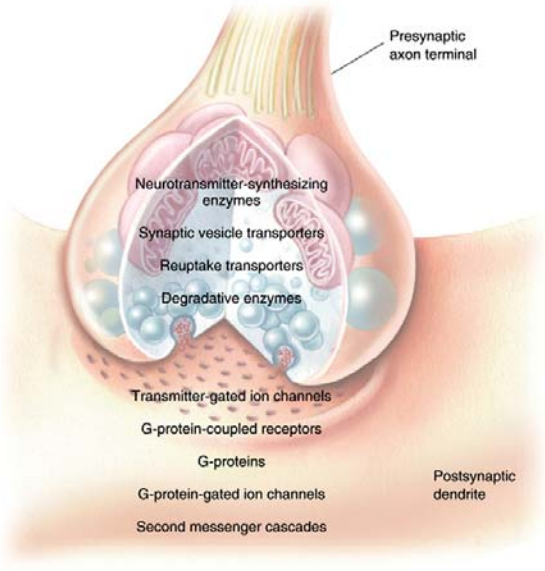
Νευροφυσιολογία και Αισθήσεις

Διάλεξη 6

Νευροδιαβιβαστές (Nerotransmitters)

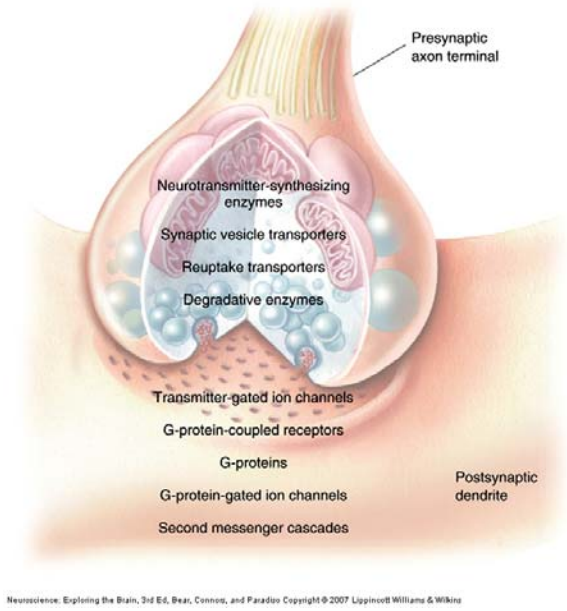
Introduction

- **Neurons communicate by releasing chemical messengers called neurotransmitters**
  - Large number of neurotransmitters are now known and more remain to be discovered
- **Neurotransmitters evoke postsynaptic electrical responses by binding to neurotransmitter receptors**
  - Members of a diverse group of proteins
- **Neurotransmitter - three criteria**
  - Synthesis and storage in presynaptic neuron
  - Released by presynaptic axon terminal (Ca^{2+} dependent)
  - Produces response in postsynaptic cell
    - Mimics response produced by release of neurotransmitter from the presynaptic neuron



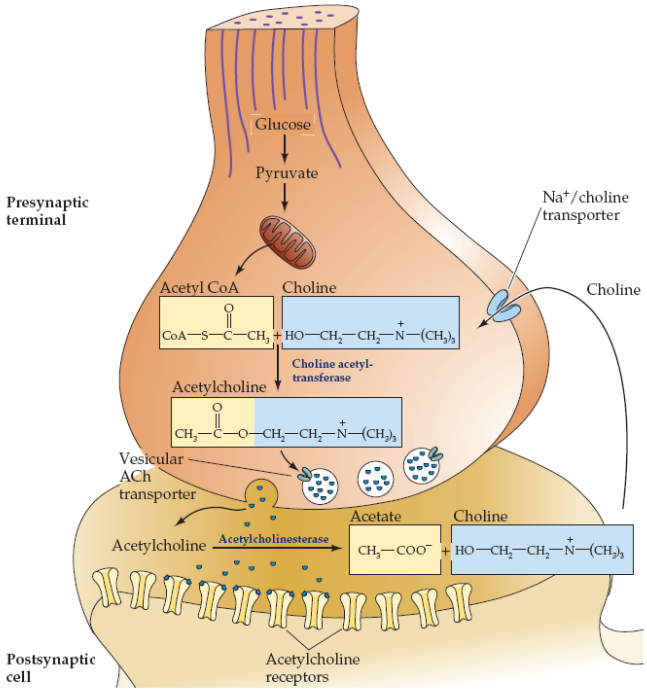
Categories of Neurotransmitters

- **More than 100 different agents are known to serve as neurotransmitters**
  - Large number of transmitters allows for tremendous diversity
- **Categories**
  - Neuropeptides
    - Relatively large transmitter molecules composed of 3 to 36 amino acids
  - Small-molecule neurotransmiters
    - Acetylcholine
    - Individual amino acids (e.g. glutamate, glycine, and GABA)
  - Biogenic amines
    - Catecholamines (Dopamine, norepinephrine, epinephrine)
    - Serotonin, and histamine



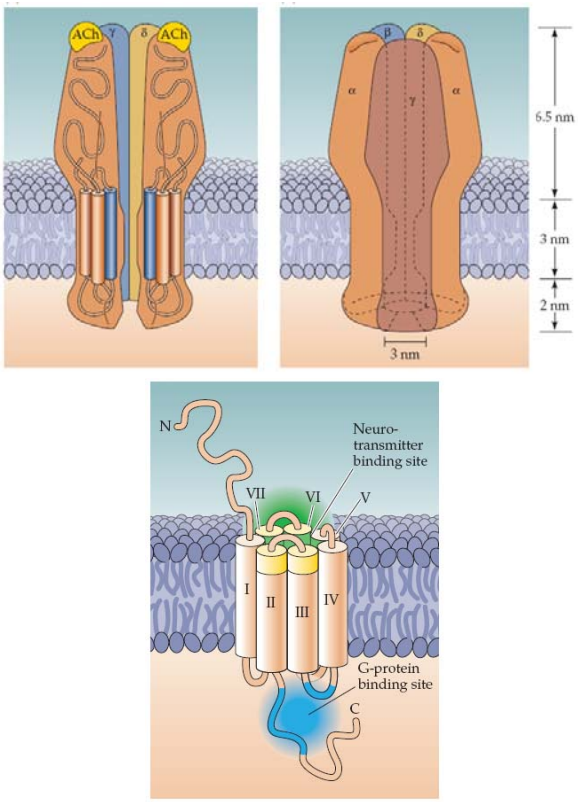
Acetylcholine

- **The first substance identified as a neurotransmitter**
- **Sites of Action**
  - Skeletal muscle junctions
  - Parasympathetic terminals
  - Ganglia of the autonomic nervous system
  - CNS
- **Synthesis**
  - In the cytosol
  - Choline transported from ECF
- **Removal**
  - AChE
  - Choline reuptake



Acetylcholine

- **Receptors**
  - Nicotinic ACh Receptors
    - Ionotropic
    - Brain, neuromuscular junction
    - Non-selective ion channels → excitatory
    - Also bind other ligands
      - Nicotine
      - Toxins
    - Fast response
  - Muscarinc ACh Receptors
    - Metabotropic
    - Brain, ganglia, autonomic innervation (parasympathetic)

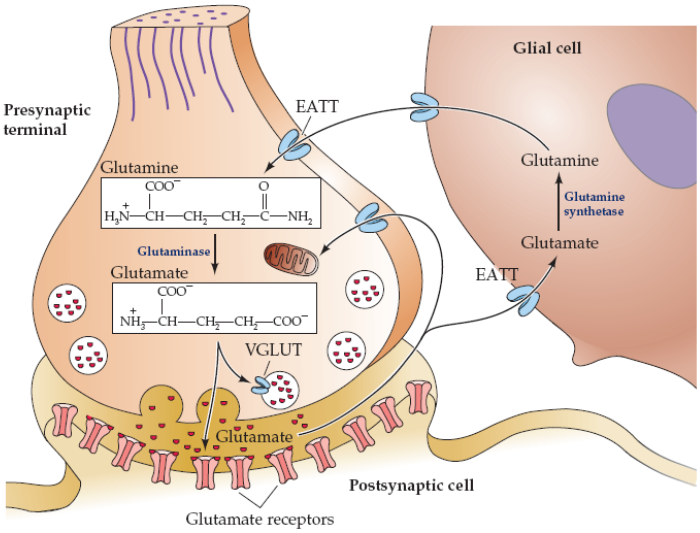


Acetylcholine

- **Neuropharmacology**
  - Organophosphates (including Sarin gas)
    - Inhibit AChE → paralysis
    - Popular insecticides
  - nAChR agonist
    - Nicotine
  - nAChR antagonist
    - α-Bugarotoxin
    - Cobra α-neurotoxin
    - Curare
  - mAChR agonist
    - Muscarine
  - mAChR antagonist
    - Atropine
    - Scopolamine

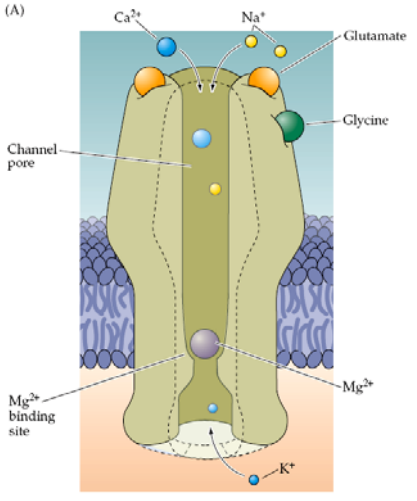
Glutamate

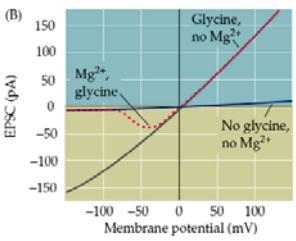
- **Sites of Action**
  - CNS (half of brain synapses!)
- **Synthesis**
  - Non-essential amino acid
  - Does not cross BBB
  - Synthesized de novo from glutamine
    - Glial cells
- **Removal**
  - Reuptake
    - Excitatory Amino Acid Transporters (EAAT)

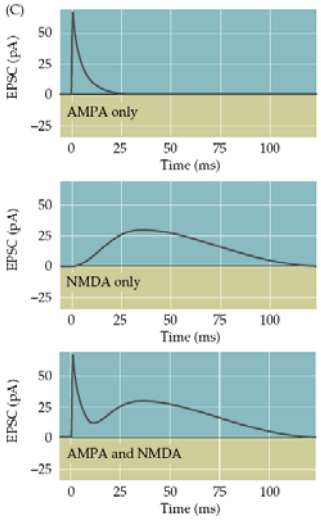


Glutamate

- **Receptors**
  - Ionotropic
    - NMDA, AMPA, Kainate
    - Non-selective cation channels → excitatory
    - NMDA Receptor additional features
      - Allows entry of Ca^{2+} too → acts as second messenger
      - Voltage dependent activity
        - At hyperpolarized state → Mg2+ binds and blocks
        - Depolarization removes Mg2+
        - Important in memory
      - Requires co-agonist glycine
  - Metabotropic (mGluR)
    - Indirectly modulate postsynaptic ion channels
    - Can be excitatory or inhibitory
    - Slow acting





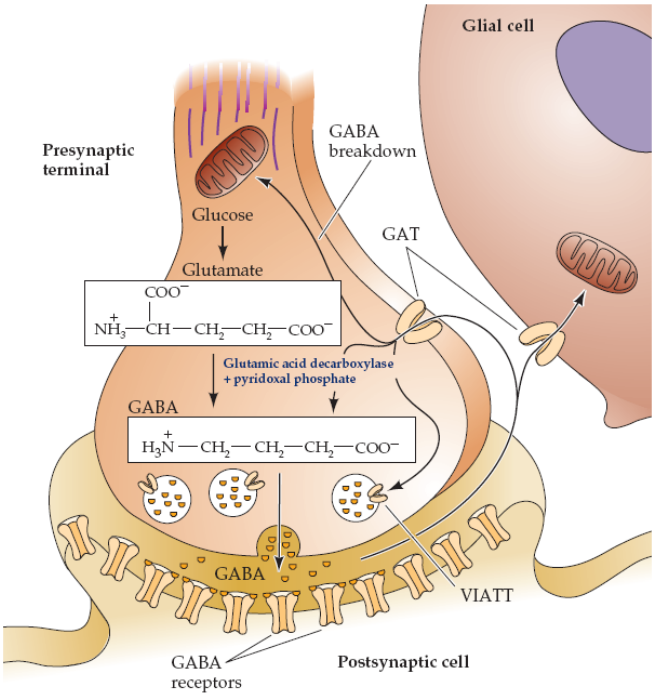


Glutamate

- **Neuropharmacology**
  - Agonists
    - Kainate
    - Quissqualate
    - Ibotenic acid, Acromelic Acid (mushrooms)
    - Domoate (algae, mussels)
  - Antagonists
    - Funnel and Orb Web Spider venoms
    - Cone snail venom

GABA

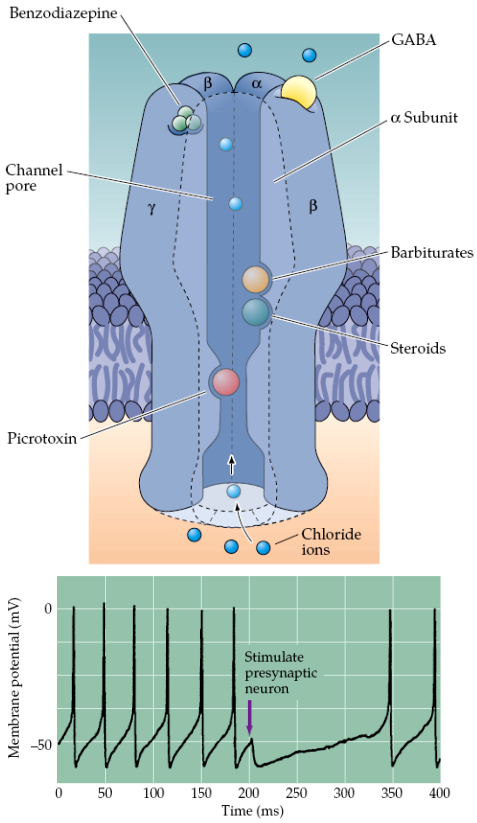
- **Sites of Action**
  - Most inhibitory synapses in brain and spinal cord → GABA and Glycine
  - 30% of synapses in the CNS are GABA
- **Synthesis**
  - Glucose → Glutamate → GABA
  - Requires cofactor derived from vitamin B6
    - ↓B6 → ↓ inhibition → seizures → infant deaths
- **Removal**
  - GABA Transporter (GAT)
  - Breakdown by mitochondrial enzymes



GABA

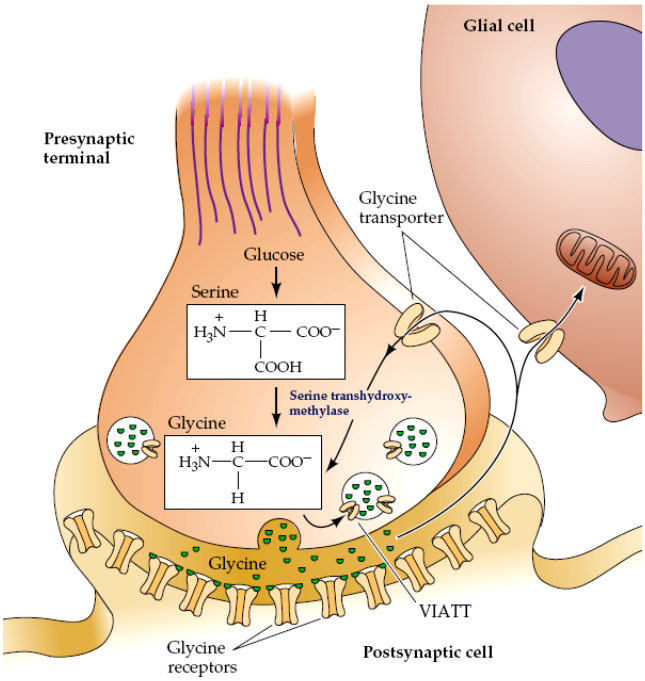
- **Receptors**
  - Ionotropic
    - $GABA_A$, $GABA_C$
    - Cl^- channels
  - Metabotropic
    - GABAB
    - Activate of K^+ channels
    - Block Ca^{2+} channels

- **Neuropharmacology**
  - Agonists
    - Benzodiazepines (Valium, Librium) → sedatives, anxiety reducing
    - Barbiturates → anesthetics
    - Alcohol
    - Steroids
    - Intermediary is γ-hydroxybutyrate → "date rape" drug → euphoria, memory deficits → unconsciousness
  - Antagonists
    - Picrotoxin



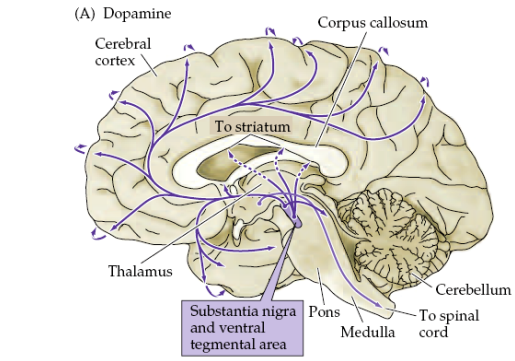
Glycine

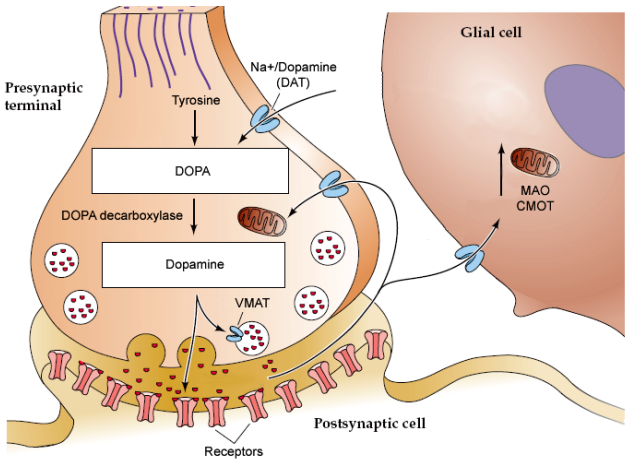
- **Sites of Action**
  - 50% of inhibitory synapses in the spinal cord
- **Synthesis**
  - From serine
- **Removal**
  - Glycine Transporter
- **Receptors**
  - Ionotropic
    - Cl^- channels
- **Neuropharmacology**
  - Antagonists
    - Strychnine → seizures



Dopamine

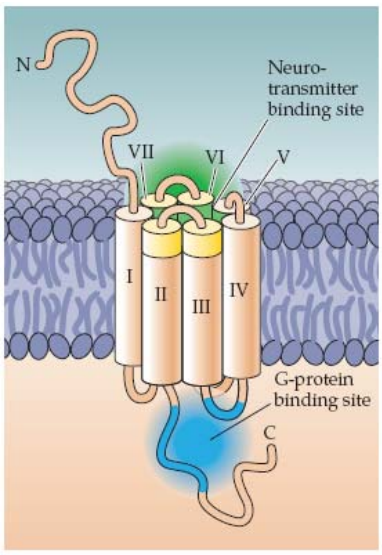
- **Sites of Action**
  - Brain
    - Movement and coordination
    - Motivation, reward, reinforcement
  - Sympathetic ganglia
    - Poorly understood role
- **Synthesis**
  - From Tyrosine
- **Removal**
  - Na+/Dopamine Transporter (DAT)
  - Dopamine catabolism enzymes include
    - Mitochondrial Monoamine oxidase (MAO)
    - Cytoplasmic O-methyl-transferase (CMOT)





Dopamine

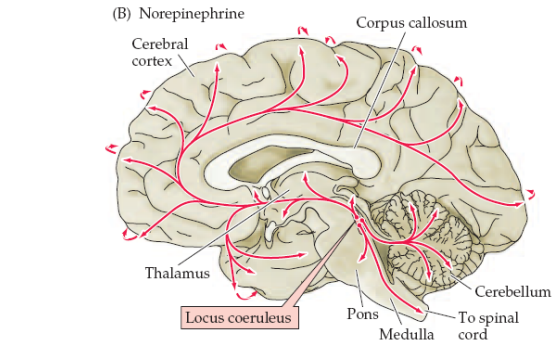
- **Receptors**
  - Metabotropic
    - G-protein coupled
    - Activating or inhibiting adenylyl cyclase
    - Complex behaviors
- **Neuropharmacology**
  - Agonists
    - Hyperactivity, inhibit vomiting, etc
  - Antagonists
    - Induce vomiting, catalepsy
  - Illicit drug action
    - Cocaine → block dopamine reuptake→ pleasure pathways remain “on”

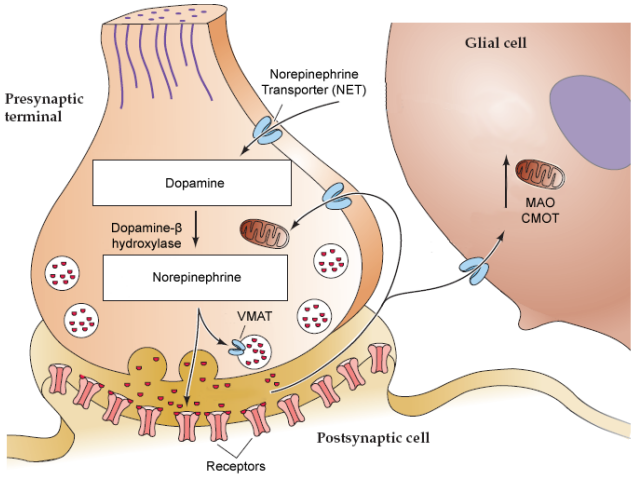


Biomedical Imaging and Applied Optics Laboratory

Norepinephrine

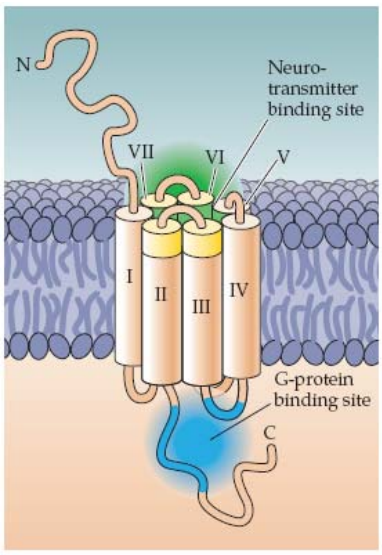
- **Sites of Action**
  - Sympathetic neurons
    - We will discuss later in the course
  - Brain
    - Sleep, wakefulness, attention and feeding behavior
- **Synthesis**
  - From Dopamine
- **Removal**
  - Norepinephrine Transporter (NET)
  - Norepinephrine catabolism enzymes include
    - Mitochondrial Monoamine oxidase (MAO)
    - Cytoplasmic O-methyl-transferase (CMOT)





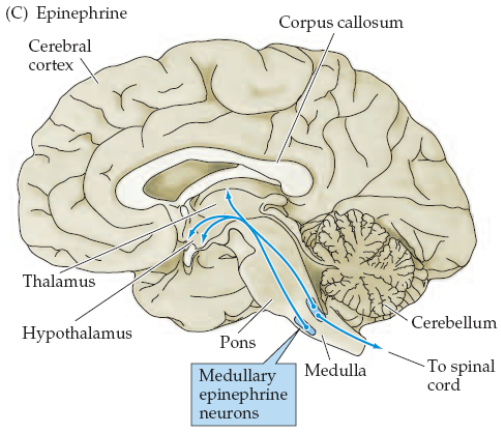
Norepinephrine

- **Receptors**
  - Metabotropic
    - α- and β-andrenergic receptors
      - G-protein coupled
      - 2 x α and 3 x β
      - α1 → slow depolarization (inhibition of K+ channels)
      - α2 → slow hyperpolarization (activation of different K+ channels)
- **Neuropharmacology**
  - We will discuss more when we cover the sympathetic system



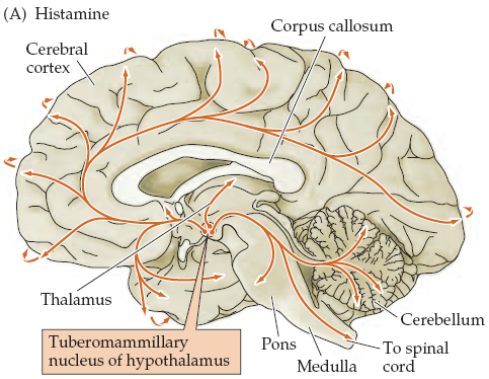
Epinephrine

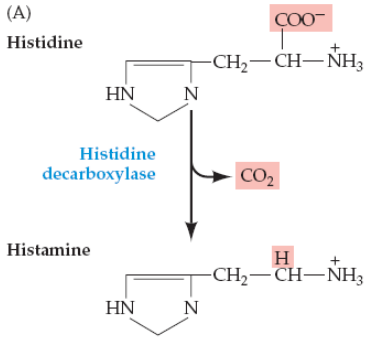
- **Sites of Action**
  - Sympathetic nervous system
    - Adrenal medula
  - Brain
    - Lower quantities
    - Role not known
- **Synthesis**
  - From Epinephrine
- **Removal**
  - No specific transporter has been identified yet
  - Norepinephrine Transporter (NET) can transfer epinephrine too
- **Receptors**
  - Can act on both α- and β-andrenergic receptors
- **Neuropharmacology**
  - We will discuss more when we cover the sympathetic system



Histamine

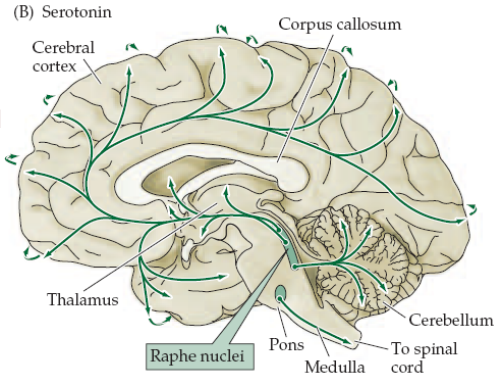
- **Sites of Action**
  - Hypothalamus
    - Arousal and attention
    - Similar to NE and ACh
- **Synthesis**
  - From Histidine
  - Transported into vesicles by VMAT
  - Degraded by histamine methyltransfarase and MAO
- **Removal**
  - No specific transporter has been identified yet
- **Receptors**
  - Three metabotrobic receptors
    - G-protein coupled
- **Neuropharmacology**
  - Antihistamines (receptor antagonists) developed for allergies, motion sickness and ulcers
  - If the cross BBB → sedative effect (e.g. Benadryl)

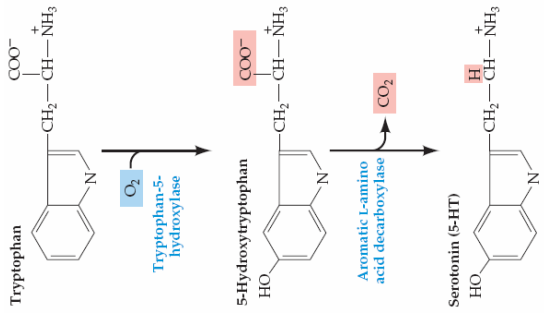




Serotonin (5-hydroxytryptamine 5-HT)

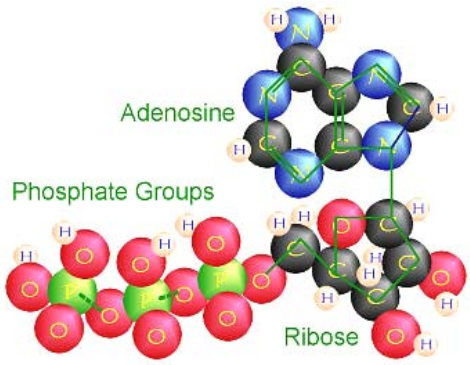
- **Sites of Action**
  - Pons
    - Sleep and wakefulness
    - Emotions, mental arousal, satiety and decreased food consumption
- **Synthesis**
  - From Tryptophan
  - Transported into vesicles by VMAT
  - Degraded by MAO
- **Removal**
  - Serotonin transported (SERT)
- **Receptors**
  - Many metabotrobic receptors
    - Implicated in psychiatric disorders
  - One type of ionotropic receptor
    - 5-HT_3: non specific cation channel → excitatory
- **Neuropharmacology**
  - Selective Serotonin Reuptake Inhibitors (SSRI)
    - Antidepressant Prozac
  - 5-HT_3 antagonists
    - Zofran → prevent nausea from chemotherapy





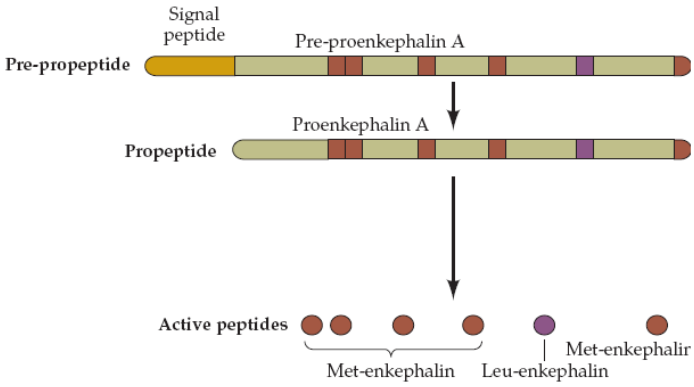
ATP and Purines

- **ATP and breakdown products (AMP and adenosine)**
  - Released and acts as co-transmitters
  - Not "classical" neurotransmitters
- **Sites of Action**
  - Spinal Cord
  - Sensory and autonomic ganglia
  - CNS
- **Synthesis**
  - Adenosine from extracellular enzymatic breakup of ATP
- **Removal**
  - Enzymatic catabolism
  - Nucleoside transporter
- **Receptors**
  - Two classes of metabotrobic receptors
    - G-protein coupled
    - One binds preferentially ATP, the other adenosine
  - One class of ionotropic receptors
    - Non specific cation channel → excitatory
    - Unclear function except mechanoreception and pain
- **Neuropharmacology**
  - Xanthines (caffeine and theophyline) block adenosine receptors
    - Stimulant effects



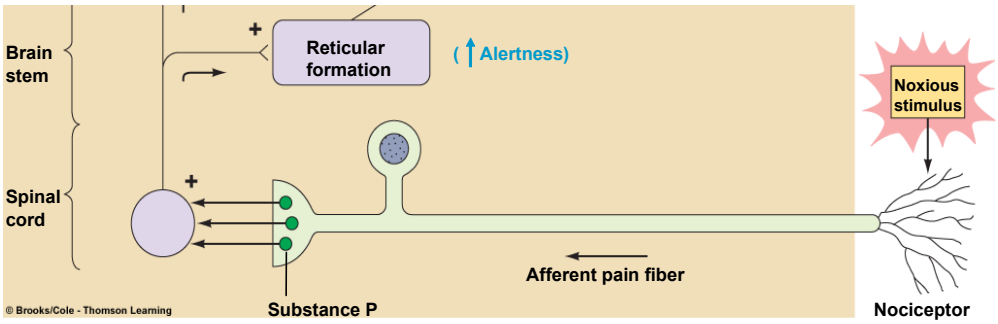
Peptide Neurotransmitters

- **Many peptides known to be hormones also act as neurotransmitters**
  - Modulating emotions
  - Perception of pain (substance P and opiades)
  - Complex responses to stress
  - Satiety and obesity (neuropeptide
  - Anxiety and panic attacks (cholecystokinin)
- **Often are co-released with small-molecule neurotransmitters**
- **Synthesis**
  - Like all proteins
  - Because of processing in vesicles many peptides packaged together
- **Receptors**
  - Virtually all metabotropic (G-protein coupled)



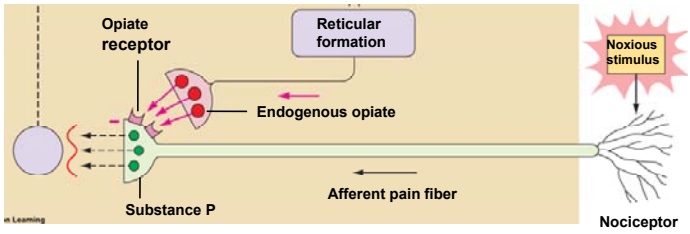
Substance P

- **Brain/Gut peptide**
  - Hippocampus neocortex, and also in the gastrointestinal tract
- **Same gene encodes for a variety of neuroactive peptides**
- **Sensory neurotransmitter in the spinal cord**
  - Conveys information about pain and temperature
  - Its release can be inhibited by opioid peptides



Opioids

- **Same postsynaptic receptors activated by opium**
- **Endogenous Opiates**
  - More than 20 opioid peptides
  - Three classes
  - Endorphins
    - Enkephalins
    - Dynorphins
- **Location**
  - Widely distributed throughout the brain
    - Co-localized with other small-molecule neurotransmitters, such as GABA and 5-HT
- **Actions**
  - Depressants, analgesics
  - Complex behaviors such as sexual attraction and aggressive/submissive behaviors
  - Hhave also been implicated in psychiatric disorders such as schizophrenia and autism
- **Receptors**
  - μ, δ, κ

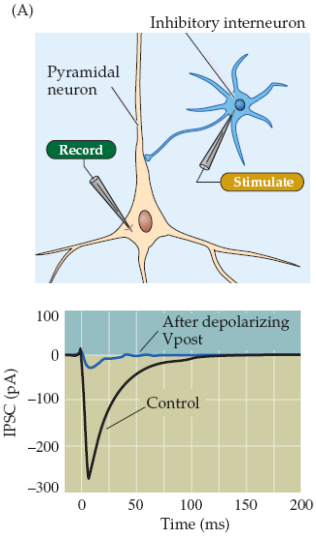


Unconventional Neurotransmitters

- **Unconventional**
  - Not stored and released in the "classical" fashion
  - Often associated with retrograde signaling
- **Endocannabinoids**
- **Nitric Oxide**

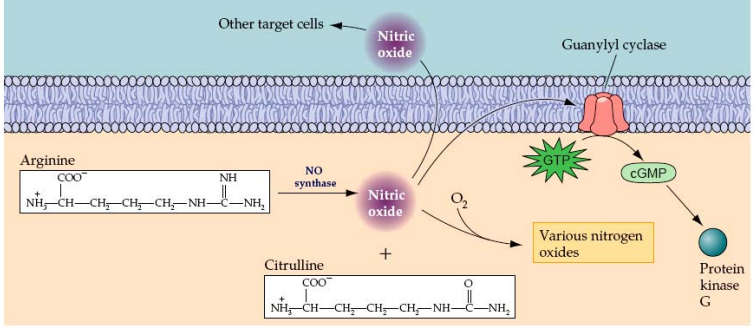
Endocannabinoids

- **Synthesis**
  - Unsaturated fatty acid with polar head groups
  - Produced by enzymatic degradation of membrane lipids
  - Degradation
    - They are hydrolyzed by the enzyme fatty acid hydrolase (FAAH)
- **Release**
  - Diffuse through the postsynaptic membrane to reach cannabinoid receptors on other nearby cells
- **Removal**
  - Action is terminated by carrier-mediated transport of these signals back into the postsynaptic neuron
- **Receptors**
  - CB1 and CB2
  - CB1 → CNS (hippocampus, cerebellum)
    - G-protein coupled
  - Inhibit communication between postsynaptic target cells and their presynaptic inputs
  - Inhibit the amount of GABA released → ↓inhibition



Nitric Oxide (NO)

- **NO is a gas**
  - Can permeate the plasma membrane
  - Travel through the extracellular medium and act within nearby cells
    - Diffusing a few tens of micrometers
    - Coordinating the activities of multiple cells in a very localized region
    - Mediating certain forms of synaptic plasticity
- **Synthesis**
  - Neuronal synthase is regulated by Ca2+ binding to the Ca2+ sensor protein calmodulin
- **NO decays spontaneously by reacting with oxygen**
- **Actions of NO are mediated within its cellular targets**
  - Regulates a variety of synapses that also employ conventional neurotransmitters
  - Presynaptic terminals that release glutamate are the best-studied target of NO in the CNS
- **NO may also be involved in some neurological diseases**



Επόμενη Διάλεξη …

Διάλεξη 7

Νευροανατομία (Neuroanatomy)