Drugs, The Brain, and Behavior

John Nyby
Department of Biological Sciences
Lehigh University
What is a drug?
What is a drug?

Difficult to define
What is a drug?

Difficult to define

Know it when you see it
What is a drug?

Difficult to define

Know it when you see it

Neuroactive vs Non-Neuroactive drugs
What is a drug?

Difficult to define

Know it when you see it

Neuroactive vs Non-Neuroactive drugs

Two major categories of neuroactive drugs:
What is a drug?

Difficult to define

Know it when you see it

Neuroactive vs Non-Neuroactive drugs

Two major categories of neuroactive drugs:

Therapeutic Drugs
What is a drug?

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Neuroactive vs Non-Neuroactive drugs

Two major categories of neuroactive drugs:

Therapeutic Drugs

Recreational Drugs
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Two major categories of neuroactive drugs:

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  Recreational Drugs (Drugs of Abuse)
What is a drug?

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Neuroactive vs Non-Neuroactive drugs

Two major categories of neuroactive drugs:

Therapeutic Drugs

Recreational Drugs (Drugs of Abuse)

Both types of neuroactive drugs affect neural functioning and behavior
How does a drug affect behavior
How does a drug affect behavior

Neuroactive Drug
(Antidepressant)
How does a drug affect behavior

Neuroactive Drug

(Antidepressant)
How does a drug affect behavior

Neuroactive Drug
(Antidepressant)

Behavioral Outcome
(Capable of positive emotions)
How does a drug affect behavior

Different Levels at which drug effects in the brain can be studied

Neuroactive Drug
(Antidepressant)

Behavioral Outcome
(Capable of positive emotions)
How does a drug affect behavior

Different Levels at which drug effects in the brain can be studied

Molecular events

Neuroactive Drug (Antidepressant)

Behavioral Outcome (Capable of positive emotions)
How does a drug affect behavior

Neuroactive Drug (Antidepressant)

Behavioral Outcome (Capable of positive emotions)

Different Levels at which drug effects in the brain can be studied

Molecular events → Cellular Events
How does a drug affect behavior

Different Levels at which drug effects in the brain can be studied

- Molecular events
- Cellular Events
- Organismal Events

Neuroactive Drug (Antidepressant) → Behavioral Outcome (Capable of positive emotions)
“Good” Therapeutic Drugs vs “Bad” Addictive drugs
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No clear boundary!
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All “good” drugs have undesirable side effects
"Good" Therapeutic Drugs vs "Bad" Addictive drugs

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Many “good” drugs can be addictive (i.e. “bad”) and deadly under the right circumstances
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Many “good” drugs can be addictive (i.e. “bad”) and deadly under the right circumstances (i.e. prescription opiates)
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Two US Federal Agencies decide if a drug is good or bad
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A “bad” drug in the US can be a “good” drug in other countries.
Neuroactive Drugs Work by Altering Chemical Signaling in the Brain
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Two Classes of Chemical Signals in the brain
Neuroactive Drugs Work by Altering Chemical Signaling in the Brain

Two Classes of Chemical Signals in the brain

Neurotransmitters
Neuroactive Drugs Work by Altering Chemical Signaling in the Brain

Two Classes of Chemical Signals in the brain

- Neurotransmitters
- Neurohormones
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Two Ways a Drug Affects Neural Signaling
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Two Ways a Drug Affects Neural Signaling
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Two Classes of Chemical Signals in the brain
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- Neurohormones

Two Ways a Drug Affects Neural Signaling
- Agonist for chemical signal
- Antagonist for chemical signal

In order to understand drug action must have a good understanding of chemical signaling in brain
Neuronal communication
Neuronal communication
Three Ways that information is transmitted in a Neuron

- Dendrite
- Soma (cell body)
- Nucleus
- Axon terminal button
- Axon
- Myelin sheath
Neuronal communication

Three Ways that information is transmitted in a Neuron

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Synapse

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Neuronal communication

Three Ways that information is transmitted in a Neuron

- dendrite
- soma (cell body)
- nucleus
- axon
- myelin sheath

Synapse

Most neuroactive drugs act by altering synaptic transmission
Generalized Synapse (Major Drug Events)
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Most neurotransmitters are either AA, modified AA, or peptides
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Generalized Synapse (Major Drug Events)
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Peptide in vesicle
AA
AA Precursor
synthetic enzymes
degradative enzymes
inactive metabolites

NT
Synaptic Vesicle
 Neurotransmitter pump
release

NT in synapse
receptor binding

Presynaptic Membrane
Synapse
Postsynaptic Membrane
Generalized Synapse (Major Drug Events)

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Peptide in vesicle

AA

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inactive metabolites

NT

release

NT in synapse

receptor binding

opening ion channel
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Presynaptic Membrane

Synaptic Vesicle

Release

NT in synapse

NT in vesicle

Peptide

AA

AA Precursor

synthetic enzymes

Degradative enzymes

Neurotransmitter pump

inactive metabolites

Postsynaptic Membrane

autoreceptor

receptor binding

opening ion channel

EPSP or IPSP
Most neurotransmitters are either AA, modified AA, or peptides.
Generalized Synapse (Major Drug Events)

Most neurotransmitters are either AA, modified AA, or peptides.

- Peptide in vesicle
- AA
- AA Precursor
  - synthetic enzymes
  - degradative enzymes
- NT
- inactive metabolites
- Synaptic Vesicle
  - NT
  - Neurotransmitter pump
- release
- inhibits
- NT in synapse
- autoreceptor
- EPSP or IPSP
  - receptor binding
  - opening ion channel

Presynaptic Membrane
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Generalized Synapse (Major Drug Events)

Most neurotransmitters are either AA, modified AA, or peptides

- Peptide in vesicle
- AA Precursor
- Synaptic Vesicle
- NT in synapse
- Neurotransmitter pump or transporter
- Reuptake
- NS in synapse
- Inactive metabolites
- Degradative enzymes
- Synthesis enzymes
- Inactive products
- EPSP or IPSP
- Opening ion channel
- Receptor binding
- Release
- Inhibits
- Autoreceptor
- Postsynaptic Membrane
- Synapse
- Presynaptic Membrane
Generalized Synapse (Major Drug Events)

Most neurotransmitters are either AA, modified AA, or peptides

- Peptide in vesicle
- AA Precursor
  - synthetic enzymes
  - degradative enzymes
- Neurotransmitter pump
- NT in synapse
- NT in synapse inhibits autoreceptor
  - neurotransmitter pump or transporter
  - inactive products
  - degradative enzymes
  - inactive metabolites
- NT in synapse releases neurotransmitter pump or transporter
- EPSP or IPSP
  - receptor binding
  - opening ion channel
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Neurotransmitter Agonists

1. serve as precursors

Peptide in vesicle

Neurotransmitter Antagonists

NT in synapse

autoreceptor

NT in vesicle

AA

AA Precursor

synthetic enzymes

degradative enzymes

inactive metabolites

NT

Neurotransmitter pump

Reuptake

neurotransmitter pump or transporter

inactive products

diffusion

release

inhibits

Presynaptic Membrane

Synapse

Postsynaptic Membrane

NT in synapse

receptor binding

opening ion channel

EPSP or IPSP
Most neurotransmitters are either AA, modified AA, or peptides

### Neurotransmitter Agonists
1. serve as precursors
2. block degradative enzymes in cytoplasm

### Neurotransmitter Antagonists
- Peptide in vesicle
- AA
- AA Precursor
- synthetic enzymes
- degenerative enzymes
- Neurotransmitter pump
- Reuptake
- neurotransmitter pump or transporter
- inactive metabolites
- inactive products
- diffusion

- Synaptic Vesicle
- NT
- Synaptic membrane
- autoreceptor
- NT in synapse
- EPSP or IPSP
- receptor binding
- opening ion channel
Generalized Synapse (Major Drug Events)

Most neurotransmitters are either AA, modified AA, or peptides

Neurotransmitter Agonists

1. serve as precursors
2. block degradative enzymes in cytoplasm
3. facilitate release

Neurotransmitter Antagonists

Peptide in vesicle

AA

AA Precursor

synthetic enzymes

degradative enzymes

Neurotransmitter pump

inactive metabolites

in active products

diffusion

Presynaptic Membrane

Synapse

Postsynaptic Membrane

release

NT in synapse

NT in vesicle

NT in synapse

opening ion channel
Generalized Synapse (Major Drug Events)

Most neurotransmitters are either AA, modified AA, or peptides

Neurotransmitter Agonists
1. serve as precursors
2. block degradative enzymes in cytoplasm
3. facilitate release
4. activate receptors directly

Neurotransmitter Antagonists
- inhibit neurotransmitter pump or transporter
- degradative enzymes
- inactive products
- diffusion
**Generalized Synapse (Major Drug Events)**

Most neurotransmitters are either AA, modified AA, or peptides

**Neurotransmitter Agonists**

1. serve as precursors
2. block degradative enzymes in cytoplasm
3. facilitate release
4. activate receptors directly
5. Block reuptake

**Neurotransmitter Antagonists**

- Peptide in vesicle
- NT in synapse
- NT in synapse opening ion channel
- NT in synapse receptor binding

- AA in inactive metabolites
- Reuptake
- Neurotransmitter pump or transporter
- inactive products
- diffusion

- Synaptic Vesicle
- Synaptic pump
- degradative enzymes
- NT
- NT in synapse
- NT in synapse
- receptor binding
- opening ion channel
- EPSP or IPSP
Generalized Synapse (Major Drug Events)

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Neurotransmitter Agonists

1. serve as precursors
2. block degradative enzymes in cytoplasm
3. facilitate release
4. activate receptors directly
5. Block reuptake
6. Autoreceptor blocker

Neurotransmitter Antagonists

Reuptake

NT in synapse

opening ion channel

EPSP or IPSP

receptor binding

NT

Synaptic Vesicle

NT in synapse

NT

Synaptic Vesicle

NT

Peptide in vesicle

AA

Precursor

synthetic enzymes

degradative enzymes

NT in synapse

opening ion channel

EPSP or IPSP

receptor binding

NT

autoreceptor

NT

Presynaptic Membrane

Synapse

Postsynaptic Membrane

neurotransmitter pump or transporter

inactive products

diffusion

inactivating enzymes

degradative enzymes

inactive metabolites

inactivating enzymes

degradative enzymes

NT

inactive metabolites

NT

inactive products

diffusion

NT

inactivating enzymes

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Generalized Synapse (Major Drug Events)

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Neurotransmitter Agonists
1. serve as precursors
2. block degradative enzymes in cytoplasm
3. facilitate release
4. activate receptors directly
5. Block reuptake
6. Autoreceptor blocker
7. deactivate degradative enzymes in synapse

Neurotransmitter Antagonists

- serve as precursors
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### Neurotransmitter Agonists
1. serve as precursors
2. block degradative enzymes in cytoplasm
3. facilitate release
4. activate receptors directly
5. Block reuptake
6. Autoreceptor blocker
7. deactivate degradative enzymes in synapse
8. Open postsynaptic ion channels

### Neurotransmitter Antagonists
- Open postsynaptic ion channels
- deactivate degradative enzymes in synapse
- block reuptake
- Autoreceptor blocker
- deactivate degradative enzymes in synapse
- serve as precursors
- block degradative enzymes in cytoplasm
- facilitate release
Generalized Synapse (Major Drug Events)

Most neurotransmitters are either AA, modified AA, or peptides

Neurotransmitter Agonists

1. serve as precursors
2. block degradative enzymes in cytoplasm
3. facilitate release
4. activate receptors directly
5. Block reuptake
6. Autoreceptor blocker
7. deactivate degradative enzymes in synapse
8. Open postsynaptic ion channels

Neurotransmitter Antagonists

1. block synthetic enzymes

Diagram:

- Peptide in vesicle
- NT in synapse
- Synaptic Vesicle
- NT in synapse
- Autoreceptor
- Reuptake
- Neurotransmitter pump or transporter
- EPSP or IPSP
- receptor binding
- opening ion channel
- diffusion

- NT (Neurotransmitter)
- AA (Amino Acid)
- inactive metabolites
- inactive products
- degradative enzymes
- synthetic enzymes
- release
- inhibits
- receptor binding
Generalized Synapse (Major Drug Events)

Most neurotransmitters are either AA, modified AA, or peptides

**Neurotransmitter Agonists**

1. serve as precursors
2. block degradative enzymes in cytoplasm
3. facilitate release
4. activate receptors directly
5. Block reuptake
6. Autoreceptor blocker
7. deactivate degradative enzymes in synapse
8. Open postsynaptic ion channels

**Neurotransmitter Antagonists**

1. block synthetic enzymes
2. Block neurotransmitter pumps in vesicles
Generalized Synapse (Major Drug Events)

Most neurotransmitters are either AA, modified AA, or peptides

Neurotransmitter Agonists

1. serve as precursors
2. block degradative enzymes in cytoplasm
3. facilitate release
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5. Block reuptake
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7. deactivate degradative enzymes in synapse
8. Open postsynaptic ion channels

Neurotransmitter Antagonists

1. block synthetic enzymes
2. Block neurotransmitter pumps in vesicles
3. Block release (docking proteins)
Generalized Synapse (Major Drug Events)

Most neurotransmitters are either AA, modified AA, or peptides

Neurotransmitter Agonists
1. serve as precursors
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5. Ion Channel blockers
Why are Some Neuroactive Drugs Addictive?
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Hallmark of addiction is compulsive drug use
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Hallmark of addiction is compulsive drug use

Older Model of Addiction
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Hallmark of addiction is compulsive drug use.

Older Model of Addiction

Tolerance and Withdrawal
Why are Some Neuroactive Drugs Addictive?

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Tolerance and Withdrawal

Problem With Older Model
Why are Some Neuroactive Drugs Addictive?

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Older Model of Addiction
  Tolerance and Withdrawal
  Problem With Older Model

Newer Model of Addiction
Why are Some Neuroactive Drugs Addictive?

Hallmark of addiction is compulsive drug use

Older Model of Addiction
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  Problem With Older Model

Newer Model of Addiction

Final Common Reward Circuitry

Tegmentostriatal branch of Mesolimbic/Mesocortical Pathway

Nucleus Accumbens
Ventral Tegmental Area
Effects of Different Drugs of Abuse
# Effects of Different Drugs of Abuse

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<th>Type of Drug</th>
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All Drugs of Abuse cause dopamine release in the nucleus accumbens!! (either directly or indirectly)
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Any Questions?