Nociception, pain
Q1  What is nociception, what is pain?
Nociception is a sensory activity, which is induced by a noxious stimulus, i.e. an actual or potential tissue damage.

Pain is a sensation that contains other components in addition to nociception.

The activation of nociceptors is not always associated with pain: pharmacologically induced anaesthesia. And, vice versa, pain is possible without the activation of nociceptors.

- nociceptive pain
- neuropathic pain
Example: neuropathic pain

the sensation is attributed to the innervated area

sensory field with nociceptors

induction of a neuronal signal by mechanical irritation

tractus spinothalamicus lateralis
Classification of nociceptors

- thermical nociceptors
- mechanical nociceptors
- polymodal nociceptors

These nociceptors have different functions and differ in their:
- afferent pathways
- axonal conduction velocity
- size of neurons/axons
- neurochemical/pharmacological properties (transmitters, peptide co-transmitters)
In comparison with other sensory systems, nociception is characterized by sensitization, i.e. a decrease of sensory threshold with stimulus repetition.

Two forms:
- **Allodynia** (normally not painful stimuli become painful: the touch of sunburned skin)
- **Hyperalgesia** (stronger perception, less tolerance against noxious stimuli, permanent pain)

2 mechanisms:
- receptor sensibilization (silent nociceptors)
- central sensibilization

**Silent nociceptors**: perception only after sensitization
Q2 How are nociceptors activated?
A, B

Nociception is based on the interaction of free nerve endings with damaged cells, mast cells and capillaries. This induces additional depolarization by means of the released pain mediators.

Peripheral mechanisms

nociceptive neuron

mast cells

histamine

bradykinin

(from plasma kininogen)

lesioned cells

serotonin

(capillaries)

HR BR

SR

K^+

depolarization according to Nernst’s equation

H^+

depolarization by H^+-activated Na^+ current

HR BR SR

noxious stimulus

lesioned cells
Another specific property of nociceptive neurons: The free endings in the sensory fields not only serve perception and receive information through pain mediators, they also release peptide transmitters ('axon reflex')

- Substance P
- CGRP

Peripheral mechanisms
The pain mediators bradykinin, serotonin and histamine facilitate the release of neuropeptides from the peripheral endings of nociceptive axons (substance P, CGRP). This leads to an enhancement of the nociceptive signals (positive feed-back).
The lesioned cells themselves can liberate sensitizing substances. This also leads to a positive feedback signaling...
The main endogenous pain mediators in humans

Peripheral mechanisms

Plasma kininogen
Thrombocytes
Mast cells, leucocytes
Cell damage
Cell damage
Cell damage

Effect on nociceptors

stimulus
sensitization

Bradykinin
Serotonin
Histamin
Kalium
Prostaglandine
Leukotriene

>10^{-7}
>10^{-7}
>10^{-3} (mol/l)
>10^{-3}
>10^{-6}
>10^{-6}
After sensitization, the pain (dolor) is accompanied by inflammation:

- local heat (calor)
- reddening (rubor)
- swelling (tumor)

Please note:
Not only pain, but also inflammation can be induced by a neurogenic mechanism, i.e. in response to

- activation of specific receptors in the membrane of nociceptive fibers: capsaicin acting on vanilloid receptors

- electrical stimulation of nociceptive fibers: elbow, tooth
Q3 How are nociceptive signals conducted to and processed in the spinal cord?
The compound action potential after electrical stimulation of a mixed nerve displays several components, according to different conduction velocities (classification of fibers according to Erlanger/Gasser).

Electrical stimulation separates signals in nociceptive afferents signals, since they have higher thresholds and lower conduction velocities.
Simultaneous stimulation of non-nociceptive sensory afferents can reduce the perception of nociceptive afferent signals (due to convergence + activation of inhibitory interneurons).
The **transmitter** of nociceptive afferents in the dorsal horn is glutamate

**Modulators** of synaptic transmission and exitability are:
- neuropeptides (substance P)
- neurotrophins (NGF, BDNF)
- endogenous opiates (enkephalines, β-endorphins, dynorphins)
Synaptically released endogenous opiates act via 3 classes of receptors (\(\mu, \delta, \kappa\)) that are coupled to G proteins.

**Spinal mechanisms**

Opiates cause - presynaptically: decrease \(g_{Ca}\), increase \(g_{K}\)
- postsynaptically: increase \(g_{K}\)
- in the network: transmitter release by disinhibition of enkephalinergic neurons
The mechanism of central sensitization (sensibilization, 'wind-up') is based, first of all, on an up-regulation of the number and open probability of NMDAR channels (LTP-like mechanism); This process is facilitated by NGF (nerve growth factor).

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**NGF**

NMDAR

AMPAR

Ca signal

TrkA

--> Increase of the discharge rate in the postsynaptic cell; In case of ongoing spontaneous activity - chronic hyperalgesia ('pain memory')
Q4 How are nociceptive signals processed above the level of the spinal cord?
The perception of pain also depends on the social environment. It is learned and stored in the pain memory.
Pain signals are orderly represented in the postcentral gyrus; changes after limb removal

Registration of activity after imagined finger movements; Imaging showed that projected pain ('phantom pain') correlates with massive changes in the cortical maps

B: 6 months after transplantation of hands - imagined finger movements without pain; hand representation has moved back

A: 4 years after amputation of both hands - imagined finger movements cause pain. Hand area has moved into the face area
At least 4 ascending systems participate in the transmission of pain signals:

- *Tr. spino-thalamicus*  
  (perception of where?)  
- *Tr. spino-reticularis*  
  (vigilance level)  
- *Tr. spino-mesencephalicus*  
  (emotional components; fear, due to connections to amygdala)  
- *Tr. spino-hypothalamicus*  
  (vegetative component)
Nociception is, at all levels, under efferent control. The latter plays a dramatic role in pain perception.

*Opiate-containing neurons are localized in the*
- spinal dorsal horn
- raphe-nuclei
- central gray

*As there is no re-uptake of opiates, they mediate more widespread reactions than other neurotransmitters. The endogenous opiates circulate in the blood ('enjoy by suffering')*
The opiates circulating with blood act, first of all, by disinhibiting local enkaphalinergic interneurons.

If the 'brake' is removed, opiates are released and the transmission of nociceptive signals is reduced.
Increased tolerance and addiction to opiates are based on different mechanisms.

**Tolerance:** reduced density of opiate receptors

**Addiction:** changes in the dopaminergic system of reward
Measurement of pain threshold
Experimental sensitization by injection of a substance into the knee joint of an experimental animal; test response to flexion.
Experimentally induced hyperalgesia