Merkel complexes, lanceolated endings, and Ruffini corpuscles.

1.2 Thermoreceptors

They are mainly C fibers and have a very slow conduction velocity (0.5 m/s). The impulse frequency is proportional to the stimulus intensity and frequency. Two different receptors have been isolated: cold receptors (<30 °C) and heat receptors (32–48 °C). There is an overlap area around 30–40 °C, where variations of temperature are more important than temperature for activation of these receptors, which explains the possibility of paradoxical cold. Temperatures lower than 20 °C or higher than 45 °C are discerned as painful.

1.3 Nociceptors

They are unmyelinated free nerve endings (Cesaro 1994). Three types are described:

- Aδ fibers, sensitive to strong mechanical stimulations (bite, pinching, cut)
- Common C fibers, sensitive to mechanical, thermal, and chemical stimuli and to numerous mediators (neurotransmitters, cytokines, eicosanoids, etc.)
- "Silent" C fibers, activated only after a chemical or biochemical sensitization, especially by mediators of inflammation

Table 1 Sensory receptors in the skin

Type	Subtype	Stimuli	Type of nerve ending
Mechanoreceptor	Type I	Quivering, touch	Meissner, Aβ, C
	Type II	Vibration, pressure	Pacini, Ruffini, Aβ
Thermoreceptor	Cold	<30 °C	C, Aδ
	Heat	32–48 °C	C
Nociceptor	Mechano-	Excessive mechanostimulation	Aβ, Aδ
	Polymodal	Inflammatory mediators	C
Pruriceptor	See Table 2		

1.4 Pruriceptors

These receptors have been recently isolated (Schmelz et al. 1997) and are specific of pruritus or rather selective for pruritus. Itch is specific of the skin and some close mucosa and seems to originate in epidermal and maybe subepidermal nerve fibers, Aδ fibers, and mainly C fibers.

It has been initially shown that there were mechano-insensitive and heat-insensitive C fibers that discharged upon histamine iontophoresis and whose firing frequency paralleled the itch magnitude rating on a visual analog scale (Schmelz et al. 1997). Then histamine-sensitive mechano-insensitive spinal neurons with very low conduction velocity and conveying impulses to a distinct part of the hypothalamus were discovered in the cat (Andrew and Craig 2001). These data point to "a specific population of chemo-nociceptors responsible for itch forming a labeled line for itch processing" (Schmelz 2002).

Since these discoveries, many others have been performed and the following classification of pruriceptors can be proposed, dividing them in two types (Misery and Ständer 2010) (Table 2):

- Histamine-dependent pruriceptors
- Histamine independent that are mainly activated by cysteine or serine proteases like mucunain or tryptase, through PAR-2 receptors.

Table 2 Pruriceptors

Fibers C	Histamine (H1R)	Cowhage (PAR-2)
Mécano-insensibles (TRPV1−)	+	−
Mécano-sensibles (TRPV1+)	+	+

2 Pain

The international definition of pain is "a sensory and emotional experience, which is disagreeable and linked to a potential or existing tissular lesion, or described as such a lesion" (Cesaro 1994). It corresponds to an excess of nociception, and accordingly, pain appears beyond a threshold. Cutaneous pain is mainly acute, and generated by physical, chemical, or thermal traumas, but can be chronic. Pain is not so frequent in the course of skin diseases (mainly in leg ulcers or in de-epidermization processes like in Lyell's syndrome) but it can be present in the course of neurological or neuro-dermatological diseases. The central integration of pain plays an important part, through its psychological repercussions.

From nociceptive receptors, painful information is conveyed by the usual ways (see above). Intimate mechanisms of pain remain far from elucidated. External painful stimuli as well as numerous chemical substances, such as bradykinin, histamine, serotonin, prostaglandins, interleukin-1, etc., are able to modify or induce nociceptor activation. Substance P is the most well known and the most important mediator of pain, but others have been more recently described (CGRP, somatostatin, glutamate, etc.).

At all levels (the skin, spinal cord, brain), a "gate control" is permanently in operation. Serotonin and norepinephrine but particularly endorphins and enkephalins have endogenous analgesic effects. Pain is usually due to an excessive stimulus but can be also related to a lack of normal sensation gate control.

3 Itch

Pruritus or itch is an unpleasant sensation that causes a need to scratch (Misery and Ständer 2010; Bernhard 1994). Pruritus does not appear as a minimal pain, as it is often thought, because they are two different sensations. It occurs on the skin and external mucous membranes (genitalia, lips) rather than internal ones; it induces scratching, is exacerbated by heat or morphine-related drugs and soothed by cold, and can be triggered by very low stimuli. Pain is not specifically cutaneous, induces withdrawal, is exacerbated by cold and soothed by heat and morphine-related drugs, and is experienced beyond a relatively high threshold.

Pruritus can be acute or chronic. It occurs in a variety of circumstances: inflammatory skin

diseases, accumulation of toxins (related to liver or kidney diseases), and systemic diseases (mainly blood and endocrine diseases). Exogenous agents (chemical products, drugs) can induce itch. But it can be only neurogenic or psychogenic.

Central integration of pruritus is very important, but there is no one itch center because itch is related to interactions between sensory, motor, and affective areas in the brain. Gate control probably exists at different levels. Senile pruritus and maybe diabetic pruritus or certain neurological pruritus seem to be due to desafferentation.

Histamine is the most well-known mediator of itch, but it plays no role in most cases. That explains why antihistamines are usually ineffective. Substance P, serotonin, and prostaglandins are probably more important factors. Endogenous or exogenous morphine-related compounds can also induce pruritus, as well as cytokines such as interleukin-2 or interferon-α, some proteases (trypsin, papain), or kinins (kallikrein, bradykinin), and can be soothed by substances such as ciclosporin.

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