MCDB 4777/5777
Molecular Neurobiology
Lecture 14- biogenic amines and modulation
2.1 Describe how information from action potentials is transmitted from neuron to neuron, and ways that this can be disrupted.

b. Compare the processes by which small molecule, biogenic amine, and peptide neurotransmitters are synthesized, released, and removed

c. Compare the functions of small molecule and peptide neurotransmitters, and the effects of disrupting these molecules

d. Distinguish between ionotropic and metabotropic receptors and the mechanisms by which they influence neuronal signaling
Synthesis and removal of the major small molecule neurotransmitters…
Glycine

What are the amine transmitters? How synthesized? How removed?

How are they pharmacologically important?

Related drugs and diseases?
Psychosis- fundamental mental derangement characterized by defective or lost contact with reality- can include hallucinations, paranoia, delusions, disconnected thought

Psychotropic- drugs that alter behavior, mood, perception

Neuroleptics- group of antipsychotics that can cause indifference to stimuli by blocking dopamine receptors

Affective disorder- mental disorder characterized by dramatic changes or extremes of mood. Affective disorders may include manic (elevated, expansive, or irritable mood with hyperactivity, pressured speech, and inflated self-esteem) or depressive (dejected mood with disinterest in life, sleep disturbance, agitation, and feelings of worthlessness or guilt) episodes, and often combinations of the two. Persons with an affective disorder may or may not have psychotic symptoms such as delusions, hallucinations, or other loss of contact with reality.
6.1 Examples of small-molecule and peptide neurotransmitters. (Part 3)

**SMALL-MOLECULE NEUROTRANSMITTERS**

**BIOGENIC AMINES**

**CATECHOLAMINES**

- **Dopamine**
  \[
  \text{HO} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{NH}_3
  \]
  \[
  \text{OH} \quad \text{OH}
  \]

- **Norepinephrine**
  \[
  \text{HO} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{NH}_3
  \]
  \[
  \text{OH} \quad \text{OH}
  \]

- **Epinephrine**
  \[
  \text{HO} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{NH}_2
  \]
  \[
  \text{OH} \quad \text{CH}_3
  \]
6.1 Examples of small-molecule and peptide neurotransmitters. (Part 4)

SMALL-MOLECULE NEUROTRANSMITTERS

BIOGENIC AMINES

INDOLEAMINE

Serotonin (5-HT)

IMIDAZOLEAMINE

Histamine
Lecture 14

Dopamine, norepinephrine, histamine and serotonin have widespread effects on modulating the overall excitation state of the brain. What method would you hypothesize was the most likely to evolve, to deliver these NT widely?

A. manufacture the NT in one or two nuclei (localized areas), project axons all over the brain

B. manufacture the NT in quite a few nuclei scattered around the brain, project axons locally around these nuclei

C. manufacture the NT in most neurons of the brain
6.4 The general architecture of ligand-gated receptors. (Part 2)

<table>
<thead>
<tr>
<th>Receptor</th>
<th>AMPA</th>
<th>NMDA</th>
<th>Kainate</th>
<th>GABA</th>
<th>Glycine</th>
<th>nACh</th>
<th>Serotonin</th>
<th>Purines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subunits</td>
<td>Glu R1</td>
<td>NR1</td>
<td>Glu R5</td>
<td>α₁⁻⁷</td>
<td>α₁</td>
<td>α₂⁻⁹</td>
<td>5-HT₃</td>
<td>P₂ₓ₁</td>
</tr>
<tr>
<td></td>
<td>Glu R2</td>
<td>NR2A</td>
<td>Glu R6</td>
<td>β₁⁻⁴</td>
<td>α₂</td>
<td>β₁⁻⁴</td>
<td>P₂ₓ₂</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glu R3</td>
<td>NR2B</td>
<td>Glu R7</td>
<td>γ₁⁻⁴</td>
<td>α₃</td>
<td>γ</td>
<td>P₂ₓ₃</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glu R4</td>
<td>NR2C</td>
<td>KA1</td>
<td>δ</td>
<td>α₄</td>
<td>δ</td>
<td>P₂ₓ₄</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NR2D</td>
<td>KA2</td>
<td></td>
<td>ε</td>
<td>β</td>
<td></td>
<td>P₂ₓ₅</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P₂ₓ₆</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P₂ₓ₇</td>
<td></td>
</tr>
</tbody>
</table>

*NEUROSCIENCE, Third Edition, Figure 6.4 (Part 2) © 2004 Sinauer Associates, Inc.*
6.5 Structure and function of metabotropic receptors. (Part 2)

<table>
<thead>
<tr>
<th>Receptor class</th>
<th>Glutamate</th>
<th>GABA&lt;sub&gt;B&lt;/sub&gt;</th>
<th>Dopamine</th>
<th>NE, Epi</th>
<th>Histamine</th>
<th>Serotonin</th>
<th>Purines</th>
<th>Muscarinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td></td>
<td>GABA&lt;sub&gt;B&lt;/sub&gt; R1</td>
<td>D1&lt;sub&gt;A&lt;/sub&gt;</td>
<td>α1</td>
<td>H1</td>
<td>5-HT 1</td>
<td>A type</td>
<td>M1</td>
</tr>
<tr>
<td>mGlu R1</td>
<td></td>
<td>GABA&lt;sub&gt;B&lt;/sub&gt; R2</td>
<td>D1&lt;sub&gt;B&lt;/sub&gt;</td>
<td>α2</td>
<td>H2</td>
<td>5-HT 2</td>
<td>A1</td>
<td>M2</td>
</tr>
<tr>
<td>mGlu R5</td>
<td></td>
<td></td>
<td>D2</td>
<td>β1</td>
<td>H3</td>
<td>5-HT 3</td>
<td>A2a</td>
<td>M3</td>
</tr>
<tr>
<td>Class II</td>
<td></td>
<td></td>
<td>D3</td>
<td>β2</td>
<td>H3</td>
<td>5-HT 4</td>
<td>A2b</td>
<td>M4</td>
</tr>
<tr>
<td>mGlu R2</td>
<td></td>
<td></td>
<td>D4</td>
<td>β3</td>
<td></td>
<td>5-HT 5</td>
<td>A3</td>
<td>M5</td>
</tr>
<tr>
<td>mGlu R3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-HT 6</td>
<td>P type</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-HT 7</td>
<td>P2x</td>
<td></td>
</tr>
<tr>
<td>mGlu R4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2y</td>
<td></td>
</tr>
<tr>
<td>mGlu R6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2z</td>
<td></td>
</tr>
<tr>
<td>mGlu R7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2t</td>
<td></td>
</tr>
<tr>
<td>mGlu R8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2u</td>
<td></td>
</tr>
</tbody>
</table>
6.10 The biosynthetic pathway for the catecholamine neurotransmitters.

Tyrosine

**Tyrosine hydroxylase**

Dihydroxyphenylalanine (DOPA)

**DOPA decarboxylase**

Dopamine

**Dopamine-β hydroxylase**

Norepinephrine

**Phenylethanolamine N-methyltransferase**

Epinephrine
6.11 Distribution of neurons & projections containing catecholamine neurotransmitters. (Part 1)

(A) Dopamine

- Cerebral cortex
- Corpus callosum
- To striatum

Substantia nigra and ventral tegmental area

- Thalamus
- Cerebellum
- To spinal cord

NEUROSCIENCE, Third Edition, Figure 6.11 (Part 1) © 2004 Sinauer Associates, Inc.
~100,000 dopaminergic nigral neurons

~85,000,000,000 neurons in whole nervous system
~16,000,000,000 in cortex

Tyrosine Hydroxylase- Sagittal Mouse Brain

Cortex

Striatum

SN
Amine release and removal

Figure 16.21 Dopaminergic synapse. The synthetic step from tyrosine to DOPA is blocked by $\alpha$-methyl-p-tyrosine (AMPT) – a competitive inhibitor of tyrosine hydroxylase. The step from DOPA to dopamine (DA) is blocked by carbidopa, which inhibits DOPA decarboxylase. The sequestration of DA into vesicles is blocked by reserpine and tetrabenazine. Monoamine oxidase (MAO) (believed to be bound to the exterior of mitochondria) converts free DA to dihydroxyphenylacetic acid (DOPAC). MAO is inhibited by pargyline (a B-type MAO inhibitor) and iproniazid (both an A- and a B-type MAO inhibitor). The release of DA into the synaptic cleft is potentiated by amphetamine (probably mainly because of its effect on reuptake). Once in the cleft DA is exposed to both COMT and MAO. COMT converts DA to 3-methoxytyramine (MT) and MAO converts MT to homovanillic acid (HVA). Amphetamine and benzotropine block the reuptake of DA back into the presynaptic terminal; reserpine and tetrabenazine block resequstration once DA gets back into the terminal. Apomorphine is a DA agonist at both post- and presynaptic sites. Perphenazine and haloperidol are antagonists at the postsynaptic membrane. Tropolone blocks the postsynaptic action of COMT.
Abnormal Behavior Associated with a Point Mutation in the Structural Gene for Monoamine Oxidase A

H. G. Brunner,* M. Nelen, X. O. Breakefield, H. H. Ropers, B. A. van Oost

Genetic and metabolic studies have been done on a large kindred in which several males are affected by a syndrome of borderline mental retardation and abnormal behavior. The types of behavior that occurred include impulsive aggression, arson, attempted rape, and exhibitionism. Analysis of 24-hour urine samples indicated markedly disturbed monoamine metabolism. This syndrome was associated with a complete and selective deficiency of enzymatic activity of monoamine oxidase A (MAOA). In each of five affected males, a point mutation was identified in the eighth exon of the MAOA structural gene, which changes a glutamine to a termination codon. Thus, isolated complete MAOA deficiency in this family is associated with a recognizable behavioral phenotype that includes disturbed regulation of impulsive aggression.
Role of Genotype in the Cycle of Violence in Maltreated Children

Avshalom Caspi,1,2 Joseph McClay,1 Terrie E. Moffitt,1,2* Jonathan Mill,1 Judy Martin,3 Ian W. Craig,1 Alan Taylor,1 Richie Poulton3

We studied a large sample of male children from birth to adulthood to determine why some children who are maltreated grow up to develop antisocial behavior, whereas others do not. A functional polymorphism in the gene encoding the neurotransmitter–metabolizing enzyme monoamine oxidase A (MAOA) was found to moderate the effect of maltreatment. Maltreated children with a genotype conferring high levels of MAOA expression were less likely to develop antisocial problems. These findings may partly explain why not all victims of maltreatment grow up to victimize others, and they provide epidemiological evidence that genotypes can moderate children's sensitivity to environmental insults.
6.5 Structure and function of metabotropic receptors. (Part 2)

<table>
<thead>
<tr>
<th>Receptor class</th>
<th>Glutamate</th>
<th>GABA$_B$</th>
<th>Dopamine</th>
<th>NE, Epi</th>
<th>Histamine</th>
<th>Serotonin</th>
<th>Purines</th>
<th>Muscarinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>GABA$_B$ R1</td>
<td>D1$_A$</td>
<td>$\alpha$1</td>
<td>H1</td>
<td>5-HT 1</td>
<td>A type</td>
<td>M1</td>
<td></td>
</tr>
<tr>
<td>mGlu R1</td>
<td>GABA$_B$ R2</td>
<td>D1$_B$</td>
<td>$\alpha$2</td>
<td>H2</td>
<td>5-HT 2</td>
<td>A1</td>
<td>M2</td>
<td></td>
</tr>
<tr>
<td>mGlu R5</td>
<td></td>
<td>D2</td>
<td>$\beta$1</td>
<td>H3</td>
<td>5-HT 3</td>
<td>A2a</td>
<td>M3</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td></td>
<td>D3</td>
<td>$\beta$2</td>
<td></td>
<td>5-HT 4</td>
<td>A2b</td>
<td>M4</td>
<td></td>
</tr>
<tr>
<td>mGlu R2</td>
<td></td>
<td>D4</td>
<td>$\beta$3</td>
<td></td>
<td>5-HT 5</td>
<td>A3</td>
<td>M5</td>
<td></td>
</tr>
<tr>
<td>mGlu R3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-HT 6</td>
<td>P type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-HT 7</td>
<td>P2x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGlu R4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGlu R6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2z</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGlu R7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2t</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGlu R8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2u</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The reason why 1000x more seroquel than benperidol is needed to treat psychosis is:

A. receptors bind seroquel more tightly  
B. receptors bind seroquel more weakly  
C. receptors have a more sensitive sensor for benperidol  
D. receptors have a less sensitive sensor for benperidol
**Figure 1** The clinical antipsychotic doses \(^{27,33,34}\) correlate with the antipsychotic dissociation constants in Table 1. The deviations for chlorpromazine and thioridazine disappear when the spinal fluid concentrations of the antipsychotic drugs are considered (Figure 2).
Figure 16.21 Dopaminergic synapse. The synthetic step from tyrosine to DOPA is blocked by α-methyl-p-tyrosine (AMPT) – a competitive inhibitor of tyrosine hydroxylase. The step from DOPA to dopamine (DA) is blocked by carbidopa, which inhibits DOPA decarboxylase. The sequestration of DA into vesicles is blocked by reserpine and tetrabenazine. Monoamine oxidase (MAO) (believed to be bound to the exterior of mitochondria) converts free DA to dihydroxyphenylacetic acid (DOPAC). MAO is inhibited by pargyline (a B-type MAO inhibitor) and iproniazid (both an A- and a B-type MAO inhibitor). The release of DA into the synaptic cleft is potentiated by amphetamine (probably mainly because of its effect on reuptake). Once in the cleft DA is exposed to both COMT and MAO. COMT converts DA to 3-methoxytyramine (MT) and MAO converts MT to homovanillic acid (HVA). Amphetamine and benzotropine block the reuptake of DA back into the presynaptic terminal; reserpine and tetrabenazine block resequestration once DA gets back into the terminal. Apomorphine is a DA agonist at both post- and presynaptic sites. Perphenazine and haloperidol are antagonists at the postsynaptic membrane. Tropolone blocks the postsynaptic action of COMT.
• cocaine

• Primary mechanism believed to be blockage of DA reuptake
Dopamine likely exerts many of its effects on behavior through…

a) Regulating the excitability of a select group of neurons in the midbrain

b) Binding to a transporter responsible for uptake of dopamine as well as other biogenic amines

c) Interaction with metabotropic receptors present on many neurons in the brain

d) Binding to monoamine oxidase
6.11 Distribution of neurons & projections containing catecholamine neurotransmitters. (Part 3)

(C) Epinephrine

- Cerebral cortex
- Corpus callosum
- Thalamus
- Hypothalamus
- Pons
- Medulla
- To spinal cord

Medullary epinephrine neurons
• Methamphetamine- *n*-methyl-*1*-phenyl-propan-*2*-amine

• Release of DA, NE, 5-HT (more pronounced than amphetamine); also DA and NE reuptake inhibition

• Amphetamine- *1*-phenylpropan-*2*-amine

• Release of DA, NE, 5-HT (high doses); also DA and NE reuptake inhibition

• Indications- ADHD, chronic fatigue syndrome, narcolepsy
Biogenic amine transport and antidepressants

- Tricyclics (amitriptyline shown)
- NE and Serotonin reuptake inhibitors
- First used to treat clinical depression in the 1950s
6.13 Synthesis of histamine and serotonin.

(A) Histidine

Histidine decarboxylase → CO₂

Histamine

(B) Tryptophan

O₂ → Tryptophan-5-hydroxylase

5-Hydroxytryptophan

Aromatic L-amino acid decarboxylase → CO₂

Serotonin (5-HT)
6.12 (B) Distribution of neurons and their projections containing serotonin.
Biogenic amine transport and antidepressants

- Tricyclics (amitriptyline shown)
- NE and Serotonin reuptake inhibitors
- First used to treat clinical depression in the 1950s

- Fluoxetine hydrochloride (Prozac)
- Selective Serotonin reuptake Inhibitor (SSRI)
- Indications- clinical depression, OCD, panic disorder
Biogenic amine transport and recreational drugs

- MDMA 3,4-methylenedioxy-methamphetamine: 'Ecstasy'

- Serotonin release and reuptake inhibition, lesser effects on DA and NE reuptake
6.12 (A) Distribution of neurons and their projections containing histamine.

(A) Histamine

Cerebral cortex

Corpus callosum

Thalamus

Tuberomammillary nucleus of hypothalamus

Cerebellum

Pons

Medulla

To spinal cord
How do serotonin reuptake inhibitor antidepressants affect mood?

a) by allowing serotonin to generate more excitation

b) by allowing serotonin to generate more inhibition

c) by keeping the synapse near serotonin receptor reversal potential

d) the mechanism is not well understood
### 6.5 Structure and function of metabotropic receptors. (Part 2)

<table>
<thead>
<tr>
<th>Receptor class</th>
<th>Glutamate</th>
<th>GABA&lt;sub&gt;B&lt;/sub&gt;</th>
<th>Dopamine</th>
<th>NE, Epi</th>
<th>Histamine</th>
<th>Serotonin</th>
<th>Purines</th>
<th>Muscarinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>GABA&lt;sub&gt;B&lt;/sub&gt; R1</td>
<td>D1&lt;sub&gt;A&lt;/sub&gt;</td>
<td>α1</td>
<td>H1</td>
<td>5-HT 1</td>
<td>A type</td>
<td>M1</td>
<td></td>
</tr>
<tr>
<td>mGlu R1</td>
<td>GABA&lt;sub&gt;B&lt;/sub&gt; R2</td>
<td>D1&lt;sub&gt;B&lt;/sub&gt;</td>
<td>α2</td>
<td>H2</td>
<td>5-HT 2</td>
<td>A1</td>
<td>M2</td>
<td></td>
</tr>
<tr>
<td>mGlu R5</td>
<td></td>
<td>D2</td>
<td>β1</td>
<td>H3</td>
<td>5-HT 3</td>
<td>A2a</td>
<td>M3</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td></td>
<td>D3</td>
<td>β2</td>
<td>5-HT 4</td>
<td>A2b</td>
<td>M4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGlu R2</td>
<td></td>
<td>D4</td>
<td>β3</td>
<td>5-HT 5</td>
<td>A3</td>
<td>M5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGlu R3</td>
<td></td>
<td></td>
<td></td>
<td>5-HT 6</td>
<td>P type</td>
<td>M1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td></td>
<td></td>
<td></td>
<td>5-HT 7</td>
<td>P2x</td>
<td>M1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGlu R4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2y</td>
<td>M1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGlu R6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2z</td>
<td>M1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGlu R7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2t</td>
<td>M1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGlu R8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2u</td>
<td>M1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>