Physiology 2nd year - Semester 1 Curricula

- Nervous system physiology
- Cardiovascular physiology

Recommended bibliography:
- Boron & Boulpaep – Medical Physiology, 3rd edition

Neuroscience Optional Lecture
- October - November, 2016

Info at www.fiziologie.ro
NERVOUS SYSTEM PHYSIOLOGY

LECTURE 1

Organization of the Nervous System.
Physiology of neurons and glial cells.

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Physiology pathway...

- dynamic study of *life*, describing the “vital” functions of living organisms and their organs, cells, molecules...

- integrative discipline, from *general physiology* (cellular & molecular physiology) to *medical physiology* (integrated understanding of events at the level of molecules, cells, organs and whole body – all in an *interdependent action*)

- *genome* with its *epigenetic modifications*: *Physiological genomics* - new branch of physiology devoted to the understanding of the genes’ function
Nervous system (NS)

- How NS is organized, how it develops and functions to generate behaviour... these questions can be explored using the tools of genetics and genomics, molecular & cellular biology, anatomy and systems physiology, behavioural observations and psychology.
Nervous system

• At **cellular level** – *neurons & glia → neural circuits*

• **Neural circuits** – primary components of *neural systems* that process specific types of information

• **Neural systems** serve one of three general functions:
  1. **sensory systems** (inform about the state of the organism and its environment)
  2. **motor systems** (organize and generate actions)
  3. **associational systems** link sensory & motor components → provide the basis for *higher order* brain functions: *perception, attention, cognition, emotion, language, rational thinking, creativity* → *understanding human beings*, their behaviour, their history, and perhaps... their future...
Challenge: to understand the physiological role of the neural circuits and systems in behaviorally meaningful contexts.
We need a leap in our understanding: from the *organism* to the *human being*.

How much we would struggle to look inside... there is still a veil that let us imagine, sense, feel, create... the thinking inside the thinking....
To the unaided eye, the most striking feature of the human brain is its curvy pattern of bumps and grooves. But within those curves is a latticework of nerve fibers that cross each other at roughly right angles (method used here is called diffusion spectrum imaging that infer the position of nerve fibers in the living human brain from the way water flows through and around them). These scans revealed an orderly texture of fibers — a much simpler organization than many scientists would have suspected (http://www.sciencemag.org/content/335/6076/1628).
White Matter Connections Obtained with MRI Tractography


Connectomics - Human Connectome Project
Genetics and the Brain

• Genomics has brought insight into how nuclear DNA provides instructions for the assembly and operation of the brain

Human genome:

  about 20,000 genes (coding & regulatory DNA)
  14,000 genes expressed in the developing/mature brain
  about 8,000 genes are expressed in all cells and tissues

→ a great deal of “brain specific” genetic information resides in the regulatory DNA sequences that control timing, quantity, variability, and cellular specificity of gene expression

→ individual genes vary in the level of expression in specific brain regions and cells (i.e. the amount of mRNA expressed)

→ foundation of the diversity & complexity of brain functions

! Gene mutations associated with brain pathology (Huntington D, Alzheimer D, Parkinson D...)
Genetics and the Brain

• Genetics & Genomics ➔ understand physiopathology ➔ develop new therapies

• But... relationship between genotype and phenotype is not just the result of following genetic instructions, and *genetic information alone cannot explain how the brain operates in normal individuals, or how disease processes disrupt normal brain functions.*

➔ the need to understand the cell biology, anatomy and physiology of the nervous system constituent cells and the circuits they form.
The Nervous System components:

- brain, spinal cord, nerves, sensory receptors

Responsible for

- sensory perceptions, mental activities, stimulating muscle movements, secretions of many glands

Subdivisions

- Central nervous system (CNS)
- Peripheral nervous system (PNS)
  - Somatic & Autonomic Nervous Systems, including Enteric NS
All elements of the nervous system work closely together in a way that has no clear boundaries.
Organization of the Nervous System
CNS, PNS & ANS

• Central nervous system (CNS):
  - brain (including cranial nerve II and retina) and spinal cord;
  - covered by the meninges (3 layers: pia mater, arachnoid, and dura mater);
  - special features: oligodendrocytes provide myelin; axons cannot regenerate

• Peripheral nervous system (PNS):
  - parts of the nervous system that lie outside the dura mater;
  - consists of peripheral ganglia (including cell bodies); sensory receptors;
    afferent & efferent peripheral portions of spinal nerves, cranial nerves
    (except CN II that is included in the CNS) and all peripheral portions of ANS.
  - special features: Schwann cells provide myelin; axons can regenerate

• Autonomic nervous system (ANS):
  - anatomically includes parts of CNS & PNS;
  - regulates & controls visceral functions through reflex arcs (visceral
    afferent/sensory neurons, control centers in the CNS that receive input, and
    visceral motor output).
  - special feature: functionally distinct system
<table>
<thead>
<tr>
<th>SUBDIVISION</th>
<th>COMPONENTS</th>
<th>SPECIAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>Brain (including CN II and retina) and spinal cord</td>
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<td>Axons cannot regenerate</td>
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<td>Autonomic</td>
<td>Selected portions of the CNS and PNS</td>
<td>Functionally distinct system</td>
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</table>

CN, cranial nerve.
Central nervous system (CNS) interfaces

Extracellular brain environment is maintained by a regulated molecular exchange between blood and the CNS, through several restricted borders/barriers:

1. blood - brain barrier (BBB) – Brain endothelial capillaries
2. blood - choroids plexus epithelium - cerebral spinal fluid (CSF)
3. blood - nerves
CNS – blood flow connections

Arterial blood

Cerebral capillary: BBB

Choroid plexus capillary: blood-CSF barrier

CSF → ependim

Brain ECF

Blood capillary in circumventricular organs (no BBB, important for neuropeptide transport, enables brain to sense and regulate blood composition)

Brain intracellular compartment

neurons ↔ neuroglia
Cerebral circulation

- Cerebral blood supply by two pairs of arteries:
  - the right and left **internal carotid arteries** → anterior 2/3 of the corresponding cerebral hemispheres,
  - the right and left **vertebral arteries**, which join to form the **basilar artery** → brain stem and posterior portion of the hemispheres

- Internal carotid arteries and the basilar artery join via **anastomotic** channels to outline the **arterial circle of Willis** around the optic chiasma, at the base of the brain

- Circle of Willis → **anterior, middle, and posterior cerebral arteries** → **pial arteries** that expand over the surface of the hemispheres, form anastomoses, and branch into penetrating **arterioles**, which further divide to continue with the **capillaries**
Neurovascular coupling

• The human brain contains on the order of 100 million capillaries containing a surface area of 12 m².
• Nearly every neuron in the brain has its own capillary, with an average distance from capillary to neuron of 8–20 μm.
Physiological changes linking neural and vascular responses

The CBF response to a brief period of neural activation is typically delayed by 1-2 sec. and peaks 4-6 sec. after the neural response.

http://www.scholarpedia.org/article/Neurovascular_coupling
Cerebrospinal fluid (CSF)

- Volume = 150 ml, daily production = 500 ml
- Formation of CSF: 2/3 as secretion from the choroid plexuses in the 4 ventricles, but mainly in the 2 lateral ventricles; 1/3 as secretion by the ependymal surfaces of the ventricles and by the arachnoid membranes
- Function:
  - mechanical protection; 1400 g → 50 g...
  - distribution of neuroendocrine factors
  - „volume buffer“: regulate ICP when tissue/ intracranial blood volume rises

Monroe-Kelly doctrine: V-CSF+V-blood+V-brain tissue = const.
Lumbar Puncture

CSF Pressure Reading
- Abnormal pressure (>15)
- Normal pressure (<15)

Puncture

- Positions
  - Lateral decubitus (L4-5)
  - Sitting
- CSF samples
  - Cell count
  - Protein
  - Glucose
  - Microbiology
- CSF pressure
- CSF removal
- Drug introduction

Diagram showing the process of lumbar puncture, including the injection site at L2 and the measurement of CSF pressure.
In the PNS, nerves have their blood vessel supply.
Nervous System: structure

1) CENTRAL NERVOUS SYSTEM (CNS):
   - brain
   - spinal cord

2) PERIPHERAL NERVOUS SYSTEM (PNS):
   - cranial nerves
   - spinal nerves

2 types of nervous tissue cells:
- neurons:
  - sensory, motor, interneurones/association neurons
- non-neuronal/neuroglial cells:
  - astrocytes, microglia, oligodendocytes / Schwann cells, ependymal cells

Spinal cord
Covered by meninges
Cells of the nervous tissue: Cellular diversity of the brain

Nerve cells: neurons and neuroglial cells.
- \( \sim 10^{11} \) neurons in the human brain
- and 10 x more neuroglia

Neurons have special shapes, physiological properties, and connections (\( \sim 1000 \) synapses/each neuron & other connecting mechanisms !)
- information transmission throughout the nervous system
- unique patterns of connectivity & regional specialization → tremendous complexity of NS

Neuroglial cells
- variable structures that are suited for their diverse functions
- provide a physiological environment for neurons
- can function as signaling cells!
Characteristics of Neurons

1) excitile
   - respond to stimuli
   - produce & conduct electrical impulses
   - release chemical regulators

2) long-lived

3) high metabolic rate

4) amitotic - cannot divide by mitosis

Most human neurons arise in about the first 4 months of intrauterine life. After birth, neurons do not divide, and if a neuron is lost for any reason, it is generally not replaced, which is the main reason for the relatively limited recovery from serious brain and spinal cord injuries (possible preserving learned behavior and memories in stable populations of neurons throughout life).

Exception: olfactory bulb neurons, which are continually renewed throughout adult life by a population of stem cells or neuronal progenitor cells.
Typical neuron has 4 regions:
- cell body, dendrites, axon, presynaptic terminals
- each region is specialized for its particular function
- information flows in a single direction…

Neuron Cell Body Location

In the central nervous system
- **Gray matter** – cell bodies and unmyelinated fibers
- **Nuclei** – clusters of cell bodies within the white matter of the central nervous system

In the peripheral nervous system:
- **Ganglia** – collections of cell bodies
The structure of a typical neuron

(1) **cell body/soma/perikaryon**
-cytoskeleton: neurofilaments, *microtubules*, *thin filaments*
→ *dynamic feature* → *plasticity*
-nucleus, ER, Golgi complex, mitochondria...

(2) **dendrites** of various complexity: tapered, limited length, contain microtubules and ER; membrane receptors for neurotransmitters; **dendritic spines** = small projections to amplify the *receiving/postsynaptic* area

The dendrites & cell body are the main areas for receiving information through the membrane receptors that bind and respond to neurotransmitters released by neighboring cells
The structure of a typical neuron

(3) the axon:
- axon hillock, a cone-shaped initial segment = the spike initiation zone (unmyelinated region where AP initiates)
- axon can extend >1 m, can be myelinated (electrical insulation, fast impulse spread – salutatory conduction), high density Na⁺ channels
- contain axoplasm (more than does the cell body - up to 1000x), microtubules and microfilaments that confer structural stability and axonal transport.
- are self-reliant in energy metabolism, taking up glucose and oxygen from their immediate environment to produce ATP

(4) the presynaptic terminals: rapid conversion of the neuron's electrical signal into a chemical signal or another kind of signal.
Neuronal compartmentalization

Neurons are **polarized cells** and have **distinct membrane protein** at each of the distinct domains of the plasma membrane.

**Protein synthesis**: occurs mainly in the cell body, less in dendrites, not in the axon (smooth & rough ER and Golgi system absent in the axon)

**Mitochondria**: present in the cell soma and presynaptic terminal, also trafficking in the axon.

**Anterograde and retrograde axoplasmic transport** of molecules in **vesicles** along **microtubules** is mediated by **microtubule-associated proteins** (**MAPs**):

1. **kinesin for anterograde transport**: always move toward the (+) end of microtubules, away from the cell body
2. **dynein for retrograde transport**: provides a mechanism for target-derived growth factors, as NGF, to reach the nucleus of a neuron where it can influence survival!
MAPs in the brain associate with microtubules and help link them to other cell components:

- high-molecular-weight proteins:
  MAP-1
  MAP-2 (only in cell bodies and dendrites)

- lower molecular weight *tau proteins.*
  Dephosphorylated tau proteins are confined entirely to axons. In cultured neurons, suppressing the expression of tau protein prevents formation of the axon without altering formation of the dendrites.
**A  ANTEROGRADE MOVEMENT**
Proteins synthesized in the "secretory pathway" are packaged by budding off in membrane-enclosed vesicles from the Golgi.

The vesicles and mitochondria are carried down the axon on microtubule "tracks" by kinesin motors that are energized by ATP.

**B  RETROGRADE MOVEMENT**
Vesicles now move in reverse, carried by motors, called MAP-1C (related to dynein), which also split ATP and move along microtubule "tracks." In axons, the microtubules have a polarity with the "+" side pointing away from the soma. In dendrites, the polarity is more random.

**C  MICROTUBULE**

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Figure 10-2  Fast axoplasmic transport. ER, endoplasmic reticulum.
<table>
<thead>
<tr>
<th>Transport Type</th>
<th>Speed (mm/day)</th>
<th>Mechanism</th>
<th>Material Transported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast anterograde</td>
<td>~ 400</td>
<td>Saltatory movement along microtubules by the motor molecule kinesin (ATP dependent)</td>
<td>Mitochondria, Vesicles containing peptide and other neurotransmitters, some degradative enzymes</td>
</tr>
<tr>
<td>Fast retrograde</td>
<td>~200-300</td>
<td>Saltatory movement along microtubules by the motor molecule dynein (ATP dependent)</td>
<td>Degraded vesicular membrane, Absorbed exogenous material (toxins, viruses, growth factors)</td>
</tr>
<tr>
<td>Slow anterograde</td>
<td>~0.2-8</td>
<td>Not clear; possibly by molecular motors</td>
<td>Cytoskeletal elements (e.g., neurofilament and microtubule subunits), Soluble proteins of intermediary metabolism, Actin</td>
</tr>
</tbody>
</table>
Neurons classified on the basis of their axonal projection, dendritic geometry, and the number of processes emanating from the cell body

**CNS nerve cells - great structural diversity, correlated with their functions.**

- **Axonal projection**
  - **Long axons**: Axonal Projection Neurons = principal neurons or Golgi type I cells
  - **Short axons** restricted to one region of the brain = interneurons/intrinsic neurons or Golgi type II cells
  - Absence of a conventional axon – **anaxonal neurons** (e.g. amacrine cell in the retina - from the Greek for “no large/long fiber”).

- **Dendrites’ geometry**
  - Pyramid-shaped dendritic branches characterizes **pyramidal cells**
  - Radial pattern of dendritic branches defines **stellate cells**
  - Presence of dendritic spines: **spiny cells** (pyramidal and stellate cells)
    - **Aspiny cells** (some stellate cells)

- **Number of processes** originating from the cell body:
  - **Unipolar neuron**: dorsal root ganglion (DRG) cell - primary sensory neuron
  - **Bipolar neurons**: retinal bipolar cell (2 processes extending from opposite sides of the cell body).
  - **Multipolar neurons** (most neurons); neurons with many dendritic processes receive large numbers of synaptic inputs.

**Examples:**
Large motor neurons in the motor cortex are multipolar, pyramidal, projection neurons. Retinal bipolar cell is both an interneuron and a bipolar cell.
DRG neurons:

- the process that extends into the CNS from this unipolar neuron is easily recognized as an axon because it carries information away from the cell body.
- the process that extends to sensory receptors in the skin and elsewhere is less easily defined. It is a typical axon in the sense that it can conduct an action potential, has myelin, and is characterized by an axonal cytoskeleton. However, it conveys information toward the cell body, which is usually the function of a dendrite.
Classification of Neurons based on their function

- **Sensory (afferent) neurons**
  - Carry impulses from the sensory receptors
  - Cutaneous sense organs
  - Proprioceptors – detect stretch or tension

- **Motor (efferent) neurons**
  - Carry impulses from the central nervous system

- **Interneurons (association neurons)**
  - Found in neural pathways only in the CNS
  - Connect sensory and motor neurons
Classification of neurons based on their function

Sensory/afferent nerves: messages from periphery to CNS
Motor/efferent nerves: messages from CNS to peripheral tissues.
<table>
<thead>
<tr>
<th>Basis for classification</th>
<th>Example</th>
<th>Functional implication</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Axonal projection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goes to a distant brain area</td>
<td>Projection neuron or Principal neuron or Golgi type I cell (cortical motor neuron)</td>
<td>Affects different brain areas</td>
<td>Dorsal root ganglion cell</td>
</tr>
<tr>
<td>Stays in a local brain area</td>
<td>Intrinsic neuron or Interneuron or Golgi type II cell (cortical inhibitory neuron)</td>
<td>Affects only nearby neurons</td>
<td>Retinal bipolar cell</td>
</tr>
<tr>
<td>2. Dendritic pattern</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyramid-shaped spread of dendrites</td>
<td>Pyramidal cell (hippocampal pyramidal neuron)</td>
<td>Large area for receiving synaptic input; determines the pattern of incoming axons that can interact with the cell (i.e., pyramid-shaped)</td>
<td>Pyramidal cell</td>
</tr>
<tr>
<td>Radial-shaped spread of dendrites</td>
<td>Stellate cell (cortical stellate cell)</td>
<td>Large area for receiving synaptic input; determines pattern of incoming axons that can interact with the cell (i.e., star-shaped)</td>
<td>Stellate cell</td>
</tr>
<tr>
<td>3. Number of processes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One process exits the cell body</td>
<td>Unipolar neuron (dorsal root ganglion cell)</td>
<td>Small area for receiving synaptic input; highly specialized function</td>
<td>Unipolar</td>
</tr>
<tr>
<td>Two processes exit the cell body</td>
<td>Bipolar neuron (retinal bipolar cell)</td>
<td>Small area for receiving synaptic input; highly specialized function</td>
<td>Bipolar</td>
</tr>
<tr>
<td>Many processes exit the cell body</td>
<td>Multipolar neuron (spinal motor neuron)</td>
<td>Large area for receiving synaptic input; determines the pattern of incoming axons that can interact with the cell</td>
<td>Multipolar</td>
</tr>
</tbody>
</table>
Non-neuronal cells: neuroglia

- smaller & more numerous than the neurons
- *they lack:* axons, action potentials, and synaptic potentials

Main types of CNS glial cells are oligodendrocytes, astrocytes, and microglial cells.

In the PNS, the main types of glial cells are satellite cells in autonomic and sensory ganglia, Schwann cells, and enteric glial cells.
Glial Cell Functions:

- Structural support, “glue”
- Metabolic support (lactate shuttle)
- Insulation (oligodendrocytes)
- Destroy pathogens, remove debris (microcytes)
- In development, guide axons
- Induce and maintain BBB; role in cerebral vasomotricity
- Cannot generate or transmit nerve signals, but are involved in information processing.
- Release gliotransmitters (ex glutamate, ATP);
Glial Cell Functions:

Glial cells have a major impact on the composition of the extracellular fluid, which in turn has a major impact on brain function:

- Glia fills in almost all the space around neurons: extracellular space between neurons and glial cells ~0.02 μm
- Clear transmitters from synapse, ion homeostasis, role in cell volume control, volume transmission
- K+ and H+ uptake vs. spatial buffering; Ca waves…
Neurovascular unit – neurovascular coupling
Tripartite unit: neuron - glial cell – cerebral capillary
Astrocytes (red and green) influence nervous-system communication and plasticity

• Primarily responsible for homeostasis of the central nervous system.
• Ensheath synapses, regulate neuronal excitability and synaptic transmission.
• Respond to injury by secreting extracellular matrix proteins.
• Implicated in neurogenesis, cell migration, many neurological and psychiatric disorders.
– astrocytes do not fire action potentials, but are Ca2+-excitable!
– astrocytes ‘listen’ to neurons (all major receptors present)
– astrocytes release neurotransmitter (Glutamate, ATP, …)
– astrocytes modulate neuronal excitability and synaptic transmission
\( \Rightarrow \) Role in regulation of synaptic function
The no. of astrocytes increases with an increase in brain size:

- The glia/neurons ratio
  - in the rat cerebral cortex ~0.4,
  - in the human cerebelar cortex ~1.65.

Increased complexity of astroglia in humans – throught size & complex process arborization

→ one human protoplasmic astrocyte contacts and integrates about 2 million synapses residing in its territorial domain, whereas rodent astrocytes cover up to 120,000 synaptic contacts.
Neuron-glia connections

Synchronous Firing Groups:
Astrocytic regulation of neural networks

Amzica, 2000
Astrocytes marked with calcein-AM (green) in a cerebellar granule cells culture, after oxygen-glucose deprivation. Dr. Ana-Maria Zagrean Neuronal Cell Culture Lab
Oligodendrocytes (green)

- Form myelin electrical insulation, increasing conduction velocity by at least 50 times.
- Provide vital metabolic support for axons (purple)
Non-neuronal cells:  
Schwann cells and oligodendrocytes  
(PNS)                      (CNS)  

Myelin Sheath Formation around a Peripheral Axon  

- Schwann cell  
- Axon  
- Nucleus  
- Sheath of Schwann  
- Myelin sheath  

Myelin Sheath Formations in the CNS by an Oligodendrocyte  

- Oligodendrocyte  
- Node of Ranvier  
- Myelin sheath  
- Axon
Myelin

-Layers of lipid membrane of oligodendrocytes (CNS) or Schwann cells (PNS)

-The signal that causes these glial cells to myelinate the axons is an epidermal GF-like ligand (neuregulin), which derives from the axon and whose potency is dependent of axonal size (usually axons > 1 micrometer in diameter are myelinated)

- voltage-gated Na+ channels are highly concentrated in the nodes of Ranvier, and in low density beneath the sheath of myelin → AP jump from one Ranvier to the next one – saltatory conduction
→ increased conduction velocity: 3-120 m/sec in myelinated axons comparing to 0.5-2 m/sec in unmyelinated axons
Myelin, Oligodendrocyts and network of intercellular channels between astrocytes (A) and oligodendrocytes (O)

Level of organization in the NS: Neurons and synapses - from cells to networks

- Electrical signals flow in neurons in a uni-directional fashion: dendrites → soma → axon.
- Neural coding – at cellular and network level
- Specific circuits → systems
- Input → processing → output

From experience to educated output