

#### 4. Neurotransmitters and Psychopharmacology

- > Neurotransmitters and Neuromodulators
- > Principles of Psychopharmacology
- > Drug Actions
- > Agonists and Antagonists
- > The Classification of Psychoactive Drugs
- > Drug Abuse




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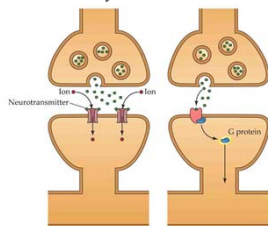
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#### Neurotransmitters and Neuromodulators

- > **Neurotransmitters**
  - endogenous, found in axon terminals, released by presynaptic neuron and bind to postsynaptic receptors
  - excitatory or inhibitory effects on postsynaptic neurons through receptor actions
    - glutamate = principal neurotransmitter with excitatory actions
    - GABA = principal neurotransmitter with inhibitory actions
    - Glycine also important neurotransmitter with inhibitory actions
- > **Neuromodulators**
  - modify the release of a neurotransmitter
  - adenosine modulates presynaptic dopamine release
  - peptides may have neuromodulatory actions




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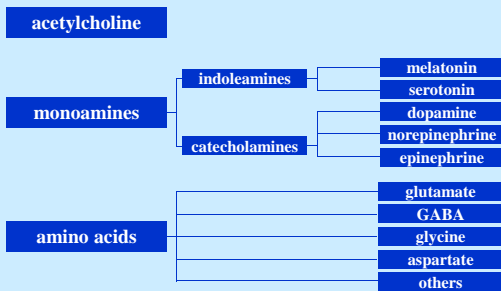
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#### Neurotransmitters and Neuromodulators

- > Classes of neurotransmitters and neuromodulators




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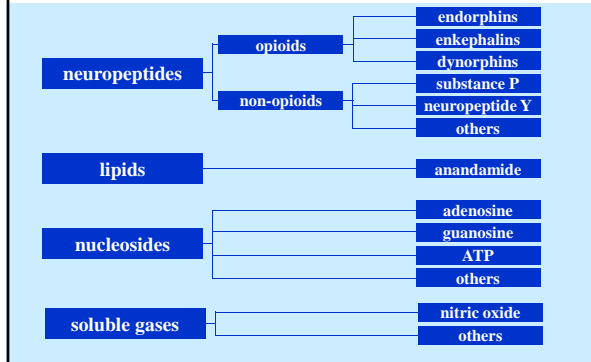
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## Neurotransmitters and Neuromodulators

### > Classes of neurotransmitters and neuromodulators




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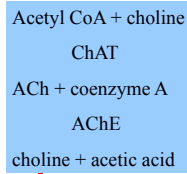
## Neurotransmitters and Neuromodulators

### acetylcholine



- released at all neuromuscular junctions
- released at ganglia of sympathetic nervous system, and at target organs of parasympathetic nervous system
- implicated in REM sleep, cognition and learning/memory

- synthesized from choline and acetyl CoA by choline acetyltransferase
- degraded by acetylcholinesterase (AChE)
- choline is reuptaken, and converted back to acetylcholine




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## Neurotransmitters and Neuromodulators

### acetylcholine

- nicotinic
- muscarinic

- nicotinic receptors:
  - ionotropic (rapid)
  - found in neuromuscular junctions, and CNS axoaxonic synapses
  - agonist = nicotine; antagonist = curare
- muscarinic receptors:
  - metabotropic (slower)
  - agonist = muscarine; antagonist = atropine

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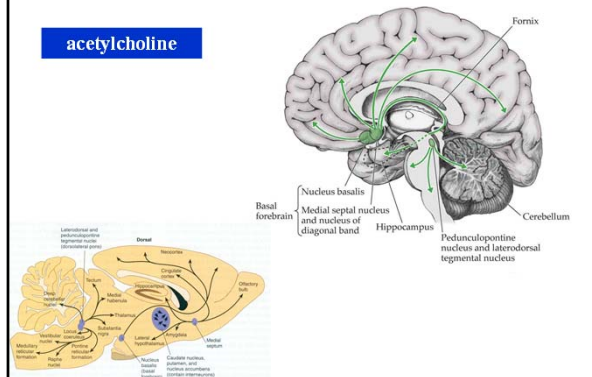
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## Neurotransmitters and Neuromodulators

### acetylcholine




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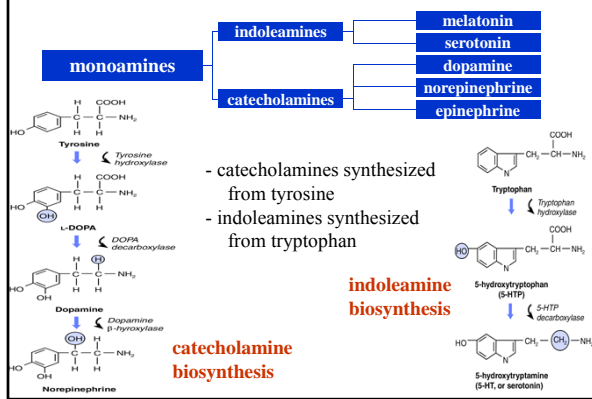
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## Neurotransmitters and Neuromodulators




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## Neurotransmitters and Neuromodulators

### monoamines

### catecholamines

- dopamine
- norepinephrine
- epinephrine

- > **norepinephrine (noradrenaline)**
  - released at target organs of sympathetic branch of ANS
  - released extensively throughout CNS from varicosities (beadlike swellings on axons) that do not form traditional synapses (neuromodulation)
  - locus coeruleus = cell body region of most extensive projection system
  - norepinephrine implicated in vigilance
- > **epinephrine (adrenaline)**
  - hormone released by adrenal medulla
  - minor neurotransmitter released in the brain




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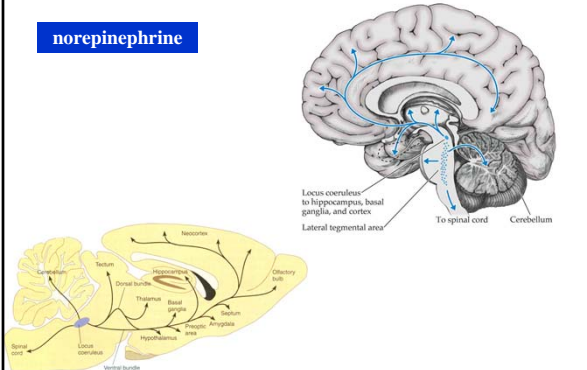
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## Neurotransmitters and Neuromodulators

### norepinephrine




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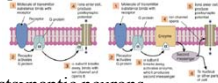
## Neurotransmitters and Neuromodulators

### norepinephrine

	$\alpha 1$
	$\alpha 2$
	$\beta 1$
	$\beta 2$
	$\beta 3$ (peripheral)

#### > norepinephrine

- $\alpha 1$ ,  $\alpha 2$ ,  $\beta 1$ , and  $\beta 2$  adrenoceptors all found in CNS and periphery
- $\beta 3$  adrenoceptors found only in periphery (especially adipose)
- all 5 types of adrenoceptors sensitive to EPI, as well as norEPI
- all 5 types are metabotropic, through G proteins
- $\alpha 2$  are CNS autoreceptors
- $\alpha 1$  = depolarization in CNS
- $\alpha 2$  = hyperpolarization in CNS
- $\beta 1$  and  $\beta 2$  = increase excitability of postsynaptic neurons
- behavioral effects of agonists are primarily excitatory




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## Neurotransmitters and Neuromodulators

### monoamines

### catecholamines

	dopamine
	norepinephrine
	epinephrine

- mesolimbic, mesocortical, and nigrostriatal systems are the major and most well-studied of the dopaminergic systems
- also infundibular
- dopamine implicated in movement, attention, learning, motivation

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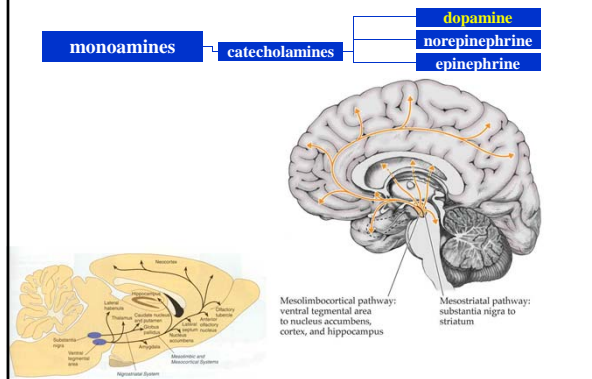
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## Neurotransmitters and Neuromodulators




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## Neurotransmitters and Neuromodulators

The diagram shows 'dopamine' leading to five receptor types: D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>, and D<sub>5</sub>. Below this, a molecular diagram illustrates the structure of a G-protein coupled receptor (GPCR) with various binding sites and signaling pathways.

- D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>, D<sub>5</sub> receptors  
all metabotropic
- D<sub>1</sub>, D<sub>5</sub>: all postsynaptic, and increase adenylate cyclase (AC)
- D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>: presynaptic and postsynaptic, and decrease AC

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## Neurotransmitters and Neuromodulators

The diagram shows 'monoamines' branching into 'indoleamines', which further branches into 'melatonin' and 'serotonin'. Below this, a microscopic image shows a neuron with varicosities.

- > **melatonin**
  - released from pineal gland
  - implicated in regulation of arousal, sleep cycles
- > **serotonin**
  - released from varicosities, rather than axon terminals
  - some varicosities (D system from dorsal raphe) do not appear to form synapses, and release is diffuse (neuromodulation)
  - some varicosities (M system from median raphe) form conventional synapses
  - implicated in regulation of mood, feeding, sleep, arousal, pain

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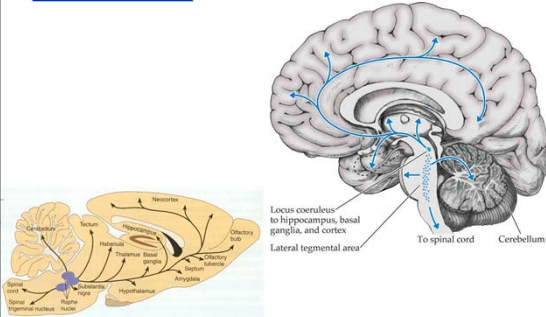
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## Neurotransmitters and Neuromodulators

monoamines

indoleamines

melatonin  
serotonin




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## Neurotransmitters and Neuromodulators

serotonin (5-HT)

- at least 14 different receptor subtypes
- 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>1D</sub>, 5-HT<sub>1E</sub>, 5-HT<sub>1F</sub>; all metabotropic
- 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, 5-HT<sub>2C</sub>; all metabotropic
- 5-HT<sub>3</sub>; ionotropic, Cl<sup>-</sup> channel, inhibitory input
- 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> are presynaptic autoreceptors

	5-HT <sub>1A</sub>
	5-HT <sub>1B</sub>
	5-HT <sub>1D</sub>
	5-HT <sub>1E</sub>
	5-HT <sub>1F</sub>
	5-HT <sub>2A</sub>
	5-HT <sub>2B</sub>
	5-HT <sub>2C</sub>
	5-HT <sub>3</sub>
	5-HT <sub>4</sub>
	5-HT <sub>5A</sub>
	5-HT <sub>5B</sub>
	5-HT <sub>6</sub>
	5-HT <sub>7</sub>

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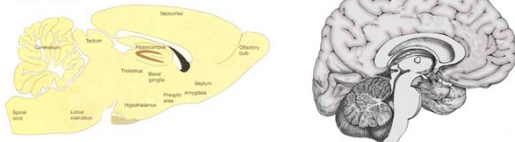
## Neurotransmitters and Neuromodulators

amino acids

glutamate  
GABA  
glycine  
aspartate  
others

### > glutamate

- glutamic acid
- excitatory effects through receptor actions on postsynaptic receptors
- ubiquitous distribution, the predominant excitatory neurotransmitter in CNS




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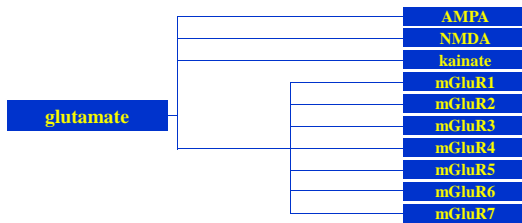
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## Neurotransmitters and Neuromodulators



- 4 major subtypes of glutamate receptors, w/ 7 types of mGluRs
- AMPA receptor; ionotropic (most abundant; Na<sup>+</sup> channel)
- NMDA receptor; ionotropic (Ca<sup>2+</sup> channel)
- kainate receptor; ionotropic (Na<sup>+</sup> channel)
- mGluR1- mGluR7; metabotropic (molecular switches and autoreceptors)

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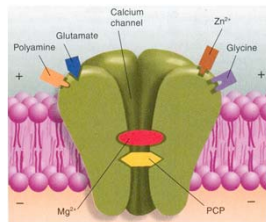
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## Neurotransmitters and Neuromodulators

### glutamate

- multiple binding sites on NMDA receptor
  - glutamate
  - glycine - co-binding required
  - Zn<sup>2+</sup> - binding decreases activity
  - polyamine (molecules that promote growth and development) - binding increases activity
  - Mg<sup>2+</sup> - blocks Ca<sup>2+</sup> conductance
- PCP - blocks Ca<sup>2+</sup> conductance




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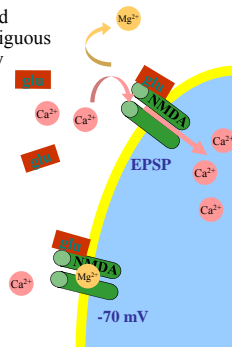
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## Neurotransmitters and Neuromodulators

### glutamate

- activation of NMDA receptor-associated ion channels is dependent upon contiguous presynaptic and postsynaptic activity
- At the resting potential, NMDA ion channels are blocked by Mg<sup>2+</sup>.
- If the postsynaptic membrane is sufficiently depolarized, Mg<sup>2+</sup> is expelled.

Therefore, NMDA receptors function as "coincidence detectors" for presynaptic neurotransmitter release, and postsynaptic depolarization.




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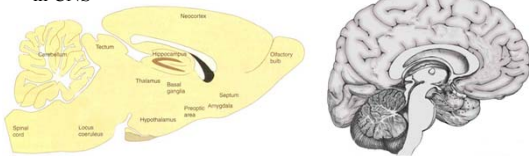
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## Neurotransmitters and Neuromodulators

amino acids

	glutamate
	GABA
	glycine
	aspartate
	others

- synthesized from glutamic acid by GAD
- inhibitory effects through receptor actions on postsynaptic receptors
- ubiquitous distribution, the predominant inhibitory neurotransmitter in CNS




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## Neurotransmitters and Neuromodulators

GABA

	GABA <sub>A</sub>
	GABA <sub>B</sub>

- 2 subtypes of GABA receptors
- GABA<sub>A</sub> receptor; ionotropic (Cl<sup>-</sup> channel, postsynaptic receptor)
- GABA<sub>B</sub> receptor; metabotropic (K<sup>+</sup> channel, G protein-coupled, postsynaptic receptor and presynaptic autoreceptor)
- problems with GABA neurotransmission implicated in epilepsy

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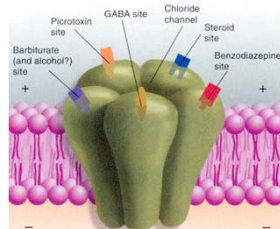
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## Neurotransmitters and Neuromodulators

GABA

- multiple binding sites on GABA<sub>A</sub> receptor
- GABA  
barbiturate  
benzodiazepine  
steroid  
picrotoxin




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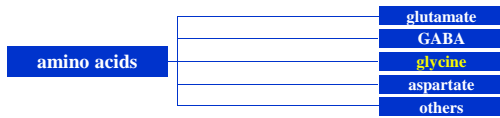
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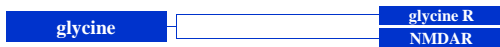
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## Neurotransmitters and Neuromodulators



- biosynthetic pathway not well characterized
- inhibitory effects throughout lower brain and spinal cord
- ionotropic glycine receptor (inhibitory, Cl<sup>-</sup> channel)
- also binds to NMDA receptor (excitatory)




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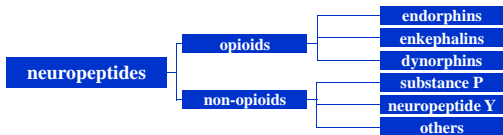
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## Neurotransmitters and Neuromodulators



- > **neuropeptides**
- short chains of amino acids, all cleavage products of larger proteins
  - manufactured in soma, and delivered to terminal by axonal transport
  - released from all parts of terminals, including extrasynaptic sites
  - extracellular peptides degraded by enzymes, no reuptake

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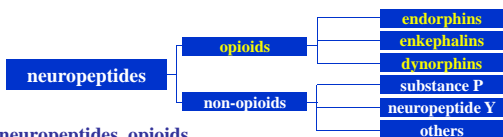
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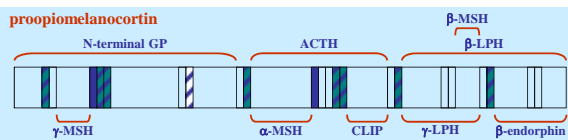
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## Neurotransmitters and Neuromodulators



- > **neuropeptides, opioids**
- opium, morphine, heroin, etc. act as counterfeit opioids
  - endogenous opioids = endorphins, enkephalins, dynorphins, N/OFQ
  - from POMC, proENK, proDYN
  - ubiquitous distribution




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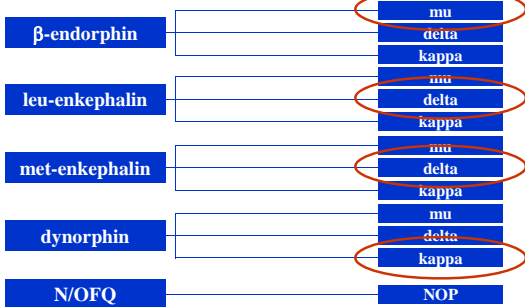
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### Neurotransmitters and Neuromodulators

#### opioid

- endogenous opioid receptors =  $\mu$ ,  $\delta$ ,  $\kappa$ , NOP




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### Neurotransmitters and Neuromodulators

#### opioid

> neuropeptides, opioids

- implicated in analgesia, socialization, feeding, behavioural reinforcement, inhibition of defense responses and anxiety responses, gastric motility
- often co-released with other neurotransmitters and other peptides, exerting regulatory functions

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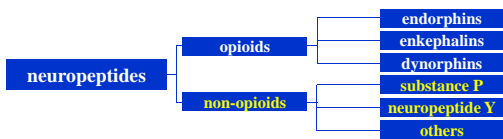
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### Neurotransmitters and Neuromodulators



- cholecystokinin (CCK)
- corticotropin releasing hormone
- neuropeptide Y
- substance P
- oxytocin

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### Neurotransmitters and Neuromodulators

lipids

anandamide

- anandamide, endogenous ligand for THC receptor
- 2-arachidonyl glycerol, another endogenous THC ligand

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### Neurotransmitters and Neuromodulators

nucleosides

adenosine

guanosine

ATP

others

- sugar + purine or pyrimidine base;  
e.g. adenosine – a purine nucleoside = ribose + adenine
- functions as a neuromodulator  
e.g. modulation of dopamine neurotransmission
- neurons that release adenosine have not been well characterized
  
- receptors: A1, A2a, A2b, A3

adenosine

A1

A2a

A2b

A3

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### Neurotransmitters and Neuromodulators

soluble gases

nitric oxide

others

- nitric oxide (NO), carbon monoxide (CO)
- NO more extensively studied than CO
- NO manufactured by at least 3 forms of nitric oxide synthase (NOS)
- NO is manufactured at many sites in cells, and diffuses immediately
- NO enters neighbouring cells, and activates second messenger mechanisms

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## Principles of Psychopharmacology

- > **Definition of a Drug**
  - an exogenous chemical not necessary for normal cellular function that significantly alters the function of certain cells when taken in fairly low doses
- > **Psychoactive Drugs**
  - drugs that alter mood, thought, or behavior
  - most used to manage/treat psychopathology
  - some used recreationally




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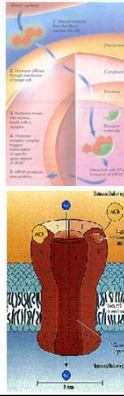
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## Principles of Psychopharmacology

- > **Effects of a Drug**
  - changes in physiological processes
    - e.g. opiates = analgesia, sedation, depressed cardiac respiratory and digestive function, hypotonia, pupillary constriction, euphoria
- > **Site of Action of a Drug**
  - locations at which molecules of drug interact with molecules located on or in cells
- > **Pharmacokinetics**
  - process by which drugs are absorbed, distributed, metabolized, and excreted




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## Principles of Psychopharmacology

- > **How Do Psychoactive Drugs Get into the Nervous System?**
  - routes of administration

**absorbed**  
 oral  
 sublingual  
 suppository  
 topical  
 skin patch

**injected**  
 subcutaneous  
 intra-muscular  
 intraperitoneal  
 intravenous

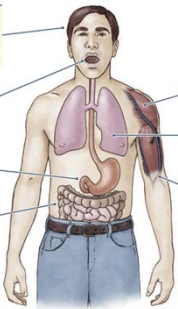
**inhaled**  
**spinal/intracranial**  
 intrathecal  
 intracerebroventricular  
 intraparenchymal

Injecting a drug directly into the brain allows it to act quickly in low doses because there are no barriers.

Taking drugs orally is the safest, easiest, and most convenient way to administer them.

Drugs that are weak acids pass from the stomach into the bloodstream.

Drugs that are weak bases pass from the intestines to the bloodstream.



Drugs injected into muscle encounter more barriers than do drugs that are inhaled.

Drugs inhaled into the lungs encounter few barriers en route to the brain.

Drugs injected into the bloodstream encounter the fewest barriers to the brain but must be hydrophilic.

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### Principles of Psychopharmacology

> **How Do Psychoactive Drugs Get into the Nervous System?**  
 - differential distribution into body and brain, the Blood-Brain Barrier

Capillaries in the brain are not leaky, have tight junctions, and are covered with astrocyte feet. These properties prevent materials from moving in and out easily, and are the basis of the blood-brain barrier.

Small, uncharged molecules are able to pass through the endothelial membrane and reach the brain.

Certain other molecules are carried across the membrane by active transport.

Capillaries in the body are leaky and have few tight junctions. Materials can move in and out relatively easily.

Large and electrically charged molecules are unable to pass out of the capillary.

Transporters: Amino acids, Glucose, Fats

Capillary, Astrocyte feet, Tight junction

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### Principles of Psychopharmacology

> **Drug Effectiveness**

- **Affinity:** the attraction of a drug for its target
- **Efficacy:** the ability of a drug to exert its biological action

**dose-response function**

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### Principles of Psychopharmacology

> **Drug Effectiveness**

- **Therapeutic Index:** most drugs = more than one effect  
 margin of safety measured as therapeutic index  
 therapeutic index =  $LD_{50}/ED_{50}$

**shift in dose-response function**

- analgesia
- respiratory depression

- **Differences in effectiveness:**  
 differing drugs = differing sites of action  
 differing drugs = differing affinities  
 differing drugs = differing efficacies

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## Principles of Psychopharmacology

### > Effects of Repeated Administration

#### - Sensitization:

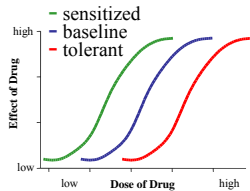
An increase in the apparent effect of a drug with repeated or chronic exposure

#### - Tolerance:

A decrease in the apparent effect of a drug with repeated or chronic exposure

#### - Cross Sensitization / Cross Tolerance:

An increase / decrease in the apparent effect of a novel drug after repeated or chronic exposure to another drug



shift in dose-response function

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## Principles of Psychopharmacology

### > Effects of Repeated Administration

#### - Withdrawal Symptoms:

rebound actions after repeated drug administration, occurs upon cessation of drug administration

generally opposite to the actions of the drug

occur because of drug-induced tolerance

alterations in receptor number or affinity

alterations in receptor-coupling to effectors (ion channels, second messengers)

**Heroin: analgesia, constipation, relaxation, euphoria**

**Withdrawal: hyperalgesia, diarrhea, agitation, dysphoria**

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## Drug Actions

### > Two Major Classes of Psychoactive Drugs

#### - Agonists:

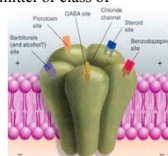
mimic or increase the effects of a particular neurotransmitter or class of neurotransmitters

#### - Antagonists:

block or decrease the effects of a particular neurotransmitter or class of neurotransmitters

#### - Competitive, Noncompetitive, and Irreversible Antagonists:

1. Competitive antagonists attach to the same binding site as the endogenous neurotransmitter and block the receptor. These are known as direct antagonists.
2. Noncompetitive antagonists attach to a different binding site than does the endogenous neurotransmitter for that receptor. These antagonists are known as indirect antagonists.
3. Irreversible antagonists actually modify the receptor so that the endogenous neurotransmitter cannot exert further effects.



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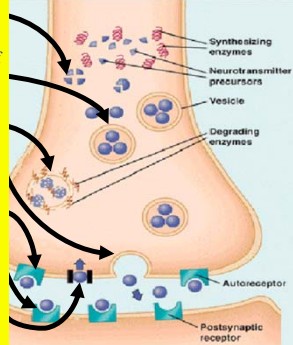
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## Drug Actions

### > Two Major Classes of Psychoactive Drugs - **AGONISTS**

1. Drug increases neurotransmitter synthesis (e.g. precursor)
2. Drug enhances packaging/transport of synthesized neurotransmitter into vesicles and granules
3. Drug destroys catabolizing enzymes
4. Drug increases neurotransmitter release
5. Drug antagonizes autoreceptors to prevent autoreceptor-mediated inhibition of synthesis and release
6. Drug binds to postsynaptic receptors and activates them
7. Drug blocks degradation or reuptake of released neurotransmitters




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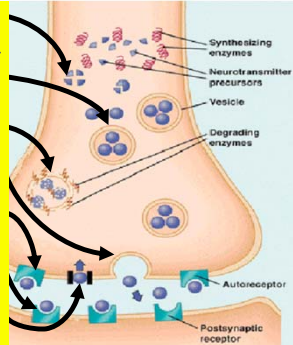
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## Drug Actions

### > Two Major Classes of Psychoactive Drugs - **ANTAGONISTS**

1. Drug decreases neurotransmitter synthesis
2. Drug interrupts packaging/transport of synthesized neurotransmitter into vesicles and granules
3. Drug increases catabolism
4. Drug decreases neurotransmitter release
5. Drug activates autoreceptors to increase autoreceptor-mediated inhibition of synthesis and release
6. Drug binds to postsynaptic receptors and antagonizes them
7. Drug increases degradation or reuptake of released neurotransmitters




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## Agonists and Antagonists

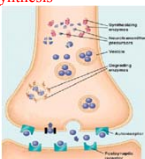
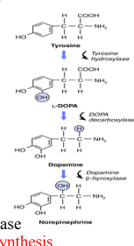
### norepinephrine

#### agonists:

- desipramine, inhibits reuptake
- moclobemide, monoamine oxidase-A inhibitor (MAOI)
- clonidine, activates  $\alpha_2$  adrenoceptors
- NSRIs

#### antagonists:

- AMPT, inactivates TH, decreases biosynthesis
- reserpine, prevents storage in synaptic vesicles, decreases release
- benserazide, inhibits dopamine-b-hydroxylase, decreases biosynthesis
- yohimbine, blocks  $\alpha_2$  adrenoceptors




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## Agonists and Antagonists

### dopamine

#### agonists:

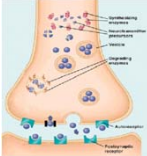
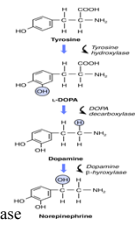
- L-DOPA, precursor, increases biosynthesis
- cocaine, blocks reuptake
- amphetamine, increases release, and blocks reuptake
- bromocriptine, agonist at D<sub>2</sub> class
- deprenyl, monoamine oxidase-B inhibitor (MAOI)

#### antagonists:

- AMPT, inactivates TH, decreases biosynthesis
- reserpine, prevents storage in synaptic vesicles, decreases release
- SCH 23390 blocks D<sub>1</sub>
- chlorpromazine, haloperidol, neuroleptics – blocks D<sub>2</sub>
- clozapine, atypical neuroleptic – blocks D<sub>2</sub> (and 5HT<sub>2</sub>)

#### mixed:

- apomorphine, activates D<sub>2</sub> higher affinity for presynaptic D<sub>2</sub> autoreceptors than for postsynaptic D<sub>2</sub> receptors
- therefore, antagonist at low doses, agonist at higher doses




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## Agonists and Antagonists

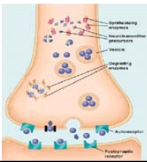
### serotonin

#### agonists:

- fluoxetine (Prozac), SSRI, inhibits reuptake, treatment of depression, anxiety, OCD
- fenfluramine, increases 5-HT release and blocks reuptake, appetite suppressant
- 8-OH-DPAT, activates 5-HT<sub>1A</sub> receptors

#### antagonists:

- reserpine, prevents storage in synaptic vesicles, decreases release
- ketanserin, blocks 5-HT<sub>2A</sub> receptors




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## Agonists and Antagonists

### glutamate

#### agonists:

- N-methyl-D-aspartic acid, activates NMDA receptors
- AMPA, activates AMPA receptors
- kainate, activates kainate receptors

#### antagonists:

- MK-801, memantine blocks NMDA receptors
- AP5, blocks NMDA receptors
- CNQX, blocks AMPA and kainate receptors

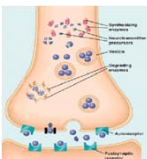
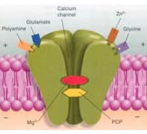
### glycine

#### agonists:

- none identified

#### antagonists:

- strychnine = convulsions, death




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## Agonists and Antagonists

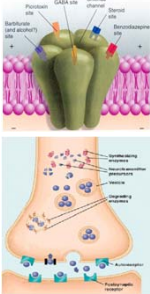
### GABA

#### agonists:

- benzodiazepines (diazepam/valium, chlordiazepoxide/librium)  
GABA<sub>A</sub> agonists, anxiolytic, sedative
- barbiturates (secobarbital, phenobarbital, pentobarbital)  
GABA<sub>A</sub> agonists, anxiolytic, sedative, low therapeutic index
- EtOH, probably binds to barbiturate binding site  
various steroids, GABA<sub>A</sub> agonists, sedatives

#### antagonists:

- picrotoxin, non-competitive antagonist at GABA<sub>A</sub> receptors
- bicuculline, blocks GABA binding on GABA<sub>A</sub> receptors



## Agonists and Antagonists

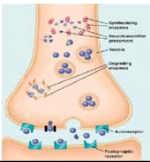
### opioids

#### agonists:

- opium, morphine, heroin;  $\mu$  agonists (somewhat selective)
- DAMGO;  $\mu$  agonist (highly selective)
- DPDPE;  $\delta$  agonist (highly selective)
- U-50, 488H;  $\kappa$  agonist (highly selective)

#### antagonists:

- naloxone/naltrexone (NARCAN),  $\mu$  antagonist, used for overdose
- CTOP/ naltrindole/nor-BNI; selective  $\mu/\delta/\kappa$  antagonists



### adenosine

#### antagonists:

- caffeine, theophylline; non selective

## The Classification of Psychoactive Drugs

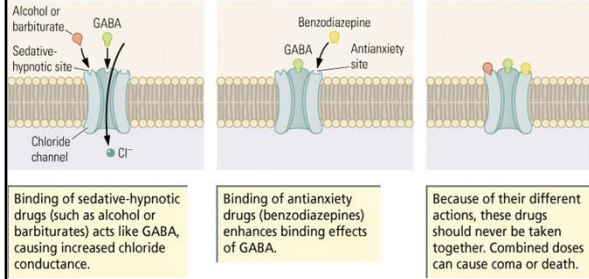
- > Sedative Hypnotics and Anxiolytics
- > Antipsychotics
- > Antidepressants
- > Narcotic Analgesics
- > Psychostimulants



## The Classification of Psychoactive Drugs

### > Sedative Hypnotics and Anxiolytics

- minor tranquilizers / anxiolytics / sleeping pills
- alcohol, barbiturates, benzodiazepines (valium)
- all these drugs produce tolerance and cross-tolerance through actions on GABA-A




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## The Classification of Psychoactive Drugs

### > Antipsychotic Agents

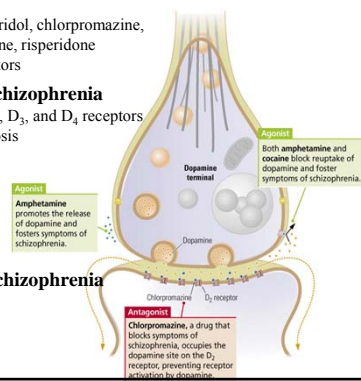
- classical neuroleptics – haloperidol, chlorpromazine, atypical neuroleptics – clozapine, risperidone
- antagonists at dopamine receptors

### dopamine hypothesis of schizophrenia

- efficacy of neuroleptics at D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> receptors
- amphetamine/cocaine psychosis

### glutamate hypothesis of schizophrenia

- PCP psychosis




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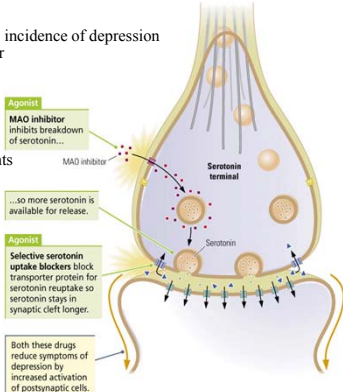
## The Classification of Psychoactive Drugs

### > Antidepressants

- 7.6-8.9% of population = lifetime incidence of depression
- usually recovery before one year
- some refractory
- high incidence of suicide

- MAOIs
- tricyclic antidepressants
- second generation antidepressants (fluoxetine - an SSRI) (Cymbalta – an NSRI)

- delay between onset of actions at synapses (immediate) and clinical efficacy (weeks) is not understood




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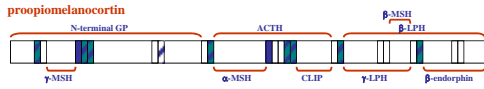
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## The Classification of Psychoactive Drugs

### > Narcotic Analgesics

derived from opium poppy or artificially synthesized  
- opium, heroin, morphine, codeine, fentanyl, etc.

agonists at endogenous  $\mu$ ,  $\delta$ , and  $\kappa$  opioid receptors  
imitate endogenous enkephalin, endorphin, and dynorphin opioid neurotransmitters



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## The Classification of Psychoactive Drugs

### > Stimulants

**behavioral stimulants**  
- increase motor behavior, elevate mood  
- cocaine and amphetamine



**psychedelic drugs**  
- alter sensory processing and cognition  
- mescaline, LSD, psilocybin



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## Drug Abuse

### > Addiction and Dependence

- *Drug Dependence: Its Significance and Characteristics*  
(Bulletin of the WHO, 1965)  
Opiate/drug addiction defined in terms of physical dependence and withdrawal symptoms

- *A Psychomotor Stimulant Theory of Addiction*  
(Wise and Bozarth, 1987)  
A common denominator of addictive substances is their ability to induce psychomotor activation, wherein positive reinforcers elicit approach, and activate dopaminergic fibers. The role of physical dependence is ascribed a secondary role, and it varies from drug to drug.

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## Drug Abuse

### > Addiction and Dependence

- *Opponent process theory of motivation...*

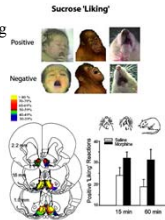
(Koob G.F., Stinus L., Le Moal M., and Bloom F.E., (1989)

Drug exposure initiates an adaptive process that opposes the hedonic effects of the drug, and persists after termination of the drug exposure, motivating further drug-taking behaviour.

- *The neural basis of drug craving: an incentive-sensitization theory of addiction* (Robinson, T.E., and Berridge, K.C., 1994)

Drug addiction theories must account for the intense craving exhibited by addicts, and for the persistence or reinstatement of drug craving long after discontinuation.

As drug craving increases, drug liking decreases.




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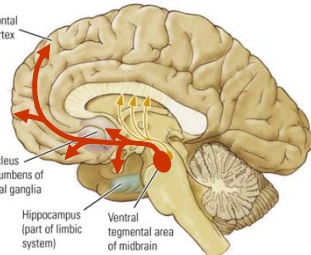
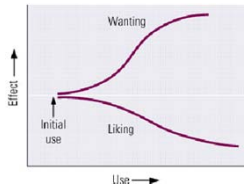
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## Drug Abuse

### > Addiction and Dependence

1. pleasurable drug effects
2. associative conditioning
3. attribution of incentive salience to drug-related stimuli




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## Drug Abuse

### > Behavior on Drugs

Common effect is behavioral disinhibition

**disinhibition theory:**

- suppression of cortical function (judgment and reasoning) while sparing subcortical function (drives)
- not very satisfactory, inhibition/disinhibition seen in different circumstances
- behavior has been described as "time out" from social rules, or alcohol myopia

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## Drug Abuse

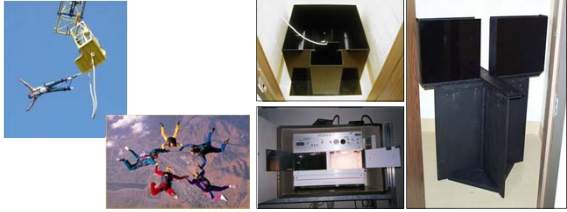
### > Individual Differences in Vulnerability to Drug Abuse

#### evidence for genetic predisposition:

- concordance in twin studies, especially identical
- adopted children of biological parents who are alcoholic, more likely to be alcoholic
- animals generally don't drink alcohol, but selectively bred strains of mice do

#### personality traits:

- risk taking behavior
- stress hyper-responsive rats




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## Drug Abuse

### > Potential Harmfulness of Recreational Drugs

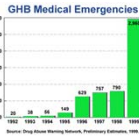
#### risk of impurities:

- ecstasy particularly known for contaminants
- MPTP contamination in synthetic heroin



#### risk from direct actions of drugs:

- **gamma hydroxybutyrate (GHB):** drowsiness, nausea, vomiting, headache, loss of consciousness, loss of reflexes, impaired breathing, coma, death
- onset of overdose is EXTREMELY rapid




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## Drug Abuse

### > Potential Harmfulness of Recreational Drugs

#### risk from direct actions of drugs:

- **ketamine:** delirium, amnesia, impaired motor function, high blood pressure, depression, fatal respiratory problems



- **rohypnol:** decreased blood pressure, visual disturbances, dizziness, confusion, gastrointestinal disturbances, urinary retention
- effects are aggravated by alcohol




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## Drug Abuse

### > Potential Harmfulness of Recreational Drugs

#### risk from direct actions of drugs:

- **methamphetamine** = memory loss, aggression, violence, psychotic behavior (amphetamine psychosis), potential cardiac damage, neurotoxic to monoaminergic neurons, decreased DA & 5-HT transporters



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## Drug Abuse

### > The Potential Harmfulness of Recreational Drugs

#### risk from direct actions of drugs:

- **lysergic acid diethylamide (LSD)** = elevated body temperature, increased heart rate and blood pressure, sweating, loss of appetite, sleeplessness, dry mouth, tremors, numbness, weakness, trembling, nausea
- two long-term disorders = persistent psychosis and "hallucinogen persisting perception disorder" (which used to be called "flashbacks")
- **phencyclidine (PCP)** = hallucinations, paranoia, disordered thinking, catatonia, garbled speech, violent or suicidal outbursts, cardiac and respiratory depression, nausea, vomiting, blurred vision, nystagmus, drooling, loss of balance, dizziness, seizures, coma, and death
- long-term effects = memory loss, difficulties with speech and thinking, depression, and weight loss



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## Drug Abuse

### > The Potential Harmfulness of Recreational Drugs

#### risk from direct actions of drugs:

- **opiates** = nausea, vomiting, respiratory and cardiac depression, coma, death



- **ecstasy** = neurotoxic to serotonergic neurons, elevated heart rate and blood pressure, dehydration, hypertension, malignant hyperthermia leading to muscle breakdown and potentially fatal kidney and cardiovascular system failure,
- continued use may also lead to heart attacks, strokes, and seizures in some users



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## Drug Abuse

> **Consequences of MDMA Use**

- impairments increase with each exposure to the drug, and with escalating dose
- heavy MDMA users have significant impairments in visual and verbal memory
- additional impairments include:
  - impaired ability to reason verbally
  - impaired ability to sustain attention
- possible deficits in mood, impulse control, and sleep cycles



**Ecstasy Use by Students, 2000: Monitoring the Future Study**

	8th-graders	10th-graders	12th-graders
Ever Used	4.3%	7.3%	11.0%
Used in Past Year	3.1%	5.4%	8.2%
Used in Past Month	1.4%	2.6%	3.6%

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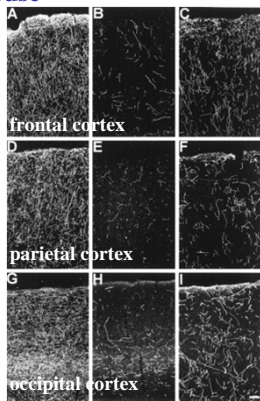
## Drug Abuse

> **Permanent damage after MDMA exposure**

- 5 mg/kg, twice daily, 4 days
- post mortem 5-HT immunoreactivity

- A,D,G = control
- B,E,H = 2 weeks recovery
- C,F,I = 7 years recovery

(Hatzidimitriou, McCann & Ricaurtes, 1999)




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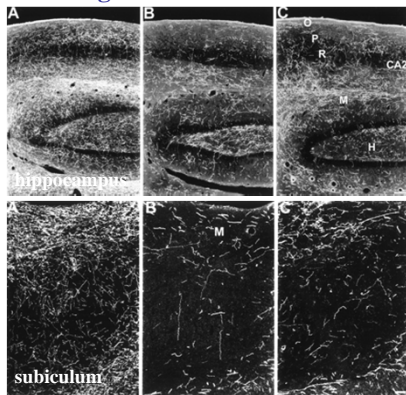
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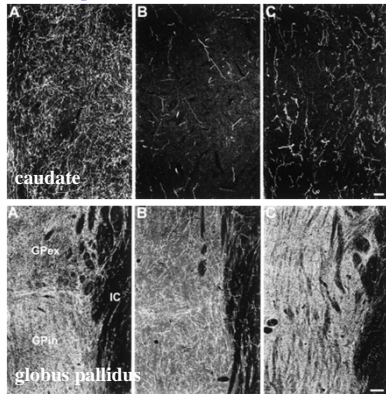
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## Reading Assignment

### Before next class

**Chapter 5:** Hormones and the Brain  
Breedlove, Rosenzweig, & Watson

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