The Cerebral Cortex
and
Higher Intellectual Functions
Lobes in a lateral view of left hemisphere
The Insula
The Hidden Lobe
Lobes in a lateral view of left hemisphere
Lobes in a anterior (ventral) view
The Insula
The Hidden Lobe
Primary, Secondary and Association

Central sulcus

PRIMARY SOMATOSENSORY AREA (postcentral gyrus)

SOMATOSENSORY ASSOCIATION AREA

Parietal lobe

COMMON INTEGRATIVE AREA

WERNICKE'S AREA

VISUAL ASSOCIATION AREA

PRIMARY VISUAL AREA

Occipital lobe

Temporal lobe

PRIMARY MOTOR AREA (precentral gyrus)

PREMOTOR AREA

PRIMARY GUSTATORY AREA

FRONTAL EYE FIELD AREA

Frontal lobe

BROCA'S SPEECH AREA

PREFRONTAL CORTEX

Lateral cerebral sulcus

PRIMARY AUDITORY AREA

AUDITORY ASSOCIATION AREA

POSTERIOR

 ANTERIOR

Lateral view of right cerebral hemisphere
Communication Between Neurons

- Synapse: A specialized site of contact, and transmission of information between a neuron and an effector cell

Anterior Motor Neuron

Figure 45-5
Communication Between Neurons

• Electrical synapse
Communication Between Neurons

- Electrical synapse
- Chemical synapse
Communication Between Neurons

- Chemical synapse

**Neurotransmitter:** is a messenger of neurologic information from one cell to another.
Action of Neurotransmitter on Postsynaptic Neuron

- postsynaptic membrane contains receptor proteins for the transmitter released from the presynaptic terminal.
- The effect of neurotransmitter on the postsynaptic neuron depend on the type of the receptor.
Action of Neurotransmitter on Postsynaptic Neuron

- Two types of receptors
  - Ion channels receptors
Action of Neurotransmitter on Postsynaptic Neuron

• Two types of receptors
  – Ion channels receptors **Ionotropic**
  – Second messenger receptors **Metatropic**
Ion Channels receptors

- transmitters that open sodium channels **excite** the postsynaptic neuron.
- transmitters that open chloride channels **inhibit** the postsynaptic neuron.
- transmitters that open potassium channels **inhibit** the postsynaptic neuron.
Seconded messenger receptors (as example G-protein)

1. *Opening specific ion channels*

2. *Activation of cAMP or cGMP*

3. *Activation of one or more intracellular enzymes*

4. *Activation of gene transcription.*
G-Protein-Coupled Receptors and Effectors

- GPCR Effector Systems (Cont’d)
  - Push-pull method (e.g., different G proteins for stimulating or inhibiting adenylyl cyclase)
G-Protein-Coupled Receptors and Effectors

- GPCR Effector Systems (Cont’d)
  - Some cascades split
    - G-protein activates PLC $\rightarrow$ generates DAG and IP$_3$ $\rightarrow$ activate different effectors
G-Protein-Coupled Receptors and Effectors

• GPCR Effector Systems (Cont’d)
  • Signal amplification
Drugs and the Synapse
1) at the receptor

- The study of the influence of various kinds of drugs has provided us with knowledge about many aspects of neural communication at the synaptic level.
- Drugs either facilitate or inhibit activity at the synapse.
  - **Antagonistic** drugs block the effects of neurotransmitters (e.g., novacaine, caffeine).
  - **Agonist** drugs mimic or increase the effects of neurotransmitters (e.g., receptors in the brain respond to heroin, LSD and cocaine)
  - **Allosteric modulation**
Drugs and the Synapse

- A drug has an **affinity** for a particular type of receptor if it binds to that receptor.
  - Can vary from strong to weak.
- The **efficacy** of the drug is its tendency to activate the receptor.
- Drugs can have a high affinity but low efficacy.
Agonists and Antagonists
Agonists and Antagonists

Agonists: Drugs that occupy receptors and activate them.

Agonist alone → Full activation
Agonists and Antagonists

**Agonists**: Drugs that occupy receptors and activate them.

**Antagonists**: Drugs that occupy receptors but do not activate them. Antagonists block receptor activation by agonists.

- Agonist alone:
  - Full activation

- Antagonist alone:
  - No activation
Agonists and Antagonists

Agonists: Drugs that occupy receptors and activate them.

Antagonists: Drugs that occupy receptors but do not activate them. Antagonists block receptor activation by agonists.

- Agonist alone: Full activation
- Agonist + antagonist: Less activation
- Antagonist alone: No activation
Allosteric modulation
Synaptic Transmission

Diagram showing the processes of synaptic transmission:

1. Ca$^{2+}$ enters the presynaptic terminal.
2. Ca$^{2+}$ activates a release mechanism, leading to the release of neurotransmitter (NT).
3. NT diffuses across the synaptic cleft.
4. NT binds to receptors on the postsynaptic membrane, causing an increase in Na$^+$ influx.
5. Na$^+$ influx leads to an increase in intracellular Na$^+$ concentration.
6. Na$^+$ influx triggers an action potential in the postsynaptic cell.
8. Glial cell activity is essential for the regulation of neurotransmitter levels.
9. Calcium ATPase pumps Ca$^{2+}$ out of the postsynaptic terminal.
10. Vesicles are refilled with neurotransmitter molecules.
11. Vesicles are transported to the presynaptic terminal for reuse.
Drugs and the Synapse 2) alter various stages of synaptic processing.

- Drugs work by doing one or more of the following to neurotransmitters:
  1. Increasing the synthesis.
  2. Causing vesicles to leak.
  3. Increasing release.
  4. Decreasing reuptake.
  5. Blocking the breakdown into inactive chemical.
  6. Directly stimulating or blocking postsynaptic receptors.
Neurotransmitters

• Synthesis: esp. rate-limiting enzyme and/or substrate
• Clearance and inactivation
• Location and pathway
• Dysfunction and CNS pathology
Neurotransmitters

• More than 50 chemical substances does function as synaptic transmitters.
  – small molecules which act as rapidly acting transmitters.
    • acetylcholine, norepinephrine, dopamine, serotonin, GABA, glycine, glutamate, NO.
  – neuropeptides.
    • endorphins, enkephalins, VIP, ect.
    • hypothalamic releasing hormones.
      – TRH, LHRH, ect.
    • pituitary peptides.
      – ACTH, prolactin, vasopressin, ect.


Fast Neurotransmitteres
Glutamate (L-glutamic acid)

- Main excitatory neurotransmitter in the mammalian CNS
- 95% of excitatory synapses in the brain are glutamatergic
- Precursor for the GABA (major inhibitory neurotransmitter)
Enzymatic Pathways Involved in the Metabolism of Glutamate

Enzymes are indicated as follows: 1) phosphate-activated glutaminase, 2) glutamine synthetase, 3) aspartate aminotransferase, 4) alanine aminotransferase, 5) glutamic acid decarboxylase, 6) GABA transaminase, 7) succinic semialdehyde dehydrogenase, 8) glutamate dehydrogenase, 9) α-ketoglutarate dehydrogenase.
GLUTAMATE

NMDAR  AMPAR  KAINATER

EXTRACELLULAR

INTRACELLULAR

IONOTROPIC  METABOTROPIC

Fast synaptic transmission  Slow synaptic transmission
95% of excitatory synapses in the brain are glutamatergic
The Glutamate Synapse

Note – significant Glu uptake (mainly astrocytes)

Interconversion of glutamate to glutamine
Glutamate and CNS disorders

1) Stroke
Ischemia ➔
Glutamate and CNS disorders

1) Stroke
Ischemia $\rightarrow$ no ATP $\rightarrow$
Glutamate and CNS disorders

1) Stroke

Ischemia $\rightarrow$ no ATP $\rightarrow$ increase Glutamate

$\rightarrow$
Glutamate and CNS disorders

1) Stroke
Ischemia $\rightarrow$ no ATP $\rightarrow$ increase Glutamate
$\rightarrow$ Over activation **NMDA R & AMPA R** $\rightarrow$
Glutamate and CNS disorders

1) Stroke
Ischemia $\rightarrow$ no ATP $\rightarrow$ increase Glutamate
$\rightarrow$ Over activation NMDA R & AMPA R $\rightarrow$
increase Ca+ $\rightarrow$ cell death

2) dysfunction of glutamatergic transmission may also involve in schizophrenia-like symptoms, cognitive dysfunction, Depression and memory impairment
GABA

- Main inhibitory neurotransmitter in the mammalian CNS
GABA

- Main inhibitory neurotransmitter in the mammalian CNS

**Ionotrophic**
- GABA$_A$
  - Heterooligomeric protein complex that consists of several binding sites coupled to an integral Cl$^-$ channel

**Metabotropic**
- GABA$_B$
  - G-protein coupled receptor, seven transmembrane domain protein
GABA-A- ionotropic receptor

- An integral chloride channel activated by competitive agonists: GABA and muscimol
- Blocked by convulsant bicuculine (competitive antagonist) and picrotoxin (noncompetitive antagonist)
- Allosterically modulated by benzodiazepines and barbiturates, which potentiate the effect of GABA
GABA<sub>A</sub> receptor

Barbiturate site
- barbiturates
- etomidate
- etazolate

GABA site
- GABA
- muscimol
- isoguvacine
- bicuculline
- SR95531

General anesthetics
- propofol
- steroids
- halothane
- ethanol

Picrotoxinin site
- bicycrophosphates
- TBPS
- tetrazoles

Benzodiazepine site
- benzodiazepines
- non-benzodiazepines

Subsynaptic membrane

Actions at GABA<sub>A</sub> Receptors
Benzodiazepines potentiate GABA-induced responses
Benzodiazepines potentiate GABA-induced responses
GABA_A and ethanol

- Ethanol facilitates GABA ability to activate the receptor and prolongs the time that the Cl^- channel remains open
GABA

Synthesis

Glutamate → **GABA**

GABA is formed by the α-decarboxylation of glutamate in the reaction catalyzed by GAD (glutamic acid decarboxylase)
GABA is catabolized into the succinic semialdehyde in the reaction catalyzed by GABA-T (GABA-Transaminase).
EEG and Seizures
Electroencephalography (EEG)

- **Electro**: relating to electricity.
- **Encephalo**: relating to the brain.
- **Graphy**: writing or representation produced in a specified manner.

Therefore, EEG produces a graphed representation of the electrical activity occurring in a person’s brain.
Origin of EEG waves

EEG is the record of electrical activity of brain (superficial layer i.e. the dendrites of pyramidal cells) by placing the electrodes on the scalp.
EEG Electrode Placement

[Diagram of brain with electrode placements labeled: Pz, P3, Pz, Fz, F3, F7, Fp1, O1, T5, T3, O2, T7, T4, T8, Cz, C3, C4, C1, C2.]

[Image of a person with EEG electrodes on their head.]

[Graph showing normal EEG with labels for frontal, temporal, and occipital sites.]

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Seizure

- Abnormal electrical discharge.
- Initially synchronous
- May have no motor component
Convulsion

- Indicative of seizure activity
- Motoric output of synchronous neuronal firing.
Primary (Idiopathic) Seizure Disorders

- No identifiable cause
- Not the result of overt disease or injury
- In short, a guess.
Secondary (Symptomatic) Seizure Disorders

- Associated with or secondary to disease or injury
- e.g. trauma, neoplasm, or infection.
Epilepsy

• Seizures and/or convulsions can be acute and isolated...
• …they can be associated with a treatable organic disorder…
• When seizures/convulsions are chronic and of undefined origin…
• …the condition is described as epilepsy.
Simple (Focal) Partial Seizures

Contralateral spread

Scheme of Seizure Spread

From M.I. Davila-Garcia, Howard Univ., 2003
Seizure Pathophysiology

- Altered ionic conductance (increased excitability) of neuron.
- Reduced inhibitory neuronal (primarily GABAergic) control.
- Increased excitatory neuronal (primarily glutamateergic) control.
- Probable mechanisms tend to overlap.
Cellular and Synaptic Mechanisms of Epileptic Seizures

- Abnormal voltage-operated channels
- Abnormal receptor-operated channels
- Alterations in extracellular ionic environment
- Recruitment of normal neurons via anatomical circuits

Steps in seizure:
- Focal epileptogenesis
- Synchronization
- Propagation

Seizure Sequence
GABA-A- ionotropic receptor

- An integral chloride channel activated by competitive agonists: GABA and muscimol
- Blocked by convulsant bicuculine (competitive antagonist) and picrotoxin (noncompetitive antagonist)
- Allosterically modulated by benzodiazepines and barbiturates, which potentiate the effect of GABA
Acetylcholine
Choline + Acetyl CoA → Acetyl choline + CoA
Acetylcholine synapse
Acetylcholine receptors
Acetylcholine receptors
Drugs acting at cholinergic terminal
Acetylcholine Pathway
Acetylcholine Pathway

• arousal and reward
• enhancement of sensory perceptions
• sustaining attention
Acetylcholine Pathway

- arousal and reward
- enhancement of sensory perceptions
- sustaining attention

Alzheimer’s disease – loss of cholinergic cells in nucleus basalis
Neuromodulators
Biogenic Amines

SMALL-MOLECULE NEUROTRANSMITTERS

BIOGENIC AMINES

CATECHOLAMINES

Dopamine

\[
\text{HO} \quad \text{OH}
\]

Norepinephrine

\[
\text{HO} \quad \text{OH}
\]

Epinephrine

\[
\text{HO} \quad \text{OH}
\]

INDOLEAMINE

Serotonin

\[
\text{HO} \quad \text{CH}_2\text{CH}_2\text{NH}_3
\]
The biosynthetic pathway for the catecholamine neurotransmitters
Biogenic Amines Synapses

MAO: Monoamine Oxidase
Dopamine
Dopamine receptors

- G protein-coupled receptors
Dopamine receptors

- G protein-coupled receptors
- D1 $\rightarrow$ excite
- D2 $\rightarrow$ inhibit
- D3 $\rightarrow$ inhibit
- D4 $\rightarrow$ inhibit
- D5 $\rightarrow$ excite
Dopamine receptors

- G protein-coupled receptors
  - D1 $\rightarrow$ excite
  - D2 $\rightarrow$ inhibit $\star$ Mainly presynaptic (Autoreceptor)
  - D3 $\rightarrow$ inhibit
  - D4 $\rightarrow$ inhibit
  - D5 $\rightarrow$ excite
3. Dopaminergic (DA) synapse
Dopamine Pathways
DOPAMINERGIC PATHWAYS

Striatum

Nucl. accumbens

Prefrontal CTX

Nigrostriatal pathway

Mesolimbic pathway

Mesocortical pathway

Substantia nigra of midbrain

Ventral tegmental area of midbrain

Cingulate cortex

Medial orbital frontal cortex

Amygdala

Hippocampus and parahippocampal gyrus
DOPAMINERGIC PATHWAYS

PATHWAY INVOLVED IN MOTIVATION TO EXPLORE THE ENVIRONMENT: CURIOSITY, INTEREST, COGNITIVE FLEXIBILITY, DRIVE FOR SOCIAL ENGAGEMENT.

*Relative hypofunction* in schizophrenia: Primary mesocortical dopamine deficiency will increase the NEGATIVE SYMPTOMS like Cognitive blunting, social isolation, apathy, anhedonia.
DOPAMINERGIC PATHWAYS

- Degeneration of nigro-striatal DA system and Decreased DAergic trans-mission in the basal ganglia will lead to
DOPAMINERGIC PATHWAYS

- Degeneration of nigro-striatal DA system and Decreased DAergic transmission in the basal ganglia will lead to Parkinson Disease.
DOPAMINERGIC PATHWAYS

PLEASURE, REWARD AND BEHAVIOR REINFORCING PATHWAY

Substantia nigra of midbrain

Ventral tegmental area of midbrain

Nucl. accumbens

Mesolimbic pathway

Medial orbital frontal cortex

Amygdala

Hippocampus and parahippocampus

PLEASURE, REWARD AND BEHAVIOR REINFORCING PATHWAY
DOPAMINERGIC PATHWAYS

PLEASURE, REWARD AND BEHAVIOR REINFORCING PATHWAY

Substantia nigra of midbrain

Ventral tegmental area of midbrain

Nucl. accumbens

Mesolimbic pathway

natural

drug-induced

cocaine
DOPAMINERGIC PATHWAYS

PLEASURE, REWARD AND BEHAVIOR REINFORCING PATHWAY

Hyperactivity of mesolimbic pathway:
- positive symptoms of schizophrenia (hallucinations, etc)

of midbrain

Nucl. accumbens

Mesolimbic pathway

natural

YES!

drug-induced

YES!

cocaine