Neurotransmitter Systems

Introduction

The dominant messengers between neurons are the neurotransmitters. A neurotransmitter system is defined by a specific neurotransmitter.

- Includes the molecular machinery responsible for neurotransmitter synthesis, vesicular packaging, reuptake and degradation, and transmitter action.
- Neurotransmitter systems are usually named after the neurotransmitter ending with the suffix *-ergic*.

Studying Neurotransmitter Systems

In order to be a neurotransmitter, the molecule must:

- Be synthesized and stored in the presynaptic neuron.
- Be released by the presynaptic neuron upon stimulation.
- Produce a response in the postsynaptic cell when applied experimentally.

Localization

- Immunocytochemistry
  - Labeled antibodies directed toward specific neurotransmitters
- In Situ Hybridization
  - Labeled complementary mRNA directed toward specific neurotransmitter transcripts

Receptors

- Generally, no two neurotransmitters bind to the same receptor.
  - However, one neurotransmitter can bind to many different receptors.
- Neuropharmacological Analysis of receptors.
  - Selective drugs reveal subtypes of receptors
- Ligand Binding Methods
  - Many drugs can be used to analyze receptors before a neurotransmitter is identified.
- Molecular Analysis
  - Modern methods for analyzing protein molecules led to the recognition of neurotransmitter-gated ion channels and G-protein coupled receptors.
  - Many different polypeptides serve as subunits of functional receptors.

Neurotransmitter Chemistry

- Most neurons seem to release a single amino acid or amine neurotransmitter.
- Many peptide containing neurons release a peptide and an amino acid or amine.

Cholinergic Neurons

Acetylcholine

- Acetylcholine (Ach) is the neurotransmitter of skeletal neuromuscular junctions and is synthesized in all the motor neurons of the spinal cord and brainstem.
- Choline acetyltransferase (ChAT) is manufactured in the cell body and transported to the axon terminal.
- Choline is taken up by axon terminals by a Na^+ linked choline co-transporter.
- The acetyl of Acetyl CoA is joined to choline by ChAT to form acetylcholine (Ach)

$$\text{AcetylCoA + Choline} \xrightarrow{\text{Choline acetyltransferase}} \text{Acetylcholine}$$

- Availability of choline is a rate limiting step.
- Acetylcholine (Ach) is then moved into a vesicle by an Ach transporter.

Catecholaminergic Neurons

Catecholamines

- The catecholaimes include dopamine, norepinephrine, and epinephrine which are neurotransmitters found in regions of the nervous system involved in regulation of movement, mood, attention, and visceral function.
- Catecholamines are synthesized from tyrosine:

$$\begin{aligned}
\text{Tyrosine} &\xrightarrow{\text{Tyrosine hydroxylase}} \text{Dopa} \\
\text{Dopa} &\xrightarrow{\text{Dopa decarboxylase}} \text{Dopamine} \\
\text{Dopamine} &\xrightarrow{\text{Dopamine } \beta \text{ hydroxylase}} \text{Norepinephrine} \\
\text{Norepinephrine} &\xrightarrow{\text{Phentolamine N-methyltransferase}} \text{Epinephrine}
\end{aligned}$$

- The activity of tyrosine hydroxylase (TH) is the rate limiting step.
- Dopamine β hydroxylase (DBH) is found in synaptic vesicles.
- Phentolamine N-methyltransferase (PNMT) is found in the cytosol.
- Action of catecholamines is terminated by selective reuptake of neurotransmitter back into the axon terminal by Na^+ linked co-transporters. (Amphetamines and cocaine block the reuptake of catecholamines.)
    - Once taken up, catecholamines may be reloaded into synaptic vesicles or destroyed by monoamine oxidase (MAO).

Serotonergic Neurons

Serotonin

- Serotonin plays a role in brain systems that regulate mood, emotional behavior, and sleep.
- Serotonin is synthesized from tryptophan

$$\text{Tryptophan} \xrightarrow{\text{Tryptophan hydroxylase}} \text{5-Hydroxytryptophan}$$

$$\text{5-Hydroxytryptophan} \xrightarrow{\text{5-Hydroxytryptophan decarboxylase}} \text{5-Hydroxytryptamine}$$

- Synthesis of serotonin (5-HT) is limited by the availability of tryptophan. (Grains, meat, and dairy products are rich in tryptophan.)
- Serotonin is removed from the synaptic cleft by a specific reuptake transporter.

Amino Acidergic Neurons

Amino Acids

- Glutamate, glycine, and GABA are the most common neurotransmitters found in the central nervous system.
    - Glutamate is the major excitatory neurotransmitter in the CNS.
    - GABA is the major inhibitory neurotransmitter in the CNS.
- Glutamate and glycine are amino acids, but can be synthesized from glucose.
- In glutaminergic neurons, a glutamate transporter concentrates glutamate in the synaptic vesicles.
- GABA is synthesized from glutamate by glutamate decarboxylase

$$\text{Glutamate} \xrightarrow{\text{Glutamate decarboxylase}} \text{GABA}$$

- Action of the amino acids is terminated by selective reuptake of neurotransmitter back into the axon terminal by Na^+ linked co-transporters.
    - GABA is inactivated by GABA transaminase.

Purinergic Neurons

ATP

- ATP is likely a neurotransmitter that binds to purinergic receptors.

Cannabinergic Neurons

Endocannabinoids

- Endocannabinoids are retrograde lipid soluble messengers released from postsynaptic neurons to act on axon terminals.
- Bind to CB1 receptors and reduce opening of Ca^{2+} channels.

Neurotransmitter Gated Channels

A neurotransmitter gated channel is a protein that functions both as a channel and as a receptor, and is only about 11 nm long.

- Most channels are constructed as a pentamer of five protein subunits arranged to form a single pore.
    - The nicotinic acetylcholine receptor is representative of this structure.
- Some channels are constructed as a tetramer of four protein subunits arranged to form a single pore.
    - The glutamate gated channels are representative of this structure.

Amino Acid-Gated Channels

Glutamate-gated channels can have AMPA, NMDA, or Kainate receptors

Glutamate Gated AMPA Receptor Channels

- AMPA receptor channels are permeable to both Na^+ and K^+, and are not permeable to Ca^{2+}.
- At normal negative membrane potential the net effect is entry of Na^+ and depolarization.

Glutamate Gated NMDA Receptor Channels

- NMDA receptor channels are permeable to Ca^{2+}, Na^+, and K^+.
- However, inward ionic current is voltage dependent.
    - At normal negative membrane potential the channel becomes clogged with Mg^{2+} and prevents other ions from passing.
    - When the membrane is depolarized, (which usually follows activation of AMPA receptors), Mg^{2+} pops out of the pore allowing Ca^{2+} and Na^+ to enter the cell.
    - Postsynaptically Ca^{2+} can activate many enzymes, regulate the opening of a variety of channels, and affect gene expression.
- Ca^{2+} entry through NMDA Glutamate gated channels may cause the changes that lead to long term memory.
- AMPA receptor channels and NMDA receptor channels coexist at many synapses

GABA Gated $GABA_A$ Receptor Channels

- $GABA_A$ receptor channels are permeable to Cl^-.
- $GABA_A$ receptor channels also have binding sites for benzodiazepines, barbiturates, ethanol, and neurosteroids.
    - These substances enhance the action of GABA and increase the frequency or duration of Cl^- channel opening.

Glycine Gated Channels

- Glycine receptor channels are also permeable to Cl^-.

G-Protein Coupled Receptors

G-protein coupled receptors (GPCRs) are a single polypeptide containing 7 membrane spanning alpha helices.

- Two extracellular loops form the neurotransmitter binding site.
- Two intracellular loops bind to and activate G-proteins.
- More than 100 GPCRs have been described.

G-Proteins

- There are so named because they bind to guanosine triphosphate (GTP)
    - There are at least 20 types of G-proteins.
- Each G-protein has three subunits: α (alpha), β (beta), and γ (gamma).
    - In the resting state a GDP is bound to the Gα and the whole complex floats on the inner surface of the cell membrane.
    - If GDP bound G-protein bumps into the proper type of receptor and if the receptor has a neurotransmitter bound to it, the G-protein releases GDP and exchanges it for GTP.
    - The GTP bound G-protein splits into 2 parts: the Gα+GTP and the Gβγ.
    - Gα is an enzyme that eventually breaks down GTP to GDP.
    - The Gα+GTP and the Gβγ influence effector proteins.
    - The Gα+GDP and the Gβγ eventually come back together.

G-Protein Coupled Effector Systems

Shortcut Pathway – G-Protein to Ion Channel

- Muscarinic-2 receptor for acetylcholine (Ach)
    - Gβγ subunit migrates laterally along the membrane until they bind an appropriate K^+ channel and open it.
- $GABA_B$ for GABA
    - Gβγ subunit migrates laterally along the membrane until they bind an appropriate K^+ channel and open it.

Second Messenger Cascade G-Protein to Enzyme(s)

- Beta-1 receptor for norepinephrine (NE)
  - Activates stimulatory G-protein (Gs).
  - Gsα subunit + GTP migrates laterally along the membrane until meeting with and activating adenylyl cyclase.
  - Adenylyl cyclase converts ATP to cAMP.
  - cAMP activates protein kinase A.
  - Protein kinases phosphorylate proteins and changes their shape; here they phosphorylate and open Na^+ and Ca^{2+} channels.
- Alpha-2 receptor for norepinephrine (NE)
  - Activates inhibitory G-protein (Gi).
  - Giα subunit + GTP migrate laterally along the membrane until meeting with and inhibiting adenylyl cyclase.
  - No adenylyl cyclase to convert ATP to cAMP.
  - No cAMP to activate protein kinase A.
- Alpha-1 receptor for norepinephrine (NE)
  - Activates G-protein (G).
  - Gα subunit + GTP migrate laterally along the membrane until meeting with and activating phospholipase C (PLC).
  - PLC splits a membrane phospholipid phosphatidylinositol (PIP2) into diacylglycerol (DAG) and inositol triphosphate (IP3).
  - DAG (lipid soluble) activates protein kinase C which phosphorylates and closes K^+ channels.
  - IP3 (water soluble) diffuses into cytosol and bins to IP3 gated Ca^{2+} channels in the smooth ER and other organelles. These organelles store Ca^{2+} and when the Ca^{2+} channels open Ca^{2+} diffuses into the cytosol.