Neurotransmitters
Objectives

1. Outline the criteria that need to be met before a molecule can be classified as “neurotransmitter”

2. Identify the major neurotransmitter types


4. Identify some clinical disorders that can arise as a result of disruption of neurotransmitter metabolism.
What are the Neurotransmitter Criteria?
Neurotransmitter Criteria

• Chemical messengers must meet 4 criteria to be considered neurotransmitters:
  1. It is synthesized by a neuron.
  2. It is present in the presynaptic terminal and is released in amounts sufficient to exert a defined action on a postsynaptic neuron or effector organ.
  3. When given as a drug, it mimics the action of naturally occurring transmitter in the body exactly.
  4. A specific mechanism exists for removing it.
Chemical Synaptic Transmission

- 4 steps:
  1. Synthesis of transmitter
  2. Storage & release of transmitter
  3. Interaction of transmitter with receptor in postsynaptic membrane
  4. Removal of transmitter from synaptic cleft.
Classifications of Neurotransmitters

- Once divided into 2 classes:
  1. Cholinergic - use acetylcholine (ACh)
  2. Adrenergic - use norepinephrine or epinephrine

- Now we know there are many more types

- 2 large classes:
  1. Small molecules
Manufacture of Large Molecule Transmitters

- Peptides
  - Examples: substance P, somatostatin, leu-enkephalin, met-enkephalin, vasoactive intestinal polypeptide (VIP), bombesin

- Peptide synthesized in rough endoplasmic reticulum
- Packaged in Golgi apparatus
  - Transported down axon to presynaptic ending of the axon terminal
    - secretory vesicles transported down axon by orthograde axonal transport
Manufacture of Small Molecule Transmitters

- Small molecule transmitters (amino acids and amines)
  - Examples of amino acid neurotransmitters: gamma-amino butyric acid (GABA), glutamate (Glu), glycine (Gly)
  - Examples of amine neurotransmitters: acetylcholine (ACh), dopamine (DA), epinephrine, histamine, norepinephrine (NE), serotonin (5-HT)

Occurs in axon terminal
Precursor molecule is transformed by synthetic enzyme into neurotransmitter molecule
Neurotransmitter molecules are gathered by transporter molecules and packaged in synaptic vesicles.
Small Molecule Neurotransmitters

• Nine such substances are accepted as neurotransmitters:
  – 8 are amines
  – The non amine is ATP
• Synthesis of these neurotransmitters is catalyzed by enzymes
• Acetylcholine - perhaps the most important small molecule transmitter
# AMINO ACIDS

<table>
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<tr>
<th>#</th>
<th>NAME</th>
<th>SITE OF SECRETION</th>
<th>ACTION</th>
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<tbody>
<tr>
<td>1</td>
<td>GABA</td>
<td>Cerebral cortex, cerebellum, basal ganglia, spinal cord and retina</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>2</td>
<td>Glycine</td>
<td>Forebrain, brainstem, spinal cord and retina</td>
<td>Inhibitory</td>
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<td>3</td>
<td>Glutamate</td>
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<td>4</td>
<td>Aspartate</td>
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<td>ACTION</td>
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<tr>
<td>1</td>
<td>Noradrenaline</td>
<td>Postganglionic adrenergic sympathetic nerve endings, cerebral cortex, hypothalamus, basal ganglia, brainstem and spinal cord</td>
<td>Excitatory &amp; Inhibitory</td>
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<tr>
<td>2</td>
<td>Adrenaline</td>
<td>Hypothalamus, thalamus and spinal cord</td>
<td>Excitatory &amp; Inhibitory</td>
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<td>3</td>
<td>Dopamine</td>
<td>Basal ganglia, hypothalamus, limbic system, neo cortex, retina and synaptic ganglia.</td>
<td>Inhibitory</td>
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<tr>
<td>4</td>
<td>Serotonin</td>
<td>Hypothalamus, limbic system, cerebellum, spinal cord, retina, GI tract, lungs and platelets.</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>5</td>
<td>Histamine</td>
<td>Hypothalamus, cerebral cortex, GI tract and mast cells</td>
<td>Excitatory</td>
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<tr>
<td>#</td>
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<td>SITE OF SECRITION</td>
<td>ACTION</td>
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<td>-----------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>1</td>
<td>Nitric oxide</td>
<td>Many parts of CNS, neuromuscular junction and GI tract</td>
<td>Excitatory</td>
</tr>
<tr>
<td>2</td>
<td>Acetylcholine</td>
<td>Pre ganglionic parasympathetic nerve endings</td>
<td>Excitatory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post ganglionic parasympathetic nerve endings</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Pre ganglionic sympathetic nerve endings</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Post ganglionic sympathetic cholinergic nerve endings</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Neuromuscular junction, cerebral cortex, hypothalamus, basal ganglia, thalamus and retina.</td>
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</table>
Neurotransmitter receptors

- Once released, the neurotransmitter molecules diffuse across the synaptic cleft.

- When they “arrive” at the postsynaptic membrane, they bind to neurotransmitter receptors.
Two main classes of receptors:

1. Ligand-gated ion channels

Transmitter molecules bind on the outside, cause the channel to open and become permeable to either sodium, potassium or chloride.

2. G-protein-coupled receptors

G-protein-coupled receptors have slower, longer-lasting and diverse postsynaptic effects. They can have effects that change an entire cell’s metabolism or an enzyme that activates an internal metabolic change inside the cell activate cAMP activate cellular genes: forms more receptor proteins activate protein kinase: decrease the number of proteins
Excitatory neurotransmitters:

Neuron - Action potential
Muscle - Contraction
Gland - secretion

CNS

Depolarization of Post-synaptic membrane (EPSP)

Eg: Glutamate
    Ach
    Asparatic acid
Inhibitory neurotransmitters:

- Reduce or block activity of postsynaptic cell.
- CNS
- Hyperpolarization of Post-synaptic membrane (IPSP)

Eg: Glycine, GABA, Dopamine
In neuroscience, an excitatory postsynaptic potential (EPSP) is a postsynaptic potential that makes the postsynaptic neuron more likely to fire an action potential. IPSP is an inhibitory postsynaptic potential
Acetylcholine

- Acetylcholine is the transmitter used by motor neurons of the spinal cord
- Released at all vertebrate neuromuscular junctions
- Present in autonomic & parasympathetic neurons
- Used in many brain synapses
Acetylcholine (ACh)

1. Transmitter at **neuromuscular junction** and in the **CNS**
2. Plays important roles in **autonomic nervous system** (part of the PNS that maintains homeostasis in the body)
3. Synthesized from
   1. choline (an essential dietary component) and
   2. acetate (donated by acetyl coenzyme A – synthesized from glucose by choline acetyltransferase (CAT))
4. Degraded extracellularly by **acetylcholinesterase** (AChE)
5. **Choline** is transported back into presynaptic terminals
Acetylcholine neurotransmission

1. Acetylcholine synthesized from choline and acetyl CoA by choline acetyltransferase (ChAT)
2. ACh loaded into synaptic vesicles by VAcChT
3. Released ACh broken down by acetylcholinesterase (notable difference from other neuro-transmitters discussed so far)
4. Choline taken up by presynaptic terminal as precursor to further ACh synthesis
Cholinergic Neurons

• Use acetylcholine as a neurotransmitter
• 2 types of receptors
  – Nicotinic receptor - transmitter-gated ion channel
  – Muscarinic receptor - G-protein-coupled receptor using short-cut pathway to close potassium channel

• Removal
  – degraded by acetylcholine esterase (AChE)
  – AChE is the target of many nerve gases and insecticides
• Indicated effects:
  – excitation or inhibition of target organs
  – essential in movement of muscles
  – important in learning and memory
Biogenic Amine Transmitters

- The rest of the 8 amines
- Includes serotonin & the catecholamines (dopamine, epinephrine & norepinephrine)
- All catecholamines are synthesized from the amino acid, tyrosine.
  - share a common biosynthetic pathway
  - pathway uses 5 enzymes
Dopaminergic Neurons

- Use dopamine, norepinephrine, or epinephrine as neurotransmitters
- Synthesis pathway:
  - Tyrosine hydroxylase (TH) makes tyrosine into dopa
  - Dopa decarboxylase makes dopa into dopamine (DA)
- If the neuron is dopaminergic, the pathway stops here
Noradrenergic & Adrenergic Neurons

• The synthesis pathway continues from dopamine:
  – Dopamine beta-hydroxylase (DBH) makes dopamine into norepinephrine

• If the neuron is noradrenergic, the pathway stops here,

• Or the pathway can continue:
  – Phentolamine N-methyltransferase (PNMT) makes norepinephrine into epinephrine

• If the neuron is adrenergic, the pathway goes the whole way to this point
Summary of Catecholamine Synthesis

- All catecholamines have a catechol nucleus & a 3,4-dihydroxylated benzene ring
- The 1st enzyme, tyrosine hydroxylase, converts tyrosine to L-dihydroxyphenylalanine (L-DOPA)
- L-DOPA is a precursor for all catecholamines
- The 2nd step converts L-DOPA to dopamine & CO$_2$
- The 3rd step converts dopamine to norepinephrine
- The 4th step converts norepinephrine to epinephrine
Catecholamine Synthesis

Tyrosine → DOPA → Dopamine → Norepinephrine → Epinephrine

- Tyrosine hydroxylase: tyrosine → dihydrobiopterin + H₂O
- Tetrahydrobiopterin + O₂: dihydrobiopterin + S-adenosylmethionine → S-adenosylhomocysteine
- S-adenosylhomocysteine: phenylethanolamine N-methyltransferase
- Dopamine β-hydroxylase: Dopamine → Norepinephrine
- Norepinephrine: H₂O → Epinephrine
Norepinephrine

- In the CNS, norepinephrine is used by neurons of the locus coeruleus, a nucleus of the brainstem with complex modulatory functions
- In the peripheral nervous system, norepinephrine is the transmitter of the sympathetic nervous system
- Norepinephrine can then be converted to epinephrine
• Involved in sleep, wakefulness, attention and feeding behavior
• At least two kinds of NE receptors: NE alpha and NE beta

• Indicated effects:
  – primarily excitatory
  – appears to modulate Fear/flight/fight system

• Too much: over arousal, mania
• Too little: under arousal, depression
  – Chemically extremely similar to Dopamine, serotonin
Epinephrine (adrenalin)

- Present in brain at lower levels than NE
- Adrenal production is part of stress response
- Adrenal gland is the primary source
- Formed by PNMT (phenylethanolamine-n-methyltransferase)
  - Endogenous cortisol increases PNMT
Dopamine -

• DOPA is converted so rapidly into Dopamine that DOPA levels are negligible in the brain

• Rate of synthesis is regulated by
  – Catecholamine acting as inhibitor of TH
  – Availability of BH$_4$ (Tetrahydrobiopterin)
  – Presynaptic DA receptors
  – Amount of activity in nigrostriatal pathway
Metabolism

- In primates and human
  - HVA major metabolite
- Accumulation of HVA in brain or CSF used as index of function of dopaminergic neurons
Removal of Catecholamines

- All three catecholamines are removed by selective reuptake by the presynaptic axon terminals
- They are either reused or degraded by monoamine oxidase (MAO)
- Amphetamines and cocaine block the reuptake of catecholamines, thereby prolonging their synaptic action
Dopamine & Norepinephrine
**Close Cousins?**

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Molecular Structure</th>
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<tbody>
<tr>
<td>Amphetamine</td>
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<td>Methamphetamine</td>
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<td>Ephedrine</td>
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<td>Pseudoephedrine</td>
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<tr>
<td>3,4-Methylenedioxyamphetamine (MDA, love drug)</td>
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<tr>
<td>3,4-Methylenedioxyamphetamine (MDMA, Ecstasy, E)</td>
<td><img src="image" alt="MDMA structure" /></td>
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<tr>
<td>3,4-Methylenedioxyethylamphetamine (MDEA)</td>
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<tr>
<td>3,4-Methylenedioxyphenyl-2-butanamine (MBDB), analog of MDMA (non-hallucinogenic; CNS stimulant)</td>
<td><img src="image" alt="MBDB structure" /></td>
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</table>
Serotonin

- Derived from the amino acid, tryptophan
- Belongs to a group of compounds called indoles
- Serotonergic neurons are found in the brainstem
- Involved in regulating attention & other complex functions
Tryptophan hydroxylase (Rate limiting)

5-Hydroxytryptophan

5-Hydroxytryptamine

In diet. Active CNS transport

5-OH Tryptophan decarboxylase

5-Hydroxyindole Acetic Acid

5-Hydroxyindole Acetaldehyde

5-Hydroxytryptamine
Serotonergic Neurons

• Use serotonin (5-HT) as a neurotransmitter

• Because tryptophan comes from the diet, serotonergic neurons can be quickly affected by dietary deficiencies in tryptophan

• Removal:
  – Selective reuptake by the presynaptic axon terminals
  – Either reused or degraded by MAO
• **Excitatory & Inhibitory**

• Control the mood of the person and important in sleep

• Also present in GIT, platelets & limbic system

• Receptors: 1A, 1B, 1D, 2A, 2C, 3, 4, 5, 6, 7

• Low levels are associated with depression and other psychiatric disorders

• May be involved in migraine
Serootonin
Histamine

- Acts as a local hormone (autocoid)
- Involved in control of blood vessels, inflammatory response, etc.
- Also acts as a neurotransmitter in invertebrates
Amino Acid Transmitters

• Unlike acetylcholine & biogenic amines, these are universal parts of cells
• Glycine & glutamate are common parts of proteins
• GABA
  – is synthesized from glutamate
  – is a major inhibitory transmitter at many sites in brain
• Common amino acids act as transmitters in some neurons, not in others
  – shows that the presence of a substance doesn’t make it a transmitter
Excitatory amino acid transporter 2 (EAAT2)
Whereas glutamate is the principal excitatory neurotransmitter, GABA is the principal inhibitory neurotransmitter in the brain.

A typical GABA presynaptic terminal
**GABA synthesis**

Biosynthetic enzyme: \( \text{GAD}_{65}, \text{GAD}_{67} \)

\( \text{GAD}_{65} \) more highly enriched in nerve terminals, therefore might be more important for neurotransmission

GAD requires pyridoxal phosphate as cofactor (might be regulated by GABA and ATP)
Summary of GABA synthesis, release, reuptake, degradation

1. GABA is formed by removal of carboxyl group of glutamate, by the enzyme GAD
2. GABA is packaged into synaptic vesicles by VIAAT and released by depolarization
3. GABA may be taken up by nerve terminal by GAT proteins for repackaging into synaptic vesicles
4. GABA may be taken up by glial cells, where it undergoes reconversion to glutamate (amine group is transferred to α-ketoglutarate, generating glutamate and succinic semialdehyde)
5. Glutamate is transported back into nerve terminal, where it serves as precursor for new GABA synthesis

Figure 7-8. The GABA shunt. This metabolic pathway traces the synthesis and degradation of the neurotransmitter pool of GABA. GAD, glutamic acid decarboxylase; GABA-T, GABA transaminase; SSADH, succinic semialdehyde dehydrogenase.
GABA\textsubscript{A} receptors belong to the ‘ligand-gated ion channel superfamily’, which also includes nicotinic acetylcholine receptors, glycine receptors, and the 5-HT\textsubscript{3} serotonin receptor.
Glycine neurotransmission

**vesicular inhibitory amino acid transporter, VIAAT**
Summary of Glycine synthesis, release, reuptake, degradation

1. Glycine is synthesized from serine by SHMT
2. Glycine is packaged into synaptic vesicles by VIAAT (same transporter as for GABA)
3. Glycine is removed from synapse by GLYT1 (glial, for clearance from synapse), and GLYT2 (neuronal, for re-uptake and packaging).
4. Glycine is cleaved by the glycine cleavage system

GCS: glycine cleavage system
Consists of 4 proteins
- T protein
- L protein
- H protein
- P protein
ATP & Adenosine

• ATP & degradation products such adenosine can serve as neurotransmitters at some synapses
Transmitter Binding

• The same transmitter can bind different receptors, resulting in different actions.
• Receptor binding determines the effect, not the transmitter itself.
• In related animals, each type of transmitter binds to a family of receptors and is associated with certain functions.
• Example: acetylcholine = synaptic excitation at neuromuscular junctions in vertebrates
Transmitter Binding