Neurotransmitter Systems I
Identification and Distribution

Reading:
BCP Chapter 6
Neurotransmitter Systems

Normal function of the human brain requires an orderly set of chemical reactions. Some of the most important chemical reactions are those associated with synaptic transmission.

Identification and Distribution
- Criteria
- Localization/function

Receptors
- Subtypes
- Activation

Neurochemistry
- Synthesis
- Cycling
Neurotransmitter systems begin with neurotransmitters. In addition to the molecule itself, a neurotransmitter system includes all the molecular machinery responsible for transmitter synthesis, vesicular packaging, reuptake and degradation, and pre/postsynaptic action.

Neurotransmitters
- 1st - acetylcholine (ACh; Loewi 1920s)
- currently 30-100

Nomenclature
- -ergic, neurons that use a particular neurotransmitter (e.g., cholinergic, glutamatergic)
The brain contains a nearly uncountable myriad of different chemicals. Over the years, scientists have established certain criteria that must be met for a molecule to considered a neurotransmitter.

Criteria:
• Synthesized and stored in presynaptic neuron
• Released by presynaptic axon terminal and produces an effect on postsynaptic cell
• When applied experimentally onto a cell, produces a postsynaptic response that mimics the response produced by natural release
• Mechanism for removal
Initial identification of a molecule as a possible neurotransmitter is often based on a hunch (e.g., a certain molecule is concentrated in a given section of brain tissue). Many methods are available to confirm that a molecule is in fact, localized in, and synthesized by, particular neurons. Two of the most important techniques used today are: immunocytochemistry; and in situ hybridization.

**Immunocytochemistry**
The method known as in situ hybridization is also useful for confirming that a cell stores and synthesizes a particular protein or peptide. In this method, a synthetic probe is constructed containing a sequence of nucleotides complementary to a strand of known mRNA. If the probe is labeled (e.g., radioactivity, fluorescent dye), then the location of cells containing the mRNA-bound probe will be revealed.

**in situ hybridization**

*Four-color fluorescence* in situ hybridization on a *Drosophila* embryo. A late blastoderm stage embryo was probed with four different RNA probes. (Kosman and Bier)
Transmitter Release

Transmitter candidate: synthesized and localized in terminal … is it released upon stimulation?

Stimulate (electricity) a specific set of \textit{in vivo} or \textit{in vitro} axons, take samples of fluids bathing their synaptic targets (PNS)

Stimulate (high [K+]) a diverse mixture of intermingled cells in an \textit{in vitro} slice (with and without Ca$^{2+}$ ions present), collect and measure all chemicals released (CNS)

Stimulate (light; optogenetics) a specific population of neurons that have been genetically modified to express light-sensitive ion channels, collect and measure chemical output
Synaptic Mimicry

Transmitter candidate: synthesized, localized, released … but is it the active molecule or a byproduct?

Qualifying condition: direct application of the molecule onto the postsynaptic cell must evoke the same response as that produced by activation of the presynaptic neuron.

Two methods of application:
• microiontophoresis
• pressure ejection

Use microelectrode to measure effects on postsynaptic membrane potential
After a neurotransmitter molecule binds to a receptor molecule, it must be removed quickly from the cleft to allow for the postsynaptic membrane to respond anew to subsequent inputs. Thus, removal mechanisms are required.

Removal of neurotransmitter can happen through one or more processes:
• degradation (1)
• reuptake (2)
• or diffusion (3)

Removal processes can be discerned/assessed by direct application of antagonists (blockers).
Their exact number is unknown, but more than 100 chemicals have been identified as neurotransmitters.

Neurotransmitters can be classified as small (about the size of an amino acid) or large.

Major neurotransmitters include:

- **Acetylcholine**
- **Amino acids**
  - Glutamate (Glu)
  - Gamma-aminobutyric acid (GABA)
  - Glycine (Gly)
- **Biogenic amines**
  - Dopamine (DA)
  - Norepinephrine (NE)
  - Epinephrine
  - Serotonin
  - Histamine
- **Neuropeptides (large)**
  - Hypothalamus
  - Pituitary
  - Gut
Acetylcholine

**Acetylcholine** is used as a neurotransmitter in both the CNS and PNS.

In the CNS, the basal forebrain and the dorsal pontine area of the reticular formation are the major sources of ACh. Important roles include learning and memory, and arousal (sleep/wake).

In the PNS, acetylcholine is used at the neuro(skeletal)muscular junction (somatic nervous system), at the first-stage targets of the autonomic nervous system and the final target organs of the parasympathetic nervous system (rest-and-digest).
The amino acid neurotransmitters (glutamate, GABA and glycine) account for the vast majority of synaptic connections in the CNS.

**Glutamate**: primary excitatory neurotransmitter (produces EPSPs that increase the probability that a cell will fire an action potential). Because of its role in synaptic plasticity, glutamate plays a role in learning and memory.

**GABA, glycine**: inhibitory neurotransmitters (produce IPSPs that reduce neuronal excitability). GABA is more prevalent in cortex, whereas glycine predominates in brainstem and spinal cord. General functions: gain control; generation of precise spike timing.
Monoamines are divided into three main groups depending upon the amino acid from which they are derived (all have one amino group connected to an aromatic ring by a two-carbon chain).

Catecholamines are derived from the amino acid tyrosine, and include dopamine, norepinephrine (nor-) and epinephrine (adrenaline).

**Dopamine**: CNS; two sources
- substantia nigra (part of basal ganglia) – movement selection
- ventral tegmental area (reticular formation) – reward/motivation

**Norepinephrine**: CNS+PNS and **Epinephrine**: PNS
- CNS – locus coeruleus of the reticular formation – alertness; attention
- PNS – sympathetic nervous system target organs (fight-or-flight)
Indolamines are monoamine neurotransmitters derived from tryptophan. Serotonin is the most prevalent example (melatonin is another one).

Serotonin is found primarily in the gastrointestinal tract (motility and secretion), but also broadly distributed in the CNS.

In the CNS, serotonin is released by neurons located in the Raphe nuclei of the reticular formation. Serotonin regulates arousal, mood, appetite, and learning and memory.
Histamine is a monoamine neurotransmitter derived from histidine.

Histamine is found predominantly in tissue-resident mast cells (a type of white blood cell: immune/inflammatory function), but also in the CNS.

In the CNS, histamine is released by the tuberomamillary nucleus of the hypothalamus. Histamine regulates arousal, appetite and learning and memory.
Neuropeptides are small protein-like molecules (chains of 2-40 amino acids). At present, about 100 neuropeptides are known to be released; they are used in both the CNS and PNS.

Neuropeptides are stored in large secretory (dense-core) vesicles far from the presynaptic membrane. They are usually released with a small neurotransmitter under strong stimulation.

Different neuropeptides are involved in a wide range of brain functions, including analgesia, arousal, reward, appetite, metabolism, reproduction, social behaviors, mood, learning and memory.