PATHOPHYSIOLOGY OF THE NERVOUS SYSTEM 3

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Pathophysiology of peripheral nerves

Peripheral nerve fibers:

- motor
- sensory, sensitive (various modalities)
- vegetative

→ Functional disorders due to extinction lesion:

- peripheral (flaccid) palsy
- perception disorders
- vegetative disorders

→ Functional disorders due to irritation lesion :

- fasciculation, convulsions...
- abnormal perceptions (paresthesia, neuropathic pain...)
- vegetative disorders

Pathophysiology of peripheral nerves

Injury of peripheral nerves

Axon break

→ Waller degeneration of the peripheral stump of the axon:

- axon swelling, strangulation and segmentation of the axon
- Schwann cells proliferate and phagocyte residua of the axon, fill empty endoneural tube.

→ Centripetal degeneration of the axon or extinction of the neuron

Regeneration of the axon from the proximal stump - necessary for guidance toward the target by the column of the Schwann cells (nerve suture is crucial), otherwise **terminal neuroma** develops.

Growth of the regenerating axon: in average 1 mm/day (max. 9 mm/day)

Regenerating axons do not always achieve their original targets.

→ incorrect localization, incorrect type of receptor → functional recovery is not complete

Pathophysiology of peripheral nerves

Injury of peripheral nerves

Nerve compression - interruption of axonal transport, compression of vasa nervorum

- short-term → transient functional disorder of the nerve
- long-term or very strong → axon degeneration

  If the integrity of the endoneural tubes is maintained, good regeneration is possible.

- Compression by pressure from the outside - especially in superficially localized nerves
- Inner compression - in anatomical spaces narrowed by the pathological process

Spontaneous action potentials generated by degenerating or regenerating fiber → **muscle fasciculation** = contraction of fibers of the motor unit

Fibrillation = spontaneous contractions of individual muscle fibers triggered by small amount of acetylcholine after hypersensitivity develops due to insufficient receptor stimulation.

Pathophysiology of peripheral nerves

Degrees of peripheral nerve damage:

1) Neurapraxia
   - a transient disorder, fiber continuity is not affected
   - disturbance of conductivity in the place of axon injury dealing, among others, with damage of the myelin sheet
2) Axonotmesis
   - break of the axon, but continuity of the endoneurium and epineurium is preserved
   - Waller degeneration, but reinnervation from the central stump of the axon is possible
3) Neurotmesis
   - breaking the axon as well as the sheets
   - Waller degeneration
   - problematic reinnervation

Neuropathies

- Mononeuropathy
- Polyneuropathy

Mononeuropathies

- Affection of one nerve only

Causes:

- Nerve injury
  - Open wounds
  - Closed wounds - traction
    - compression

Neuropathies

Polyneuropathies

- systemic affection of several or all nerves
- many diseases with different etiology and pathogenesis
- predominance of involvement of different types of fibers → distribution on the body (symmetrical, asymmetric, multifocal), the nature of the functional deficit (motor, sensitive - various modalities, vegetative)

Causes:

- Hereditary polyneuropathies
- Metabolic and endocrine disorders: DM, hepatic insufficiency, uremia, hypothyroidism
- Disorders of nutrition: vit. B1, B12 deficiency, alcoholism, malnutrition
- Inflammations (autoimmune, infection): systemic autoimmune diseases (SLE...), Guillain-Barré syndrome, Lyme disease (Borrelia), HIV...
- Affection of vasa nervorum: vasculitis, contribution to diabetic neuropathy
- Toxins: alcohol, heavy metals, medicaments, organophosphates...
- Paraneoplastic syndromes
- Idiopathic polyneuropathies

Pathophysiology of peripheral nerves

Tumors of peripheral nerves

- tumors
- Tumor-like structures

Affection of nerve function

- sensitive extinction manifestations - sensitivity reduction
- sensitive irritation manifestations - pain, paresthesia...

Extrapyramidal disorders

- Muscle tone, posture, background for voluntary movements, automatic motor programs

Extrapyramidal system

- Basal ganglia
- Motor brainstem nuclei
- Motor thalamic nuclei
- Cerebellum

Hypokinetic symptoms

- **Rigidity** = long-term increase in basic muscle tone

- plastic character of hypertonus, the muscle resists to both active and passive movement through whole its range („lead pipe“ phenomenon)
- with passive limb extension, the „cogwheel phenomenon - reflexive contractions of stretched flexors

  X the „folding knife“ phenomenon in spasticity
- can cause muscle pain

- **Bradykinesia** = slow movements
- **Hypokinesia** = reduced amplitude of voluntary movements
- **Akinesia** = voluntary movement initiation disorder
- **Freezing** = sudden stop in movements, a form of akinesia

Hyperkinetic symptoms

- they intensify in emotions and during voluntary movements that are disrupted by them
- **Chorea** = fast non-stereotyped twisting movements, namely putamen damages
- **Athetosis** = slow twisting movements
- **Torticollis** = slow twisting movements of the neck
- **Ballisms** = rapid movements of the limb arising from the proximal segments of the limbs, large amplitude - in case of damage nc. subthalamicus (unilateral lesion → hemiballism), a variant of chorea
- **Myoclonus** = short muscle twitches, usually irregular, affect antagonistic muscles simultaneously
  - focal, multifocal, segmental, generalized
  - increased irritability and synchronization of stimuli at the level of the cerebral cortex, reticular formation, brainstem nuclei or spinal cord
  - etiology: idiopathic myoclonus, secondary myoclonic syndromes
- **Tics** = rapid non-rhythmic but stereotypical twitches or sound manifestations (twitches in the face, coughing, nail biting), even in sleep
  - compulsive character, suppressible by will

Hyperkinetic symptoms

- **Dystonia** = persisting muscle contractions → twisting or repeated movements, abnormal position of body parts
  - often triggered or amplified by voluntary movements → disrupts voluntary movements by increasing the force of contraction or activating other muscles
  - focal, multifocal, segmental, generalized
  - Examples of focal dystonias: blepharospasm, graphospasm, laryngeal dystonia, oromandibular dystonia, torticollis spastica
  - Examples segmental dystonias: torsion dystonia - neck and trunk (dystonia musculorum progressiva)
  - etiology: idiopathic dystonia, secondary dystonic syndromes (storage diseases, Wilson‘s disease, cerebrovascular disorders, inflammations, brain trauma...)
- **Stereotypies** = complex structured movements of longer duration, similar to purposeful activity, often in mental illness
- **Akathisia** = restlessness, compulsive movements, sometimes accompanies mental disorders

Hyperkinetic symptoms

Tremor

= rhythmic oscillating movement of a part of the body caused by alternating contractions of agonistic and antagonistic muscles

- the most common extrapyramidal symptom

Classification of tremor

Resting tremor - at rest (parkinsonian sy)

Static (postural) tremor - in a static position (physiological tremor)

Kinetic - during each movement

- during goal-directed movements = intention tremor (cerebellar sy)
- during a specific movement (e.g. psychogenic)

Essential tremor

- postural, but also kinetic or resting
- AD heredity
- does not shorten life

Pathophysiology of the basal ganglia

Nuclei functionally belonging to the basal ganglia:

striatum (nc. caudatus + putamen), globus pallidus (internum et externum), nc. subthalamicus Luysi, substantia nigra

Functions of the basal ganglia:

- modulation of movements and muscle tone
- modulation of oculomotor functions
- system of reward and punishment (connections with the limbic system)
- cognitive functions

→ manifestations of basal ganglia disorders

Pathophysiology of the basal ganglia

Mediators in the basal ganglia:

- glutamate (+) - inputs to the basal ggl., nc. subthalamicus
- dopamine (+ via D1, - via D2) - substantia nigra pars compacta, inputs from the ventral tegmental area
- acetylcholine (+) - nc. subthalamicus, interneurons in the striatum
- GABA (-) - striatum, substantia nigra pars reticulata
- other mediators

Functional circuits

brain cortex → basal ganglia → thalamus → brain cortex

Inner circuitries:

- Direct pathway

  brain cortex → striatum → thalamus → brain cortex

- Indirect pathway

  brain cortex → striatum → globus pallidus externus → nc. subthalamicus → globus pallidus internum → thalamus → brain cortex

Pathophysiology of the basal ganglia

Extrapyramidal syndromes due to basal ganglia disorders:

- hypertonic-hypokinetic (parkinsonian)
- hypotonic-hyperkinetic

= various combinations of these symptoms:

- muscle tone disorders
- reduced motor activity x involuntary movements

Hypertonic-hypokinetic syndrome = parkinsonian

- Low activity of the nigrostriatal dopaminergic system

Causes:

- Parkinson‘s disease
- Other neurodegenerative diseases - corticobasal degeneration, progressive supranuclear palsy, dementia with Lewy bodies, multiple system atrophy
- Ischemia, hypoxia
- Trauma
- Toxins
- Infections - encephalitis lethargica
- Dopamine receptor blockade

Hypertonic-hypokinetic syndrome = parkinsonian

Manifestations:

- Tremor - resting, „money counting“, intensifies with emotions, disappears in sleep
- Rigidity, predominance of the tone of flexors → flection position of the body and limbs
- Bradykinesia, hypokinesia, akinesia, freezing

Quiet, slow speech, hypomimia, decreased blinking frequency, slow walking, short steps, standing instability, difficulty changing movement already started (inability to stop or change walking direction)

Hypotonic-hyperkinetic syndrome

- reduced muscle tone + some of the forms of involuntary movements

Huntington's disease

- AD heredity - mutation (CAG repeat) in the huntingtin encoding gene→ polyglutamine tract
- degeneration of neurons in the striatum and brain cortex → chorea, hypotonia, behavioral disorders, dementia

Sydenham chorea (chorea minor)

- children, adolescents
- after streptococcal infection in relation to the rheumatic fever (not always all its manifestations)
- autoimmune process based on cross-reactivity
- affection of the nc. caudatus and nc. subthalamicus
- chorea, tics or dystonia
- emotional lability, behavioral changes

Hypotonic-hyperkinetic syndrome

Vascular chorea

- affection of the putamen or nc. subthalamicus with ischemia or hemorrhage

Chorea gravidarum

- sensitization of dopaminergic receptors during gravidity
- rather in women having already previous experience with chorea

Drug-induced chorea

- e.g. side effect of Parkinson's disease treatment

Metabolic causes of chorea

- hyper- or hypoglycemia, hyperthyroidism, ion disbalances

Basal ganglia lesions

- ischemia, inflammation, injuries, tumors, demyelinating processes...

Pathophysiology of the thalamus

- a group of sensory (specific), associative and unspecific nuclei
- reconnection of sensory tracts (with the exception of olfaction)

The basic causes of thalamic damage are similar to those in other areas of the CNS.

Disorders of the thalamus:

- Thalamic pain - irritation lesion
- Permanent coma (thalamocortical connections are involved in maintenance of vigilance and attention)
- Thalamic ataxia - mild (clumsiness), due to damage of connections between the cerebellum and brain cortex reconnected in the thalamus
- Extrapyramidal manifestations - due to damage of connections with the basal ganglia
- Thalamic hand - anteflexion of the wrist and finger extension
- Disorders of episodic memory - connections with the hippocampus
- **Thalamic syndrome** = contralateral hemiparesis, hemihypesthesia, hemialgia, hemiataxia, hemichorea, contralateral homonymous hemianopia

Pathophysiology of the subthalamus

Nc. subthalamicus Luysii belongs to the basal ganglia

Damage → ballism (unilateral damage → hemiballism)

Pathophysiology of the hypothalamus

- connections with many brain areas, information from receptors, hypothalamus itself contains many receptors, encoded optimum levels of homeostatic parameters
- center of vegetative function control
- influence on behavior
- endocrine function

Basic causes of hypothalamic damage are similar to other areas of the CNS, incl. idiopathic and neurodegenerative diseases.

Functional disorders according to the localization of the damage.

Pathophysiology of the hypothalamus

Global hypothalamic syndrome

- damage to the entire hypothalamus
- combination of manifestations of damage of individual parts

Partial hypothalamic syndromes

- disfunction of the autonomic nervous system
- circadian rhythm disorders
- food intake disorders
- thermoregulation disorders
- adiposogenital dystrophia (e.g. Fröhlich syndrome)
- central diabetes insipidus
- syndrome of inappropriate secretion of ADH
- Disorders of statin, liberin secretion = tertiary disorders in the hypothalamus-adenohypophysis-peripheral gland (pubertas praecox, growth disorders...)

Pathophysiology of the limbic system

- Disorders of the limbic system are determined by damage of its various components - complex and variable issue with overlap to other areas
- lesions in experimental animals, historical case reports (H.M.)

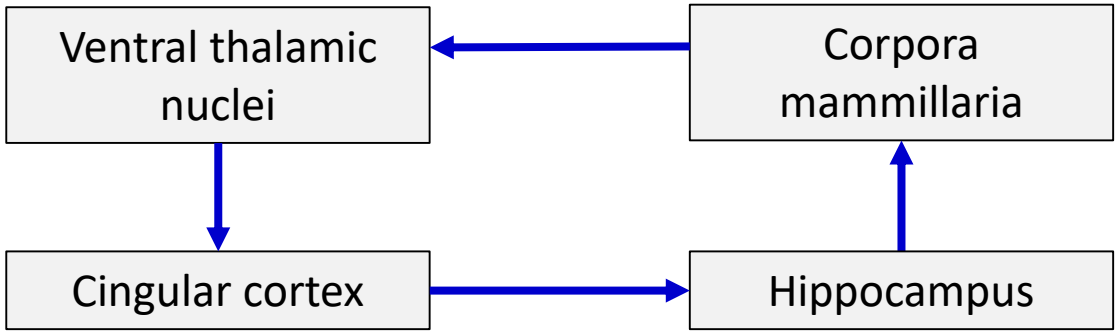
Klüver-Bucy syndrome

- bilateral destruction of ventral parts of temporal lobes, dominant affection of the amygdala

→ loss of fear, visual agnosia, compulsive exploration of all objects, hyperphagia, hypersexuality

Lesion of the cingular gyrus - agitation, insomnia

Papez circuit



Pathophysiology of the vegetative system

Vegetative (autonomic) nervous system - control of organ functions - smooth muscles including vasomotor activity, activity of glands and parenchymatous organs

- hypothalamus
- cardiovascular and respiratory center in the brainstem
- + effect of other parts of the CNS
- sympathetic system - thoracolumbar
- parasympathetic system - craniosacral

Sympathetic system activation (+ activation of the adrenal cortex = sympathoadrenal system) is a part of the stress response.

- stressors including pain and physical activity, hypoglycemia, hypotension

Excessive and long-lasting activation contributes to development of psychosomatic diseases.

Pathophysiology of the vegetative system

Causes of vegetative system disorders:

- neuropathies
- damage of central components - brain diseases, spinal cord lesions
- neurodegenerative diseases - a severe disorder of vegetative functions in the multiple system atrophy and pure autonomic failure, milder in the Parkinson‘s disease.

Common manifestations of vegetative system disorders

- local or general

- Blood pressure control (orthostatic hypotension)
- Heart rate changes
- Disorders of thermoregulation and perspiration
- Disorders of GIT functions
- Disorders of urination and defecation, sphincter disorders
- Sexual dysfunction
- Vasomotor disorders
- Mydriasis, miosis
- Role of the sympathetic system in neuropathic pain

Pathophysiology of the vegetative system

Disorders of the peripheral vegetative system

- Disorders of vasomotor activity - e.g.:
  - Raynaud disease
  - local hyperemia after sympathectomy (usually transient)
  - mucosal erosions in the GIT due to local ischemia
- Dyspeptic problems

Disorders of vegetative system on the CNS level

- see pathophysiology of the hypothalamus, brainstem and spinal cord

Pharmacologically induced changes of vegetative system functions

- medicaments, poisons
- parasympatholytics, parasympathomimetics, sympatholytics, sympathomimetics

Organophosphate intoxication - acetylcholinesterase blockade → activation of both the parasympathetic and sympathetic systems, muscle contraction

THE END