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Pathophysiology of the pain

Pain

- pain is subjective unpleasant feeling with emotional component
- it represents most frequent complaint in medicine
- diagnosis of causes of the pain and therapeutic intervention contributed to progress of medicine

A stimulus that causes tissue damage usually elicits a sensation of the pain.

Pain mostly represents

1. signal of danger – after pain sensation may follow disturbance of the tissue

2. can help in the location and diagnose of pathological processes

There exist different types of pain without signalling of the danger, pain have no reason in character, also neurological examination is normal …. **neuralgias**

Pain can be modified by

- past experiences
- suggestion
- emotion – particularly by anxiety
- simultanneous activation of other sensory modalities
- different state of attention

Pain stimulates

- **sympathetic neural system** (hypertension, vasoconstriction, tachycardia, mydriasis, sweating)
- **parasympathetic neural system** (nausea, bradycardia, hypotension, disturbances of consciousness)
- **motor response** (escape, changes in muscle tone etc.)

Nociceptors = free nerve endings of several types of fibers.

They are **chemoreceptors**, are created by ion channels

1. They are sensitive on the **pH changes** (pH in acute abscess, phlegmona reaches 5,8 = pain, pH in chronic abscess is normal, without pain)

2. Nociceptors register the **ratio K^+:Ca^{2+}** (treshold for pain is lower in the lower Ca^{2+} level in ECV)

Further substances influence free-nerve endings

- evoking inflammation (permeability of vessel wall, oedema) histamin, bradykinin, serotonin
- direct influence of free-nerve endings potassium, histamin, bradykinin serotonin
- sensitisation of nociceptors prostaglandins, esp. PgE_2, interleukin-1, interleukin-6, cyclooxygenases (COX-1, COX-2)
- From activated free nerve endings P-substance is relea-sed. It influences vessel wall (vasodilation, permeability of vessel wall, oedema) and mast cells (release of histamin after degranula-tion)

Fibres conducting nociceptive stimuli

- **C-fibres** – without myelin sheets, impulsi are convected slowly, fibres convect deep, non-accurate localized, diffuse pain
- **Aδ-fibres** – with thin myelin sheet, fibres mediate fast convection of sharp, accurate localized pain
- **Aα/Aβ-fibres** – large myelinated. Fibres do not convect nociceptive stimuli, they mediate convection of tactile stimuli
- Afferent fibres enter dorsal spinal roots. In this region exist excitatory and inhibitory interneurons. Inhibitory interneurons mediate convection of informations into thalamus and cortex.

Excitatory and inhibitory neurotransmitters at spinal level

- **excitatory** – aminoacids, esp. glutamic acid, GABA
- **inhibitory** – glycin, encephalins, dynorphins

Pathways convecting nociceptive stimuli

- **Spino-thalamo-cortical system.** Stimuli are convected into thalamus, after switching into assotiation regions of cortex. System rapidly convects sharp pain, acuratelly localized pain
- **Spino-reticulo-thalamic system.** System plays a role in behavior and emotions at the pain, in activation of autonomous system, in remembering of the pain etc. After switching in reticular formation, **limbic system** and thalamus are stimuli convected into brain cortex. System slowly convects deep, difuze pain
- **Spinomesencephalic system** is efferent, serves by central modulation of pain. Efferent fibres are convected from periaqueductal gray matter, reticular formation to spinal dorsal roots, here inhibitory neurons are stimulated.

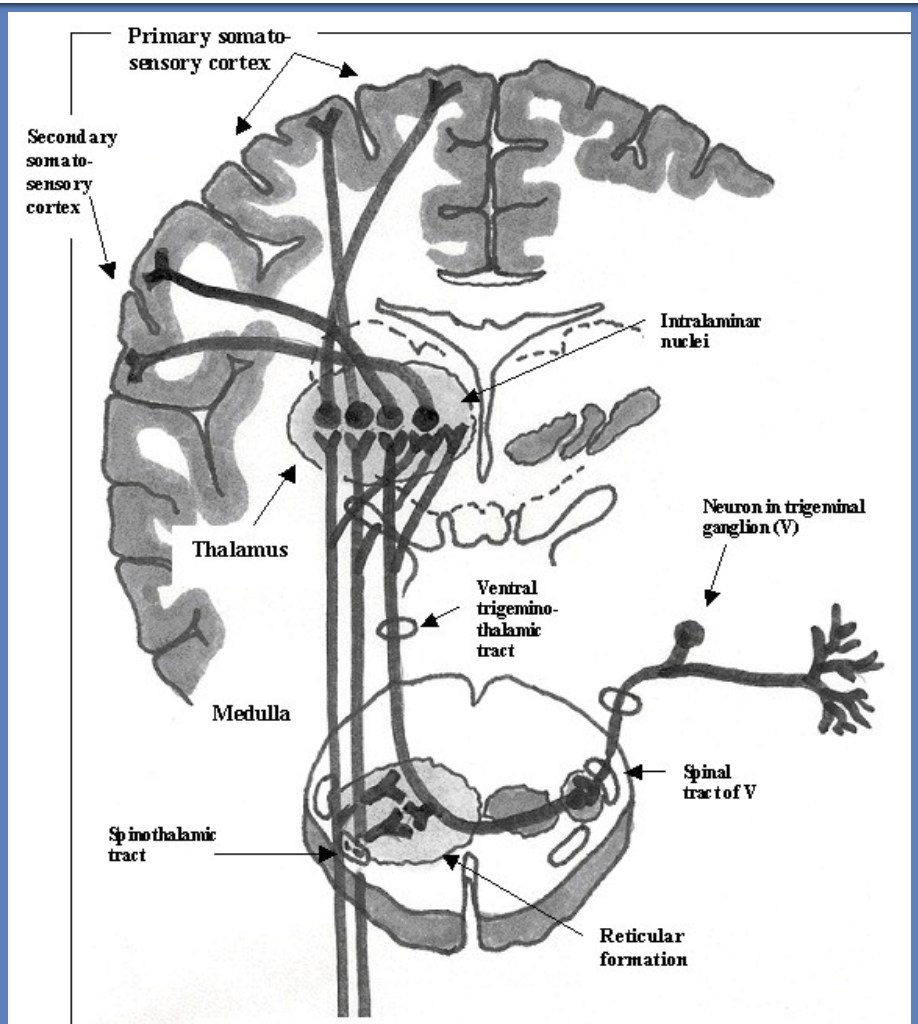
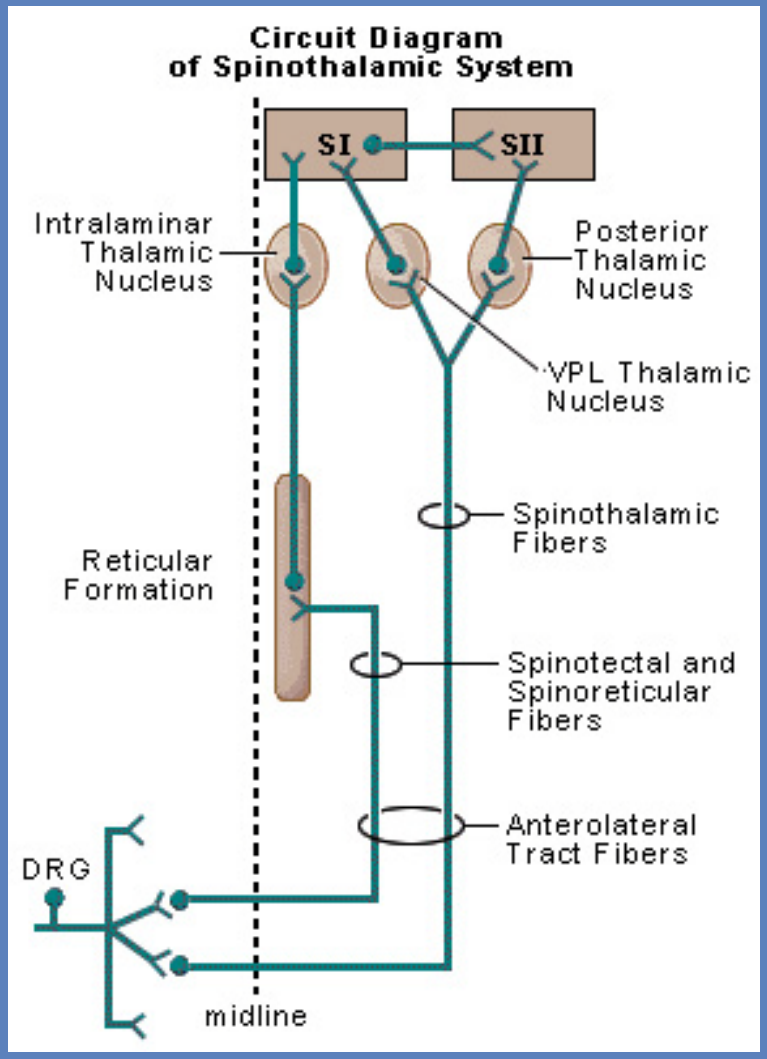


Fig. A7. Interconnections of Reticular formation, Spinothalamic tract, Trigeminal tract, and Thalamus


Circuit Diagram
of Spinothalamic System
SI
SII
Intralaminar
Thalamic
Nucleus
Posterior
Thalamic
Nucleus
VPL Thalamic
Nucleus
Spinothalamic
Fibers
Reticular
Formation
Spinotectal and
Spinoreticular
Fibers
Anterolateral
Tract Fibers
DRG
midline

Elaboration of stimuli from periphery

- **Brain cortex** = analysis of nociceptive stimuli
- **Efferent fibres =** realization motor or other responses on the stimuli
- **Central elaboration** modifies the pain (learning, attention, work etc.)

Modulation of the pain on the spinal level

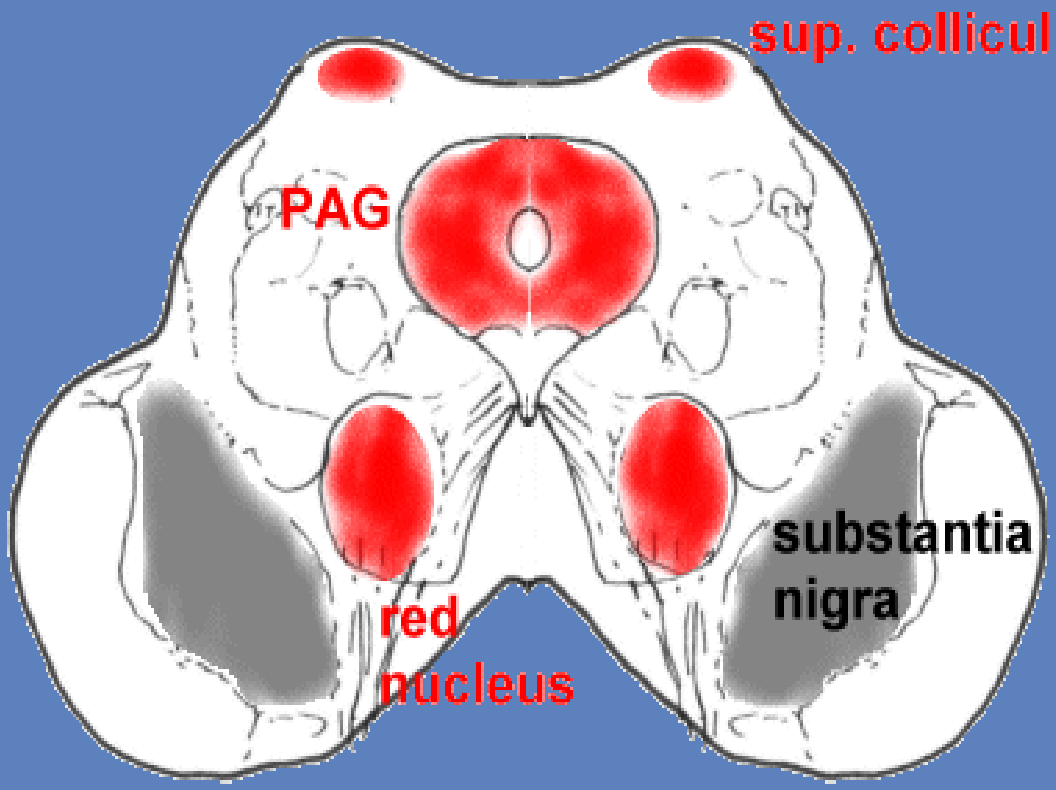
- Aα/Aβ fibres – stimulation of inhibitory interneurons
- inhibitory interneurons – inhibition of the synaptic transferr of nociceptive stimuli
- Aδ and C-fibres – stimulation of the excitatory neurons – facilitation of the synaptic transferr of the nociceptive stimuli

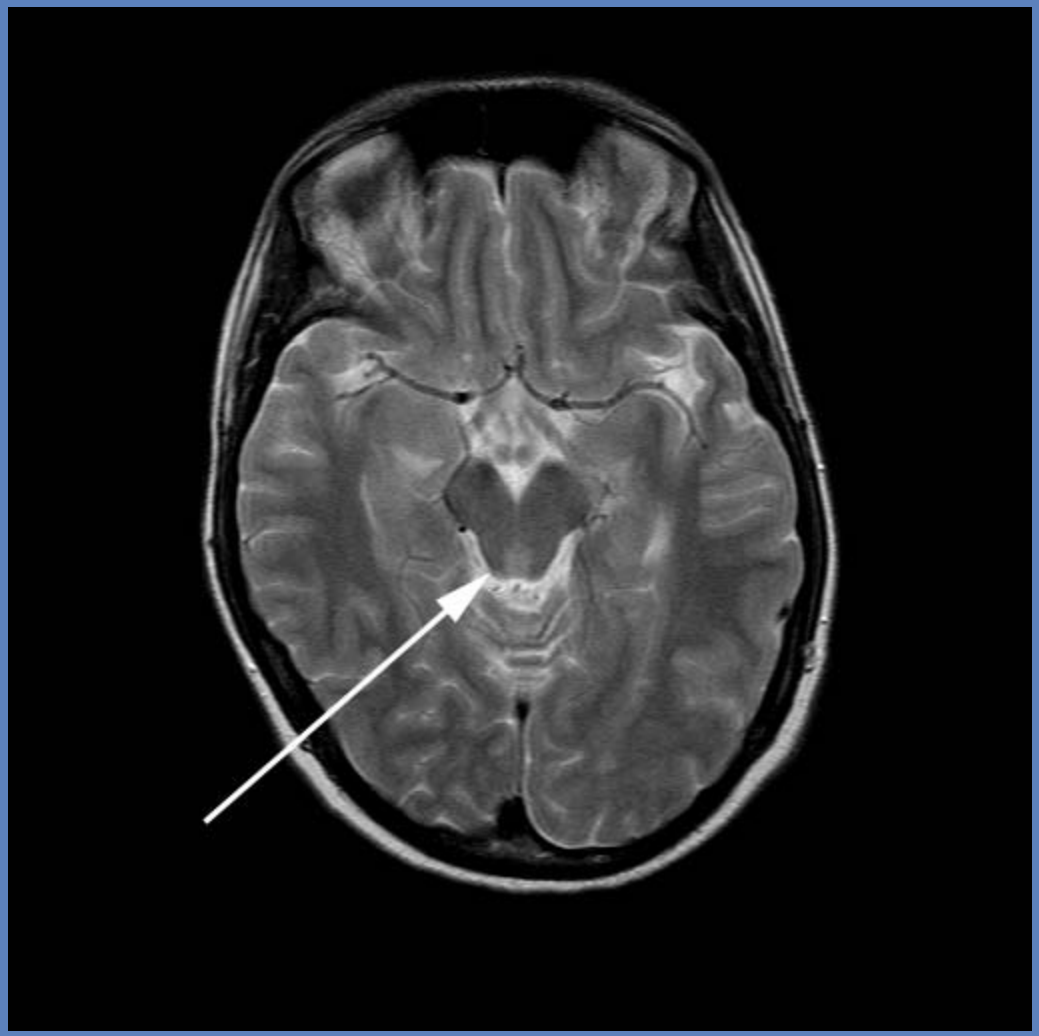
Modulation of the pain in central level

- Direct stimulation of the **gray matter in periaqueductal and periventricular spaces** evokes **analgesia** (tactile and thermic perception is preserved) due to activation of inhibitory internerneurons in spinal level
- Stimulation of the additional descending pathway from **brain stem** nuclei (locus ceruleus, nc. reticularis gigantocelularis) also evokes **analgesia**

Modulation of the pain on central level II

- **Cells in gray matter** at both periaqueductal and periventricular spaces content on the their surface receptors for endogeneos opioid peptides and morphin.
- Endogeneous opioids are at theese places sythesised.
- Analgetic action of morphin is due to binding to the receptors in CNS


sup. colliculus
PAG
substantia nigra
red nucleus



Endogeneous opioid peptides

- **encephalins**
  dynorphins
  propiomelanocortins (POMC)
- **homology** – sequence of AA: tyr-gly-gly-phe
  opioid peptides are products of similar genes
- localization: **POMC** – gray matter
  encephalins and dynorphins – gray matter, spinal medulla, dorsal spinal roots
  β-endorphin – hypothalamus – influence of gray matter
- Opioid peptides are **inhibitory** neurotransmitters

Types of the pain I.

- **acute pain** – sharp pain, arising immediately after nociceptive stimuli in mucose membranes, muscles, skin, eyes, orbita, teeth,joints
- **chronic pain**
- Chronic pain is characterized by **non-synaptic (ephatic)** transferr of nociceptive stimuli (similarly as in **neuralgias**). Chronic stimulation of axons leads to creation of **sprouts** from the axon surface, sprouts contact near axons/sprouts and due to impules are enlarged into all nerve

Types of the pain II.

- **Superficial pain** – from the skin. Pain is good located, it is sharp in character; also as pain from pleura – **parietal pain**
- **Deep somatic** and **visceral pain** – pain has a blunt, diffuse character.

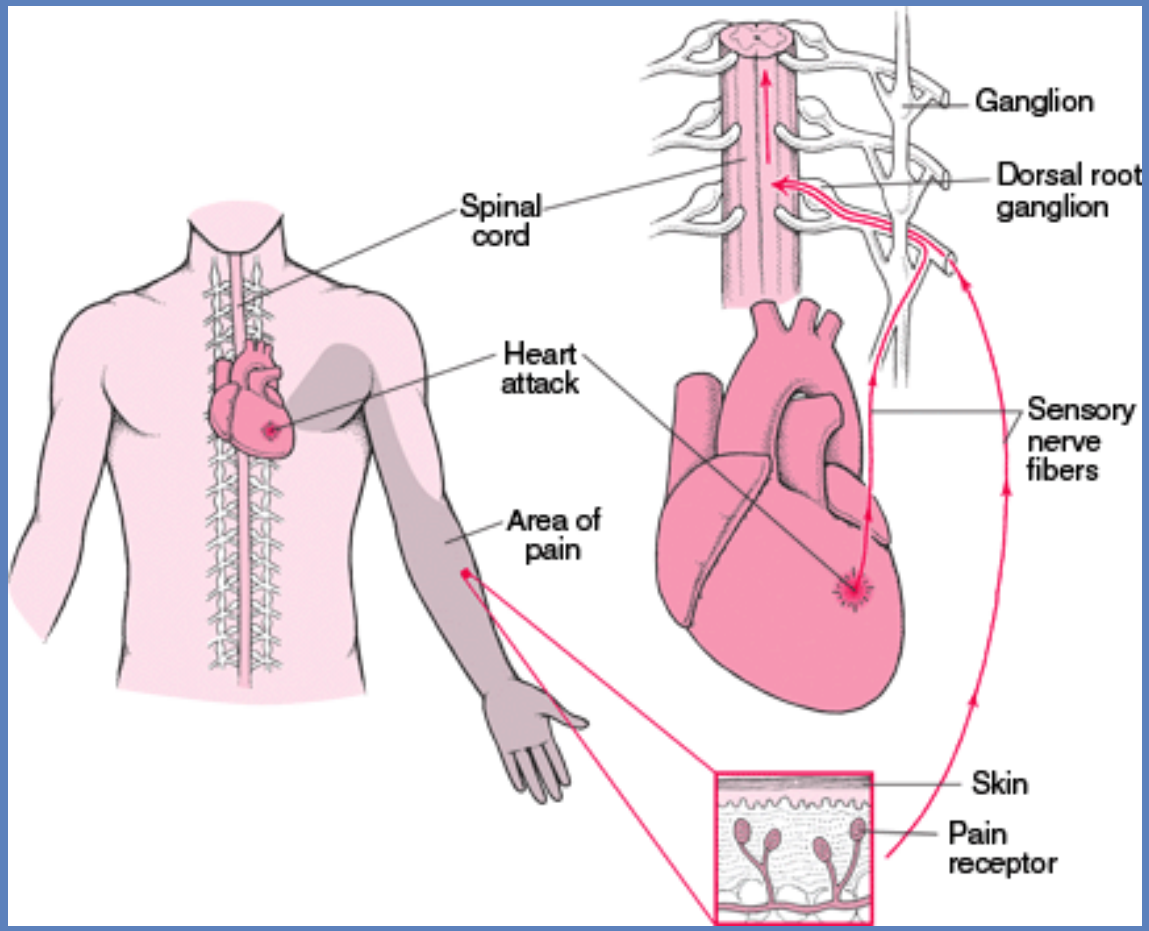
Deep visceral pain is characterized by phenomenon of **reffered pain**

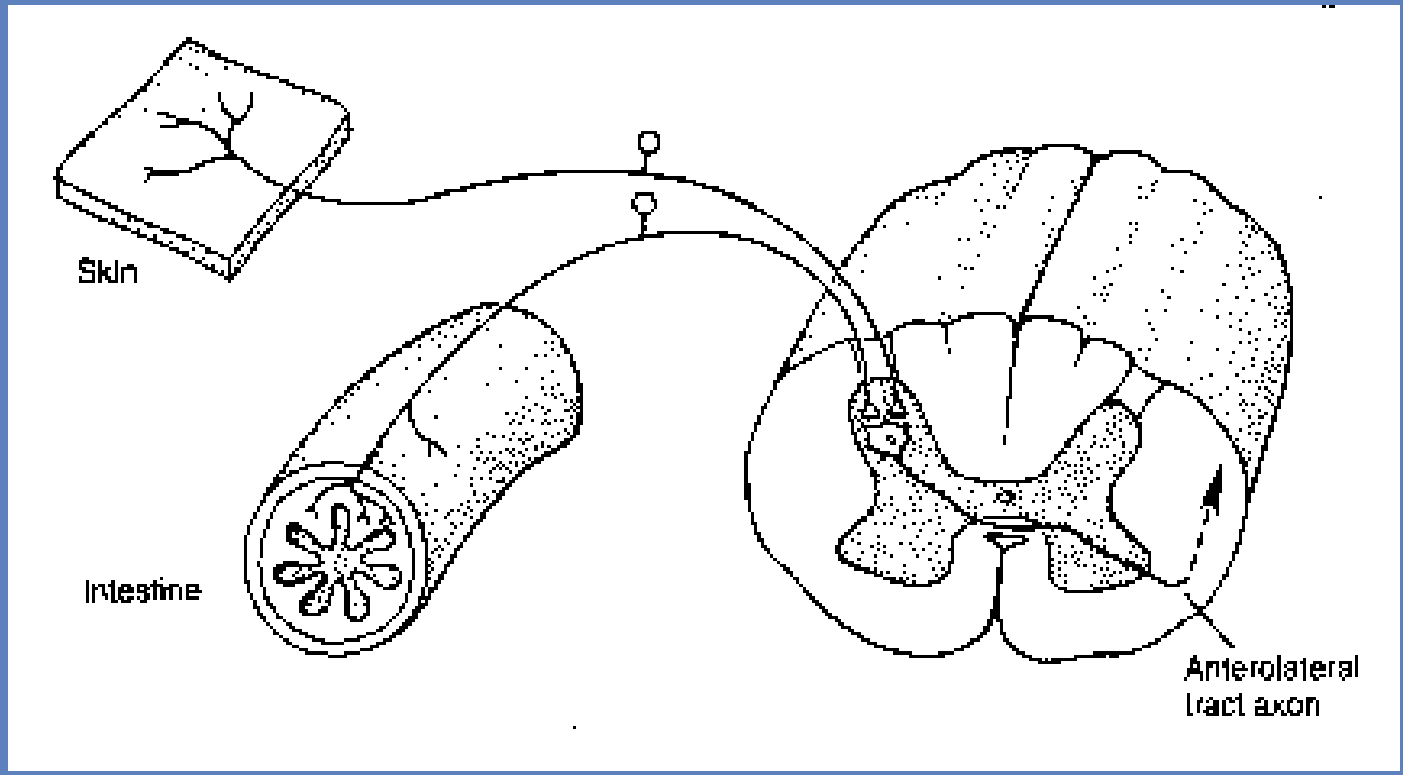
Referred pain

Sensation of pain is experienced at a site other than on the injured or sick part of body

Reffered pain occurs because both visceral and somatic afferents converge to the same intercostal nerve, it conducts impulsi from the injured organ and from the skin (maximum tactile, thermic impulses)

Assotiation brain cortex projects the pain into places, from which are convected maximum afferent stimuli (tactile, thermic etc.)


Ganglion
Dorsal root ganglion
Spinal cord
Heart attack
Sensory nerve fibers
Area of pain
Skin
Pain receptor


Skin
Intestine
Anterolateral
tract axon

Types of the pain III.

Radicular pain rises after irritation of dorsal spinal roots (after eg. spinal injury, spine disturbances)

Pain enlarges into zones of innervation

Pain is sharp, intermittent in character, among attacks of sharp pain rises deep pain owing to muscle contraction

Types of pain IV.

Neuralgias result from damage of the nerve resulting in ephatic conduction among nerve fibers.

The most common types are trigeminal and glossopharyngeal neuralgias. They are characterized by extremely intense lancinating pain

Pain is usually evoked from trigger zones localized around the mouth and inside the mouth, from this reason the patients are reluctant to eat – signs of malnutrition are often evident

Patients have usually normal neurologic examination

Headache I. – extracranial, intracranial sources of pain

In extracranial space all structures are innervated by afferent nerves, including nociceptive fibres. Afferent nerves are convected from the skin, ligamenta, mucose membranes, teeth, orbita, globe, periosteum, middle-ear cavity, lining of sinuses. Bone does not content nociceptive fibres.

Intracranial sources of pain – meninges, vessels in subdural and subarachnoidal space

The parenchyma of the brain and intraparenchymal vessels are not pain sensitive

Headache II.

Headaches – division:

a) primary (functional) headaches
- migraine
- cluster headache
- tension headache

b) secondary (organic) headaches

Migraine haedache I.

Migraine occurs in 15-30% of women, in 3-13% of men.
It occurs usually in younger age also in 5% of prepubertal children

Clinical features:

1. pain
2. general symptoms – photophobia, phonophobia
3. nausea, vomiting
4. neurologic symptoms
5. mood changes

Migraine headache II.

Migraine pain – throbbing, pounding type, in 48% unilateral

Pathogenesis of the pain

Pain is related to the trigeminal innervation of the vessels in subarachnoidal space.Trigeminal afferents release to vessel wall mediators: P-substance, neurokinin,bradykinin, serotonin and CgRp (calcitonin-gen-related-peptide). Theese mediators produce sterile inflammation and consequently painfull vasodilation.

The triggering of released mediators is unknown.

Migrain headache III.

Photophobia, phonophobia – pathogenesis is unknown

Nausea, vomiting – as sequelae of parasympathetic stimulation

Neurologic symptoms – are thought to be related to the neurophysiologic phenomenon of **spreading cortex depression**

positive and negative visual symptoms

transient hemiparesis

transient quadruparesis

hemisensory loss

Mood changes – usually depression – pathogenesis is unknown

Cluster headache

Prevalently in younger men – frequency 4,5-5:1 over women

Clinical features

Cluster headache has **highly stereotyped pattern.** Patients have the **cycles (clusters) of pain attacks** at the same time every year. The cycles can vary in their frequency from twice/year to 8-10/year.

Headache is always **unilateral** with projection to orbita.

Attack of pain is rapid, it can last for **10-15 minutes**, after this period the pain can remit very rapidly.

Etiology is entirely unknown. Syndrom may be related to the petrosal ganglion, it is located close to the mucosa of the nose at lateral recess

Tension headache

It is **most common type** of headache. It occurs equally in women and men and may occur essentially any time throughout life.

Clinical features

Tension headache is described as steady aching pain (patients feel like a skullcap that is too tigh). The headache is **bilateral** and last for variable time periods ranging from minutes to hours, to days, weeks to years. Tension headache can respond to simple analgesics.

Etiology and pathogenesis. Headache is evoked by **muscle contraction** on the head owing to **psychological stress**. Musles are during contraction hypoxic. Due to, **potassium is shifted** from the cells into ECV and directly stimulates free-nerve-endings, also lactate is produced and **pH** in surroundings of nociceptors is **lowered.**

Secondary (organic) headache

- **Toxic headache –** usually results when **low level chronic or acute toxicity** is applied. In acute overwhelming intoxication, patients usually develop encephalopathy rapidly, they do not complain of headache.
- **Metabolic headache –** hepatic, renal diseases; hypoglycaemia; hyponatremia; insuff. of adrenal cortex; hypothyroidism
- **Vascular headache –** subdural, subarachnoidal hemorrhage; ruptured intracranial aneurysm; intracranial arteriovenous aneurysm, vasculitis
- **Headaches evoked by tumour** due to increasing of intracranial pressure similarly as in brain **oedema**