Neurotransmitters acting on G-protein coupled receptors

Part 1: Dopamine and Norepinephrine

BIOGENIC AMINES

Monoamines

Diamine

dopamine
norepinephrine
serotonin
histamine

Figure 3-16 Principles of Neurobiology (© Garland Science 2016)
Overview of Neurotransmitters and Their Receptors

Criteria for defining a neurotransmitter

1. Neurotransmitter present
2. Neurotransmitter released
3. Neurotransmitter receptors activated

### Classification of Neurotransmitters by Chemistry and Function

#### Table 3–2: Commonly used neurotransmitters

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Major uses in the vertebrate nervous system¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine (ACh)</td>
<td>motor neurons that excite muscle; ANS² neurons; CNS excitatory and modulatory neurons</td>
</tr>
<tr>
<td>Glutamate</td>
<td>most CNS excitatory neurons; most sensory neurons</td>
</tr>
<tr>
<td>GABA</td>
<td>most CNS inhibitory neurons</td>
</tr>
<tr>
<td>Glycine</td>
<td>some CNS inhibitory neurons (mostly in the brainstem and spinal cord)</td>
</tr>
<tr>
<td>Serotonin (5-HT)</td>
<td>CNS modulatory neurons</td>
</tr>
<tr>
<td>Dopamine</td>
<td>CNS modulatory neurons</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>CNS modulatory neurons; ANS² neurons</td>
</tr>
<tr>
<td>Histamine</td>
<td>CNS modulatory neurons</td>
</tr>
<tr>
<td>Neuropeptides</td>
<td>usually co-released from excitatory, inhibitory, or modulatory neurons; neurosecretory cells</td>
</tr>
</tbody>
</table>

¹ See text for variations in invertebrate nervous systems.

² ANS, autonomic nervous system; as will be discussed in more detail in Chapter 8, acetylcholine and norepinephrine are used in different subtypes of ANS neurons.

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**Excitatory, Inhibitory and Modulatory**
Classification of Neurotransmitters by the Type of Receptor they bind to

(A) Ionotropic or Ligand-gated ion channels
Fast on
Fast off

(B) Metabotropic or G-protein coupled receptors
Slow on
Slow off

Figure 3-22 Principles of Neurobiology (© Garland Science 2016)
The same NT can bind to both types of receptors but some NTs (Glycine, most biogenic amines and peptides) only bind to one type of receptor.

### Table 3–3: Ionotropic and metabotropic neurotransmitter receptors encoded by the human genome

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Ionotropic</th>
<th>Metabotropic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Name</td>
<td>Number of genes</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>nicotinic ACh receptor</td>
<td>16</td>
</tr>
<tr>
<td>Glutamate</td>
<td>NMDA receptor</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>AMPA receptor</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>others</td>
<td>7</td>
</tr>
<tr>
<td>GABA</td>
<td>GABA_A receptor</td>
<td>19</td>
</tr>
<tr>
<td>Glycine</td>
<td>glycine receptor</td>
<td>5</td>
</tr>
<tr>
<td>ATP</td>
<td>P2X receptor</td>
<td>7</td>
</tr>
<tr>
<td>Serotonin (5-HT)</td>
<td>5-HT_3 receptor</td>
<td>5</td>
</tr>
<tr>
<td>Dopamine</td>
<td>dopamine receptor</td>
<td>5</td>
</tr>
<tr>
<td>Norepinephrine (epinephrine)</td>
<td>a-adrenergic receptor</td>
<td>6</td>
</tr>
<tr>
<td>Histamine</td>
<td>histamine receptor</td>
<td>4</td>
</tr>
<tr>
<td>Adenosine</td>
<td>adenosine receptor</td>
<td>3</td>
</tr>
<tr>
<td>Neuropeptides</td>
<td>neuropeptide receptors</td>
<td>dozens</td>
</tr>
</tbody>
</table>

Abbreviations: GABA, y-aminobutyric acid; P2X receptor, ATP-gated ionotropic receptor; P2Y, ATP-gated metabotropic receptor; 5-HT, serotonin (5-hydroxytryptamine) receptor subtype #; ACh, acetylcholine; NMDA, N-methyl-D-aspartate; AMPA, 2-amino-3-hydroxy-5-methylisoxazol-4-proanoic acid.

Data from the IUPHAR (International Union of Basic and Clinical Pharmacology) database (www.iuphar-db.org).

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Table 3-3  Principles of Neurobiology  (© Garland Science 2016)
G-Protein-Coupled Receptors at a Glance
Wesley K. Kroeze, Douglas J. Sheffler and Bryan L. Roth

Agonists: light, peptides, neurotransmitters, amino acids, hormones, lipids and chemokines

~800 GPCR in the Human genome

© Journal of Cell Science 2003 (116, pp. 4867-4889)
Structural features that are common to all GPCRs

Figure 3-31a Principles of Neurobiology (© Garland Science 2016)
Temporal/spatial amplification of the signaling events triggered by activation of G-protein coupled receptors
Example of how activation of GPCRs leads to changes in ion channel opening kinetics

Figure 3-31c Principles of Neurobiology (© Garland Science 2016)
The time constant of activity for a G-protein depends on the function of the intrinsic GTPase activity in the α-subunit and on extrinsic factors such as GAPs and GEFs.

**Diagram:**
- **Upstream regulators**
  - GTPase
  - GAP
  - GEF
  - GTP
  - GDP
  - H₂O
- **GTPase Activating Proteins**
  - GTPase
- **Downstream effectors**
**TABLE OF DIFFERENT G PROTEINS AND MECHANISMS OF ACTION**

- **Gs** $\rightarrow \alpha_s$ activates Adenylate Cyclase (AC) $\rightarrow \uparrow$ cAMP

- **Gi** $\rightarrow \alpha_i$ inhibits Adenylate Cyclase (AC) $\rightarrow \downarrow$ cAMP

- **Gq** $\rightarrow \alpha_q$ activates Phospholipase C (PLC)
  $\uparrow$ DAG+IP3 $\rightarrow \uparrow$ Ca$^{2+}$

- **Go** $\rightarrow \alpha_o$ inhibits Adenylate Cyclase (AC) $\rightarrow \downarrow$ cAMP
  activates PLC$\beta$ $\rightarrow \uparrow$ DAG+IP3 $\rightarrow \uparrow$ Ca
  and has other functions in the cell

- **Gt (transducin)** $\rightarrow \alpha_t$ regulates cGMP-PDE
  ChTx +PTx sensitive

- $\beta\gamma$ are also functional but there are not specific for each G protein:
  stimulate AC types II and IV, stim. K and Ca channels, inhibit AC, stim. PLC$\beta$, PLA2 and PI3K

- Inhibited by Cholera toxin
- Inhibited by Pertussis toxin
Ion channels can be regulated by G-protein α or βγ subunits

GIRK = G protein-coupled inwardly-rectifying potassium channel
Example of a GPCR coupled to Gs

A-kinase anchor proteins (AKAPs), R regulatory subunit, C catalytic subunit of protein kinase A (PKA)
Chemical structure of Catecholamines: Dopamine, Norepinephrine, Epinephrine
Catecholamine Synthesis

TH, Phenylalanine hydroxylase and Tryptophan hydroxylase all require BH4 as co-factor and O2.

Aromatic Amino acid decarboxylase (AAAD) is encoded by the DDC gene. This enzyme decarboxylases other amino acids such as 5-hydroxy-tryptophan

Clinical relevance: L-DOPA (levodopa) is sometimes used to increase dopamine levels in the brain of patients with Parkinson’s disease. AAAD is not inhibited dopamine but TH is.
Catecholamine Synthesis

TYROSINE → Tyrosine hydroxylase (TH)
L-DOPA
DOPA decarboxylase (DDC)
DOPA → DOPAMINE → Dopamine-β-hydroxylase (DBH)
NOREPINEPHRINE → Phenylethanolamine-N-methyltransferase (PNMT)
EPINEPHRINE

BH4
Vitamin B6
Vitamin C
SAM
Catecholamine Synthesis and Release

Large neutral amino acid transporter (LNAAT) is the blood brain barrier transporter mediating the uptake of tyrosine, tryptophan, and L-DOPA to the brain.
Catecholamine Inactivation

MAO

COMT Catechol-o-methyl transferase

Monoamine oxidase

AR

ADH

3,4-Dihydroxyphenylglycol (DHPG)

3-Methoxy-4-hydroxyphenylglycol (MHPG)

3-Methoxy-4-hydroxymandelic acid

Vanillylmandelic acid (VMA)
Localization of dopaminergic neurons in the brain

Overactive in schizophrenia and drug abuse/gambling

Degenerates in Parkinson’s disease
Localization of catecholaminergic neurons in the brain

Please note that NE (a.k.a. noradrenaline) and E (a.k.a. adrenaline) are also released by the adrenal gland and NE is also used as the main NT in the sympathetic ANS!
Localization of catecholaminergic neurons in the rodent brain

Modified from Zigmond, 1999. Fig. 8.6
Critical step in synthesis:
Tyrosine + TH

Critical steps in termination
1. Reuptake mechanism
2. COMT and MAO
Monoamines have both post-synaptic and pre-synaptic receptors.

**Autoreceptors**  
Inhibit synthesis or release of MAs

Figure 12.10
MA release and interaction with both presynaptic and postsynaptic receptors.
### TABLE 12-3. PROPERTIES OF DOPAMINE RECEPTOR SUBTYPES

<table>
<thead>
<tr>
<th></th>
<th>D1</th>
<th>D5</th>
<th>D2S/D2L*</th>
<th>D3</th>
<th>D4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effector pathways</strong></td>
<td>▲cAMP</td>
<td>▲cAMP</td>
<td>▼cAMP</td>
<td>▼cAMP</td>
<td>▼cAMP</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>CP</td>
<td>Hi</td>
<td>CP</td>
<td>OT</td>
<td>FC</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>Hy</td>
<td>NA</td>
<td>Hy</td>
<td>MB</td>
</tr>
<tr>
<td></td>
<td>OT</td>
<td>OT</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** Caudate Putamen: CP; Nucleus Accumbens: NA; Olfactory Tubercle: OT; Hippocampus: Hi, Hypothalamus: Hy, Frontal cortex: FC; Midbrain: MB
Parkinson’s disease is caused by degeneration of dopaminergic neurons in the substantia nigra.

Given what you know of dopamine biosynthesis, metabolism, and physiology, oral doses of which of the following compounds would help patients increase dopamine levels and transmission in their brains?

A. Tyrosine  
B. Dopamine  
C. L-DOPA  
D. AAADC inhibitors  
E. VMAT inhibitors  
F. O-methyl-dopamine
If a patient with Parkinson’s disease consumes high amounts of food containing tyramine such as aged cheeses, smoked fish, chocolate, etc., how would the dose of L-DOPA need to be adjusted?

A. Increased
B. Decreased
C. No need to adjust

What side effects could happen if the patient takes too much L-DOPA?