Targets of Psychopharmacological Drug Action

(page 33 in syllabus)

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Individual Disclosure Statement

Faculty Editor / Presenter

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Learning Objectives

• To explore transporters as drug targets
• To explore G protein-linked receptors as drug targets
• To explore ligand-gated ion channels as drug targets
• To explore voltage-sensitive ion channels as drug targets
Transporters and G Protein-Linked Receptors as Targets of Psychopharmacological Drug Action
Major Targets of Psychopharmacologic Drug Action

12 transmembrane region transporter  
~ 30% of psychotropic drugs

7 transmembrane region G protein linked  
~ 30% of psychotropic drugs
Other Targets of Psychopharmacologic Drug Action

4 transmembrane region
ligand-gated ion channel
~ 20% of psychotropic
 drugs

6 transmembrane region
voltage-gated ion channel
~ 10% of psychotropic
drugs

enzyme
~ 10% of psychotropic
drugs
Targets of Psychopharmacological Drug Action

- Transporters
- G protein-linked receptors
- Ligand-gated ion channels
- Voltage-sensitive ion channels
- Enzymes
Presynaptic transporters are a primary mode of inactivation for which of the following?

1. Monoamines
2. Amino acid neurotransmitters such as GABA and glutamate
3. Neuropeptides
4. 1 and 2
5. 1, 2, and 3
Pretest Question 2

The vesicular monoamine transporter 2 (VMAT2) is utilized by which neurotransmitter?

1. Serotonin
2. Norepinephrine
3. Dopamine
4. 2 and 3
5. 1, 2, and 3
Monoamine Transporters

presynaptic neurons

VMAT\textsubscript{2}

SERT

NET

DAT

5HT

NE

DA
serotonin (5HT)

vesicles

proton pump

VMAT 2

ATPase

Na⁺

Cl⁻

Na⁺

Cl⁻

K⁺

K⁺

add fluoxetine
fluoxetine (Prozac)
Acetylcholine and Choline Transporters

presynaptic neuron

VACHT

ACh

choline transporter

ACh

choline
GABA Transporters

presynaptic neuron

VIAAT

GAT-1

GABA

GAT-2

GAT-3

GAT-4

glial cell
Glutamate Transporters

presynaptic neuron

VGlut1

Glu

EAAT

postsynaptic neuron

EAAT

glial cell

EAAT

Glu

glutamine
Targets of Psychopharmacological Drug Action

- Transporters
- G protein-linked receptors
- Ligand-gated ion channels
- Voltage-sensitive ion channels
- Enzymes
Pretest Question 3

An antagonist is the opposite of an agonist.

1. True
2. False
The Agonist Spectrum

agonist

partial agonist

antagonist

inverse agonist
No Agonist: Constitutive Activity
Full Agonist: Maximum Signal Transduction
"Silent" Antagonist: Back to Baseline, Constitutive Activity Only, Same as No Agonist
Partial Agonist: Partially Enhanced Signal Transduction
Pretest Question 4

A partial agonist can be a net agonist when neurotransmission is deficient but a net antagonist when neurotransmission is excessive.

1. True
2. False
FULL AGONIST —
light is at its brightest

PARTIAL AGONIST —
light is dimmed but still shining

NO AGONIST —
light is off
Inverse Agonist: Beyond Antagonism; Even the Constitutive Activity Is Blocked
Agonist Spectrum

- Agonist
- Partial agonist
- No agonist or silent antagonist
- Inverse agonist
Ion Channels and Enzymes as Targets of Psychopharmacological Drug Action
Targets of Psychopharmacological Drug Action

- Transporters
- G protein-linked receptors
- Ligand-gated ion channels
- Voltage-sensitive ion channels
- Enzymes
The Agonist Spectrum

- Agonist
- Partial agonist
- Antagonist
- Inverse agonist
Pretest Question 5

A receptor will stop responding to an agonist:
1. When the agonist stops binding to it
2. When the receptor becomes desensitized
3. When the receptor becomes inactivated
4. 1 and 3
5. 1, 2, and 3
Channel in resting state
Channel open
Channel closed
Channel desensitized
Channel inactivated
Opening, Desensitizing, and Inactivating of Ligand-Gated Ion Channels by Agonists

- **Resting state**
- **Open state** activated by acute agonist
- **Desensitized state** activated by prolonged agonist
- **Inactivated state** not immediately reversed by removal of agonist

**order of hours**
GABA A receptors

resting

agonist

GABA

open

Cl

benzodiazepine

positive allosteric modulation

open further
Benzodiazepines: Indirect Effect on GABA Neurotransmission
Targets of Psychopharmacological Drug Action

- Transporters
- G protein-linked receptors
- Ligand-gated ion channels
- Voltage-sensitive ion channels
- Enzymes
Pretest Question 6

When voltage-sensitive sodium channels are open and activated, the flow of sodium is:

1. Into the neuron
2. Out of the neuron
The Pore of a Voltage-Sensitive Ion Channel Has 6 Transmembrane Regions

outside the cell

inside the cell
The Loop Between Regions 5 and 6 is an Ionic Filter

Voltage-sensitive sodium channel (VSSC)

outside the cell

inside the cell

Voltage-sensitive calcium channel (VSCC)

Na+

Ca++
Four Subunits Combine to Form the Alpha Pore Subunit, or Channel, for Sodium of a VSSC (Voltage-Sensitive Sodium Channel)

outside the cell

inside the cell

pore inactivation

Outside the cell

$Na^+$

pore inactivation

Inside the cell
Structure of Voltage-Sensitive Sodium Channels (VSSCs)
Pretest Question 7

Which of the following has evidence that it binds the alpha subunit of voltage-sensitive sodium channels?

1. Gabapentin
2. Pregabalin
3. Lamotrigine
4. 1 and 2
5. 1, 2, and 3
Possible Binding Sites for Certain Mood Stabilizers on VSSCs

- lamotrigine
- carbamazepine
- oxcarbazepine
Pretest Question 8

The alpha-2 delta subunit of voltage-sensitive calcium channels is believed to help regulate opening and closing of the voltage-sensitive calcium channel.

1. True
2. False
VSCCs (Voltage-Sensitive Calcium Channels) Have Multiple Associated Regulatory Proteins
Opening a Presynaptic Voltage-Sensitive N or P/Q Calcium Channel Triggers Neurotransmitter Release

![Diagram of neurotransmitter release](image)
Structure of Voltage-Sensitive Calcium Channels (VSCCs)
Site of Action of Alpha-2 Delta Ligands as Selective Inhibitors of Presynaptic Voltage-Sensitive N and P/Q Calcium Channels

\[ \text{open} \quad \rightarrow \quad \text{closed} \]

= alpha-2 delta ligand
Molecular Action of Alpha-2 Delta Ligands
Pretest Question 9

Which of the following are involved in regulating neurotransmission via excitation-secretion coupling?

1. Voltage-sensitive sodium channels
2. Voltage-sensitive calcium channels
3. Both 1 and 2
4. Neither 1 nor 2
Nerve Impulse Propagation in Presynaptic Neuron: Serial Opening of VSSCs (Voltage-Sensitive Sodium Channels)

- reception
- integration
- chemical encoding
- electrical encoding
- signal propagation
- signal transduction
Presynaptic Release of Neurotransmitter by Excitation-Secretion Coupling: VSSCs, VSCCs, and Synaptic Vesicles

- reception
- integration
- chemical encoding
- electrical encoding
- signal propagation
- signal transduction
Synaptic Neurotransmission With Vesicular Release
Range of Synaptic Neurotransmission
Summary

- The major targets of psychopharmacologic drug action are transporters and G protein-linked receptors.

- Ion channels, both ligand gated and voltage sensitive, are also important targets of psychopharmacologic drug action.

- Enzymes also are the targets of some important psychopharmacological drugs.