Topic 4 - Neurotransmitters

1. Criteria and types
   - Located in presynaptic region (usually in vesicles).

2. Synthesis, release and re-uptake
3. Drug interactions and poisons
4. Disorders

Neurotransmitter vs. Neuromodulator??

Criteria for classification as a NT:

1. Located in presynaptic region (usually in vesicles).

Criteria for classification as a NT:

2. Released with activation or depolarization of the presynaptic terminal (Ca\(^{2+}\) dependent).

Criteria for classification as a NT:

3. Specific receptors must be present on the postsynaptic cell.

Types of Neurotransmitters -

Two major categories (based on size):
1. Small-molecule neurotransmitters
   - the amino acids, acetylcholine, purines and biogenic amines
2. Neuropeptides
1. Small-molecule neurotransmitters

Amino Acids –
- Glutamate (widespread) \( \text{excitatory} \)
- Asparate
- GABA (widespread) \( \text{inhibitory} \)
- Glycine

1. Small-molecule neurotransmitters

Biogenic Amines –
- Dopamine
- Norepinepherine
- Epinepherine
- Serotonin
- Histamine

1. Small-molecule neurotransmitters

Acetylcholine (ACh)
- neuro-muscular junctions
- 2 main R (nicotinic & muscarinic)
1. Small-molecule neurotransmitters

Purines -
- ATP
- Adenosine

2. Neuropeptides

Opioids
enkephalin
β-endorphin etc.

Posterior Pituitary
vasopressin
oxytocin

Pancreatic
neuropeptide Y

Tachykinins
substance P
neurokinin etc.

Glucagon-related
VIP
glucagon etc.

Other
somatostatin

A note on “-ergic”

e.g. “glutamatergic”
“GABAergic”
“Cholinergic” etc…
**Typical (but not only!) NT Effects**

1. **Fast Excitatory**  
   (ionotropic R)  
   e.g. PNS: ACh (nicotinic R)  
   CNS: Glutamate

2. **Fast Inhibitory**  
   (ionotropic R)  
   e.g. GABA  
   Glycine (spinal cord)

3. **Slow, modulatory**  
   (metabotropic R)  
   e.g. Biogenic amines  
   ACh (muscarinic R)  
   Neuropeptides
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Life Cycle of Neurotransmitter

1. Neurotransmitter is synthesized in cell body or terminal
2. Neurotransmitter is packaged into vesicles
3. Neurotransmitter is released when vesicles fuse
4. Neurotransmitter binds to and activates postsynaptic receptors
5. Neurotransmitter diffuses away and is metabolized and/or transported back into terminal


Neuronal Transport

- occurs in both directions
- allows delivery of organelles & macromolecules from cell body to axon terminal

Source: Lundy-Ekman, Neuroscience: Fundamentals for Rehabilitation, Saunders, 2002
Neuronal Transport


NT Production

1.2 - Enzymes for NT synthesis produced in soma & released from Golgi apparatus

3 - Slow axonal transport to presynaptic terminal

4 – NT substrates transported into terminal and assembled using enzymes from soma

5,6 - Packaged in vesicles (5) for release (6)

Source: Nolte, The Human Brain, Mosby, St. Louis, 2002

NT Production - Example: DA

- transport into synaptic vesicles often requires ATP

**Neurotransmitter Release**

- Ca**++** triggers link between membrane and vesicular docking proteins
- formation of fusion pore

Source: Haines, Fundamental Neuroscience, Churchill-Livingstone, 2002

**Vesicle membrane recycling**


**Neurotransmitter Removal**

NT must be removed from the synaptic cleft quickly…

- to prevent desensitization of postsynaptic cell to future signals
- to prevent damage to the postsynaptic cell
**Neurotransmitter Removal**

1. Reuptake into neighbouring astrocytes (GLU)
2. Reuptake into presynaptic terminal (DA, NE)
3. Enzymatic breakdown in synaptic cleft (ACh)

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**Drug Effects on Neurotransmitters**

- Synthesis $\uparrow/\downarrow$
- Release $R$
- Binding
Agonists and Antagonists -

**Agonist** - a drug that binds to a receptor and creates the same effect as a naturally occurring NT

**Antagonist** - a drug that prevents NT release of “clogs” receptors, blocking the effects of naturally occurring NT

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Neurotoxins

α - bungarotoxin

conotoxins

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Poisons Acting At NMJ (affecting ACh)

Botulism

nerve gas e.g. sarin

curare
Myasthenia Gravis (MG)

- affects an estimate of 50 to 125 individuals in a million
- autoimmune – production of antibodies to nicotinic R (Acetylcholine)
- # ACh R reduced to 10-30% of normal levels
- disrupts transmission at the neuromuscular junction
- reduced folding of post-synaptic membrane

Neuromuscular Junction

Myasthenia Gravis

Normal Myasthenia Gravis

Muscle fibre

Axon terminal

Junctional folds

ACh receptors

ACh release

AChE breaks down ACh in the synaptic cleft

Myasthenia Gravis – Treatments

Patient with MG

One minute after AChE Inhib.
**Lambert-Eaton Syndrome**

- also affects transmission at NMJ
- antibodies versus Ca2+ channels
- muscle weakness

**Other Disorders in Neurotransmitter Metabolism**

- Parkinson’s Disease – death of neurons producing dopamine in the substantia nigra
- Schizophrenia – hyperdopaminergic hypothesis
- Alzheimer’s disease – disruptions in normal function of cholinergic neurons