Skin Innervation
Prof. Martin Schmelz
Karl-Feuerstein-Professorship
Dept. Anesthesiology Mannheim
Heidelberg University
Germany

Overview

• Structure and sensory function in healthy skin
• Skin innervation changes in disease
  – Loss of innervation: polyneuropathy
  – Increased innervation: itch and pain?
• Neuronal function beyond sensory tasks

Neuronal structure
and sensory function in healthy skin
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Myelinated fibers

- Touch and texture: corpuscular sensors
- Rapidly and slowly adapting subtypes

<table>
<thead>
<tr>
<th>Slowly adapting</th>
<th>Rapidly adapting</th>
<th>Functional significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>Merkel receptors</td>
<td>Small innervation</td>
</tr>
<tr>
<td>Deep</td>
<td>Ruffini endings</td>
<td>Large innervation</td>
</tr>
</tbody>
</table>

Myelinated fibers – functional significance

Beyond sense of touch, flutter and vibration...
- Detection of texture (Braille)
- Sensor-motor interaction: Grip force, speech
- Position sense (stretched skin above joints)

“Small fibers”:
unmyelinated or thinly myelinated

<table>
<thead>
<tr>
<th>Fiber class</th>
<th>Diameter (µm)</th>
<th>Conduction velocity (ms⁻¹)</th>
<th>Functional significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A alpha</td>
<td>15</td>
<td>50-90</td>
<td>Afferent and efferent muscle innervation</td>
</tr>
<tr>
<td>A beta</td>
<td>8</td>
<td>30-70</td>
<td>Low threshold mechanoreceptors (skin)</td>
</tr>
<tr>
<td>A gamma</td>
<td>5</td>
<td>15-30</td>
<td>Efferent muscle innervation</td>
</tr>
<tr>
<td>A delta</td>
<td>&lt;3</td>
<td>5-20</td>
<td>Mechanoreceptors, heat receptors</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>0.5-2</td>
<td>Mechanoreceptors, heat receptors, Pruriceptors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Warm receptors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C-touch fibers (social touch)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sympathetic effferent vasoconstrictors, Sedoceptors,</td>
</tr>
</tbody>
</table>

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Myelinated vs. unmyelinated fibers: “hear the difference”

A-fiber response
C-fiber response

Microneurography recordings from human cutaneous nerve: single fiber activity

Temperature, itch, pleasure and pain: epidermal free nerve endings

- Sense of temperature: cold and warm fibers
- Nociception: pain and itch
- Pleasant touch: low threshold C-fibers ("C-touch")

Sensors for thermoregulation

**Warm fibers**
- Unmyelinated
  - Small innervation territory, rare
- Activated by mild warming
- Inhibited by cooling

**Cold fibers**
- Thinly myelinated
  - Few recordings in humans
- Activated by mild cooling
- Inhibited by warming
  - Paradox activation by strong heat

Contrast enhancement by differential activity pattern
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Nociceptors detect threats: behavioral consequences

External threats:
• Localized mechanical stress, friction
• Noxious heat, freezing cold
  \[\text{Withdrawal!}\]

Internal threats:
• Chemical stimuli (acidic pH, inflammatory mediators)
  \[\text{Protect!}\]
• Localized noxious stimuli in the epidermis (mites etc.)
  \[\text{Scratch!}\]

Functional classes of nociceptors

Mechano-heat sensitive nociceptors
• A-delta fibers: sharp, pricking pain
• C-fibers: burning pain
• Immediate, phasic response to external threats
• Implication: withdrawal!

Functional classes of nociceptors (2)

Mechano-insensitive chemo-nociceptors
• A-delta and C-fibers: burning pain
• Delayed, tonic response
• Mainly to slowly developing internal threats
• Implication: protect!
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**Functional classes of nociceptors (3)**

**Cold nociceptors**
- C-fibers: burning pain
- Delayed, tonic response
- Axons resistant to low temperatures (NaV1.8)
- Implication: **seek warm!**

**Functional classes of nociceptors (4)**

**Pruriceptors**
- C-fibers (possibly also A-delta): itch
- Delayed, tonic response to histamine
- Non-histaminergic itch in human yet unclear
- Implication: **scratch!**

**Classification of nociceptors**

**Structural markers**
- Peptidergic vs. non-peptidergic
- CGRP, trkA, TRPV1 vs. IB4, GDNF, P2X3
  - Valid for mouse, less so for rat, unclear for human
- New approach: functional markers of mas-related G-protein receptor – family **mrgpr**
  - In mice: mrgprC11, mrgprA3, mrgprD linked to pruriceptors, mrgprB4 linked to C-LTM
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**Functional classes of nociceptors**

- Correlate to specific behavioral responses
- Specific molecular sensors and specific axonal proteins yet unclear
- Important future task: structural markers for functional classes (such as B-type natriuretic peptide, mrgpr-family, …)

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**Recent advances in itch mechanisms**

**Central mediators / markers**
- Gastrin releasing peptide (GRP)
- VGLUT2

**Peripheral mediators / markers**
- B-type natriuretic peptide (NPPB)
- IL-31
- Lysophosphatidic acid (LPA)
- Chloroquine / MrgprA3
- BAM8-22 / MrgprC11

**Functional nerve fiber classes**
- Cowhage sensitive
- Histamine sensitive

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**C-touch fibers: pleasant touch**

Microneurography recordings from human cutaneous nerve: single fiber activity
C-touch fibers: pleasant touch (2)

- Optimal activation by slowly stroking the skin
- Optimal stroking velocity coincides with peak in pleasantness
- No overt perception linked to activation
- Yet central activation of prefrontal cortex and insula
- Pattern compatible with role in “social touch”

Efferent sympathetic innervation of the skin

Mainly thermoregulatory:
- Sudomotors (muscarinergic; ACh)
- Vasoconstrictors (alpha1; norepinephrine)
- Piloarrectors (cholinergic)
- Vasodilators (blushing, unclear transmitter)

No parasympathetic innervation of the skin

Functional tests of small fibers

Quantitative sensory testing (thermoreceptors, nociceptors)
- Warm/Cold detection threshold
- Heat pain threshold

Neurogenic vasodilation (chemonociceptors)
- Chemically/Electrically induced

Sudometry (sympathetic sudomotor fibers)
- Chemically/Electrically induced
Reduced epidermal innervation density: small fiber neuropathy

- Epidermal fiber density (number of nerve fibers penetrating dermo-epidermal junction per mm of epidermal length)
- Skin biopsy and neuronal PGP 9.5 staining

Functional correlates:
- Reduced superficial innervation: Cold/warm thresholds
- Dermal innervation: Heat pain, sudomotor function

Epidermal innervation and sensory function

Decreased innervation = neuropathy! Increased innervation = pain and itch?

- Is there a structure-function relationship for itch and pain in neuropathy?
- Does chronic itch imply increased epidermal innervation?
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Structure-function relation between epidermal innervation and chronic pain?

Decreased innervation = neuropathy!
Increased innervation = pain and itch?

Pathologically increased function of skin sensory nerve fibers in chronic pain and chronic itch:
• Primarily functional changes
• Structural changes not required

Neuronal function in the skin - beyond sensory tasks

• “Neurogenic inflammation”
• Nociceptors and inflammatory cells
• Keratinocyte/nociceptors communication
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Neurogenic inflammation

"Neurogenic inflammation"

Nociceptor stimulation

Mediation

Protein extravasation

Immunomodulation

CNS: sensation (pain, itch)

Neurogenic inflammation – dermal microdialysis

1 Hz, 80 mA, 0.5 ms
or 4 Hz, 30 mA, 0.5 ms
30 min each

No neurogenic protein extravasation in healthy human skin

Rat

Human

Total protein, mg/mli

Time (min)

4 Hz control

5 Hz control

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Neuropeptide-induced vasodilation

SP induced protein extravasation and vasodilation

SP but not CGRP induces histamine release

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Neurogenic inflammation
1. Activation of nociceptors
2. Release of neuropeptides
3. Vasodilation, (protein extravasation)
   local immunomodulatory effects, trophic effects

- Activated nociceptors release neuropeptides
- Neuropeptides do not directly activate nociceptors

Communication between keratinocytes and nerve endings

Communication between keratinocytes and nerve endings (2)
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Complex interaction between neurons and skin cells

- Excitatory interactions
- Inhibitory interactions

Complex interactions include:
- Substance P (SP)
- CGRP
- Endorphins
- Enkephalins
- Eicosanoids
- Tryptase
- Histamine
- PACAP
- IL-1
- IL-8
- IL-4
- TNF
- IL-10
- IL-1ra
- CRH
- PACAP
- NEP

Innervation of air-exposed skin equivalent

Epidermal growth increased by neuropeptides from nerve endings:

- Untreated
- CGRP
- SP
- CGRP + SP
Keratinocytes from atopic dermatitis patients: increased innervation and epidermal thickness

Mechanisms of nociceptor sensitization

Thank you for your interest!

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