CNS ----INTRODUCTION
The diagram illustrates the NMDA receptor system. At the receptor site, Glutamate activates the channel, allowing ions to pass. At the modulatory sites, Glycine and Polyamines modulate the receptor activity. NMDA antagonists and Channel-blocking drugs inhibit the receptor function. Calcium ions (Ca$^{2+}$) and Sodium ions (Na$^+$) are also shown to interact with the receptor.
ANATOMICAL REGIONS OF BRAIN &
THEIR MACROFUNCTIONS

1-CEREBRAL CORTEX

2-Limbic sys
   Basal ganglia(neostriatum)
      i-Caudate nucleus, putamen, globus pallidus, lentiform nucleus
      ii-Hippocampus
      iii-Amygdala
      iv-Olfactory tubercle, septum

3-Diencephalon
   i-thalamus
   ii-hypothalamus
DIENCEPHALON

- Thalamus
- hypothalamus
MIDBRAIN & BRAIN STEM (MESENCEPHALON)

- Mesencephalon, pons & medulla oblongata
- Bridge portions of CNS, connect cortex, thalamus, hypothalamus to the spinal cord.
- The contain:
  - a) inflow & outflow tracts from cortex and spinal cord
  - b) reticular activating system
  - c) coordination of essential reflexes e.g. swallowing, vomiting, cardiovascular, respiratory
  - d) primary receptive regions visceral afferent
MICROANATOMY/CELLULAR ORGANIZATION OF BRAIN

• Neurons

**According to function**----sensory, motor, interneurons

**According to transmitter release**-----

- cholinergic,
- adrenergic,
- serotonergic,
- dopaminergic etc.
SUPPORTIVE CELLS

• Macroglia
  1) astrocytes--- act as
     i- house-keeper
     ii- inexcitable neurons, with slow communication role

respond to signals from neurons & microglia
control the chemical envi in which neurons operate

  2) oligodendroglia (myelin producing cells)

• Microglia (related to macrophage/monocyte lineage)
NEURONAL REGULATION
(CENTRAL TRANSMITTERS)

- **NEUROTRANSMITTER**
  - It is a chemical/substance produced by nerve cells to communicate with other nerve cells

- **NEUROTRANSMITTER RECEPTORS**
  - Mostly they are ion channels
    - voltage- gated
    - ligand –gated
  - metabotropic
    - membrane delimited
A  Voltage-gated

B  Ligand-gated ion channel (ionotropic)


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NEUROMODULATOR

• Released by neurons and by astrocytes produce slower pre- or postsynaptic responses via G protein recep
• Dopamine
• Neuropeptides
Subs not stored & released like conventional transmitter
• Prostanoids, AA metabolites, NO
NEUROTROPHIC FACTOR

• Released by non-neuronal cells, act on tyrosine kinase-linked receptors that regulate gene expression that controls neuronal
i-growth
ii-morphology
iii-function
<table>
<thead>
<tr>
<th>Timescale</th>
<th>Process</th>
<th>Chemical mediators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ms</strong></td>
<td>Impulse conduction</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Transmitter release</td>
<td>$[Ca^{2+}]_i$</td>
</tr>
<tr>
<td></td>
<td>Fast synaptic transmission</td>
<td>Fast transmitters (e.g. glutamate, GABA, ACh)</td>
</tr>
<tr>
<td></td>
<td>Slow synaptic transmission</td>
<td>Slow transmitters (e.g. monoamines, peptides, ACh)</td>
</tr>
<tr>
<td></td>
<td>Neuromodulation</td>
<td>Slow transmitters + others (e.g. NO, arachidonic acid metabolites)</td>
</tr>
<tr>
<td><strong>min</strong></td>
<td>Synaptic plasticity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delayed pharmacological effects</td>
<td>Many neuroactive drugs (e.g. antidepressants, Ch. 39)</td>
</tr>
<tr>
<td></td>
<td>Pharmacological tolerance</td>
<td>Many neuroactive drugs (Ch. 43) (e.g. opioids, benzodiazepines)</td>
</tr>
<tr>
<td><strong>h</strong></td>
<td>Structural remodelling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Degeneration, regeneration and repair</td>
<td>Chemokines</td>
</tr>
<tr>
<td></td>
<td>(very limited in CNS)</td>
<td>Cytokines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Growth factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>? Adhesion molecules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>? Steroids</td>
</tr>
</tbody>
</table>
SYNAPSE & SYNAPTIC POTENTIALS

- Steps in synaptic transmission include:
  a) action potential generation
  b) opening of Ca channel
  c) fusion of synaptic vesicles thus exocytosis of neurotransmitter
  d) its binding with post synaptic membrane causes brief increase of membrane conductance resulting in EPSP
  e) if sufficient EPSPs generated threshold is achieved AP is generated
• INHIBITORY POSTSYNAPTIC POTENTIAL (IPSP)
• produces hyperpolarization e.g. Cl channel opening, negative ions move inside
SITES OF DRUG ACTION
SECONDARY ADAPTIVE RESPONSES

e.g. if drug causes

inc in transmitter release or

interference with transmitter uptake

adaptation

inhi of transmitter synth

up-regulation of receptors

more commonly observed with psychiatric drugs
CELLULAR ORGANIZATION OF BRAIN

• a) Hierarchial systems  b) nonspecific or diffuse

HIERARCHIAL SYSTEM

Information/order will reach its destination after being processed at different relay stations

  a) pathways directly involved in motor control & sensory perception
  b) composed of large myelinated nerve fibers
• C)relay nuclei consist of
  • relay or projection neurons
  • form interconnecting pathways transmit signals over long distances usually produce glutamate
• local circuit neurons
• small cells, release GABA, feed forward & recurrent feedback pathways
B

A xoaxonic interaction

Local circuit neuron

Relay neurons
DIFFUSE OR NONSPECIFIC NEURONAL SYSTEMS

- Contain one of monoamines
- Small neurons with fine unmyelinated, slow conducting neurons,
- Axons branch repeatedly, very divergent, & innervate functionally different parts of CNS
CENTRAL NEUROTRANSMITTERS

• BIOGENIC AMINES
  • epinephrine, norepinephrine, dopamine,
• Serotonin, histamine
• AMINO ACIDS
  • GABA, Glycine, glutamate, aspartate
• NEUCLEOTIDES
• Adenosine, ATP etc
• PEPTIDES
Table 21–2 Summary of Neurotransmitter Pharmacology in the Central Nervous System.

<table>
<thead>
<tr>
<th>Transmitter</th>
<th>Anatomy</th>
<th>Receptor Subtypes and Preferred Agonists</th>
<th>Receptor Antagonists</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>Cell bodies at all levels; long and short connections</td>
<td>Muscarinic (M₁): muscarine</td>
<td>Pirenzepine, atropine</td>
<td>Excitatory: ↑ in K⁺ conductance; ↑ IP₃, DAG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Muscarinic (M₂): muscarine, bethanechol</td>
<td>Atropine, methotramine</td>
<td>Inhibitory: ↓ K⁺ conductance; ↓ cAMP</td>
</tr>
<tr>
<td></td>
<td>Motoneuron-Renshaw cell synapse</td>
<td>Nicotinic: nicotine</td>
<td>Dihydro-β-erythroidine, α-</td>
<td>Excitatory: ↑ cation conductance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>bungarotoxin</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>Cell bodies at all levels; short, medium, and long connections</td>
<td>D₁</td>
<td>Phenothiazines</td>
<td>Inhibitory (?): ↑ cAMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D₂: bromocriptine</td>
<td>Phenothiazines, butyrophenones</td>
<td>Inhibitory (presynaptic): ↑ Ca²⁺; Inhibitory (postsynaptic): ↓ in K⁺ conductance, ↓ cAMP</td>
</tr>
<tr>
<td>GABA</td>
<td>Supraspinal and spinal interneurons involved in pre- and postsynaptic</td>
<td>GABA&lt;sub&gt;A&lt;/sub&gt;: muscimol</td>
<td>Bicuculline, picrotoxin</td>
<td>Inhibitory: ↑ Cl⁻ conductance</td>
</tr>
<tr>
<td></td>
<td>inhibition</td>
<td>GABA&lt;sub&gt;B&lt;/sub&gt;: baclofen</td>
<td>2-OH saclofen</td>
<td>Inhibitory (presynaptic): ↑ Ca²⁺; Inhibitory (postsynaptic): ↑ K⁺ conductance</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Relay neurons at all levels and some interneurons</td>
<td>N-Methyl-D-aspartate (NMDA): NMDA</td>
<td>2-Amino-5-phosphonovalerate,</td>
<td>Excitatory: ↑ cation conductance, particularly Ca²⁺</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dizocilpine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMPA: AMPA</td>
<td>CNQX</td>
<td>Excitatory: ↑ cation conductance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kainate: kainic acid, domoic</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>acid</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Metabotropic: ACPD, quisqualate</td>
<td>MCPG</td>
<td>Inhibitory (presynaptic): ↑ Ca²⁺ conductance + cAMP; Excitatory: ↑ K⁺ conductance, ↓ IP₃, DAG</td>
</tr>
<tr>
<td>Glycine</td>
<td>Spinal interneurons and some brain stem interneurons</td>
<td>Taurine, β-alanine</td>
<td>Strychnine</td>
<td>Inhibitory: ↑ Cl⁻ conductance</td>
</tr>
<tr>
<td>5-Hydroxytryptamine (serotonin)</td>
<td>Cell bodies in midbrain and pons project to all levels</td>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;: LSD</td>
<td>Metergoline, spiperone</td>
<td>Inhibitory: ↑ K⁺ conductance, ↓ cAMP</td>
</tr>
<tr>
<td>Neuropeptide</td>
<td>Synaptic sites</td>
<td>Receptors</td>
<td>Agonist(s)</td>
<td>Antagonist(s)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------------------------------------------</td>
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</tr>
<tr>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;</td>
<td>Cell bodies in pons and brain stem project to all levels</td>
<td>5-HT&lt;sub&gt;1&lt;/sub&gt;: 2-methyl-5-HT</td>
<td>Ondansetron</td>
<td>Excitatory: ↑ K&lt;sup&gt;+&lt;/sup&gt; conductance, ↑ IP&lt;sub&gt;3&lt;/sub&gt;, DAG</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;</td>
<td>Cell bodies in pons and brain stem project to all levels</td>
<td>5-HT&lt;sub&gt;1&lt;/sub&gt;: 2-methyl-5-HT</td>
<td>Ondansetron</td>
<td>Excitatory: ↑ K&lt;sup&gt;+&lt;/sup&gt; conductance</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Cell bodies in pons and brain stem project to all levels</td>
<td>5-HT&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Ketanserin</td>
<td>Excitatory: ↑ K&lt;sup&gt;+&lt;/sup&gt; conductance, ↑ IP&lt;sub&gt;3&lt;/sub&gt;, DAG</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Cell bodies in pons and brain stem project to all levels</td>
<td>α&lt;sub&gt;1&lt;/sub&gt;: phentolamine</td>
<td>Prazosin</td>
<td>Excitatory: ↑ K&lt;sup&gt;+&lt;/sup&gt; conductance, ↑ IP&lt;sub&gt;3&lt;/sub&gt;, DAG</td>
</tr>
<tr>
<td>α&lt;sub&gt;1&lt;/sub&gt;: phentolamine</td>
<td>Cell bodies in pons and brain stem project to all levels</td>
<td>α&lt;sub&gt;1&lt;/sub&gt;: phentolamine</td>
<td>Prazosin</td>
<td>Excitatory: ↑ K&lt;sup&gt;+&lt;/sup&gt; conductance, ↑ IP&lt;sub&gt;3&lt;/sub&gt;, DAG</td>
</tr>
<tr>
<td>α&lt;sub&gt;2&lt;/sub&gt;: phentolamine</td>
<td>Cell bodies in pons and brain stem project to all levels</td>
<td>α&lt;sub&gt;2&lt;/sub&gt;: phentolamine</td>
<td>Prazosin</td>
<td>Excitatory: ↑ K&lt;sup&gt;+&lt;/sup&gt; conductance, ↑ IP&lt;sub&gt;3&lt;/sub&gt;, DAG</td>
</tr>
<tr>
<td>Histamine</td>
<td>Cells in ventral posterior hypothalamus</td>
<td>H&lt;sub&gt;1&lt;/sub&gt;: 2(m-fluorophenyl)-histamine</td>
<td>Mepyramine</td>
<td>Excitatory: ↑ K&lt;sup&gt;+&lt;/sup&gt; conductance, ↑ IP&lt;sub&gt;3&lt;/sub&gt;, DAG</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;: dimaprit</td>
<td>Cell bodies in ventral posterior hypothalamus</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;: dimaprit</td>
<td>Ranitidine</td>
<td>Excitatory: ↑ K&lt;sup&gt;+&lt;/sup&gt; conductance, ↑ IP&lt;sub&gt;3&lt;/sub&gt;, DAG</td>
</tr>
<tr>
<td>H&lt;sub&gt;3&lt;/sub&gt;: R-α-methyl-histamine</td>
<td>Cell bodies in ventral posterior hypothalamus</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;: R-α-methyl-histamine</td>
<td>Thioperamide</td>
<td>Inhibitory autoreceptors</td>
</tr>
<tr>
<td>Opioid peptides</td>
<td>Cell bodies at all levels; long and short connections</td>
<td>Mu: bendorphin</td>
<td>Naloxone</td>
<td>Inhibitory (presynaptic): ↓ Ca&lt;sup&gt;2+&lt;/sup&gt; conductance, ↓ cAMP</td>
</tr>
<tr>
<td>Delta: enkephalin</td>
<td>Cell bodies at all levels; long and short connections</td>
<td>Delta: enkephalin</td>
<td>Naloxone</td>
<td>Inhibitory (postsynaptic): ↑ K&lt;sup&gt;+&lt;/sup&gt; conductance, ↓ cAMP</td>
</tr>
<tr>
<td>Kappa: dynorphin</td>
<td>Cell bodies at all levels; long and short connections</td>
<td>Kappa: dynorphin</td>
<td>Naloxone</td>
<td>Inhibitory (postsynaptic): ↑ K&lt;sup&gt;+&lt;/sup&gt; conductance, ↓ cAMP</td>
</tr>
<tr>
<td>Tachykinins</td>
<td>Primary sensory neurons, cell bodies at all levels; long and short connections</td>
<td>NK1: Substance P methylester, aprepitant</td>
<td>Aprepitant</td>
<td>Excitatory: ↑ K&lt;sup&gt;+&lt;/sup&gt; conductance, ↑ IP&lt;sub&gt;3&lt;/sub&gt;, DAG</td>
</tr>
<tr>
<td>NK2</td>
<td>Primary sensory neurons, cell bodies at all levels; long and short connections</td>
<td>NK2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NK3</td>
<td>Primary sensory neurons, cell bodies at all levels; long and short connections</td>
<td>NK3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocannabinoids</td>
<td>Widely distributed</td>
<td>CB1: Anandamide, 2-arachidonylglycerol</td>
<td>Rimonabant</td>
<td>Inhibitory (presynaptic): ↑ Ca&lt;sup&gt;2+&lt;/sup&gt; conductance, ↓ cAMP</td>
</tr>
</tbody>
</table>
GLUTAMATE

• Excitatory A.A
• Inotropic rec
• a) AMPA&KA
• Present on all neurons, permeable to Na, K, & in some inhibitory neurons permeable to Ca
• b) NMDA
• permeable to Na,K, highly permeable to Ca
• Activation of channel needs simultaneous binding of glycine
• Voltage dependent block of channel with Mg only leave the channel when highly depolarized
• May cause LTP or LTD
• METABOTROPIC GLU RECEPTORS
• Gp1----post synaptic, activate nonselective cation channel
• Gp11&111----presynaptic, autoinhibitory, block Ca channel
DOPAMINE

• Generally exerts slow inhibitory effect on CNS neurons
• **Dopamine receptors**
  • metabotrpic
  • D1,D5------ Gs
  • D2 ,D3 ,D4--------Gi,activate receptor operated K& ligand gated Ca channels so presynaptically decrease the release of dopamine
• Also suppress synthesis by decreasing phosphorylation of tyrosine hydroxylase
DOPAMINE PATHWAYS Nigrostriatal, Mesolimbic, mesocortical, (behavior), Tuberohypophyseal (endocrine control)
NIGROSTRIATAL PATHWAY
NORADRENALINE

• RECEPTORS
  • Alpha 2-----hyperpolarization by increased K conductance, decreased transmitter release
  • Alpha1& beta-----exitation due to blockade of K conductance

• LOCATION
  a) Diffuse adrenergic input to all areas of brain
  b) locus caeruleus
SEROTONIN (5-HT)

- RECEPTORS
  - HT1A, B, C
  - 5-HT2
  - 5-HT3
  - 5-HT4

- LOCATION
  - Neurons mainly present in median raphe nuclei, diffusely innervate most areas of brain
**Dopamine Pathways**

- Frontal cortex

**Functions**
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

**Serotonin Pathways**

- Striatum
- Substantia nigra
- Nucleus accumbens
- VTA
- Hippocampus
- Raphe nuclei

**Functions**
- Mood
- Memory processing
- Sleep
- Cognition
CHOLINERGIC SYSTEM

• Cholinergic receptors
  Nicotinic----ionotropic receptors
  Muscarinic receptors
    M1---slow excitation by decreasing K permeability
    M2----inhibition by increasing K permeability

Location
a) gigantocellular neurons of reticular formation at the junction of mid brain & spinal cord, fibers divide in two branches, one passes to brain and other to spinal cord
  Stimulation leads to acutely awake & excited nervous system
b) From cortex to caudate nucleus & putamen
  Form caudate nucleus to putamen
c) hippocampus & other memory areas