



Brain and Behaviour – S2

PSYC 304

Learning objectives

1. Describe the physiological correlates of stress and contrast acute and chronic stress responses.
2. Discuss individual differences in stress vulnerability and responses to stressful situations.
3. Evaluate the role of early life experiences in lifelong stress responses.
4. Describe the form and function of communication between the nervous system and the immune system.
5. Summarize the impact of chronic stress on health, and offer some ways to mitigate its effects

Announcements

- ***FINAL EXAM – AUGUST 15, 7pm SWING 121 (or Zoom)***
- ***Reading CLUB 4A and 4B – AUGUST 5th***
- ***Don't forget your tweets!***
- ***Midterm 3 grades are out – Avg – 75%***
 - ***Looks like we found the sweet spot!***
 - ***Great work!***
 - ***Midterm 3 review – next Thursday (last 30 minutes of class)***

Stress defined

Stress

- is any circumstance that upsets homeostatic balance.
- **Allotasis** – adjust physiological parameters to accommodate current or anticipated stressors

Alarm reaction:

- initial response to stress.

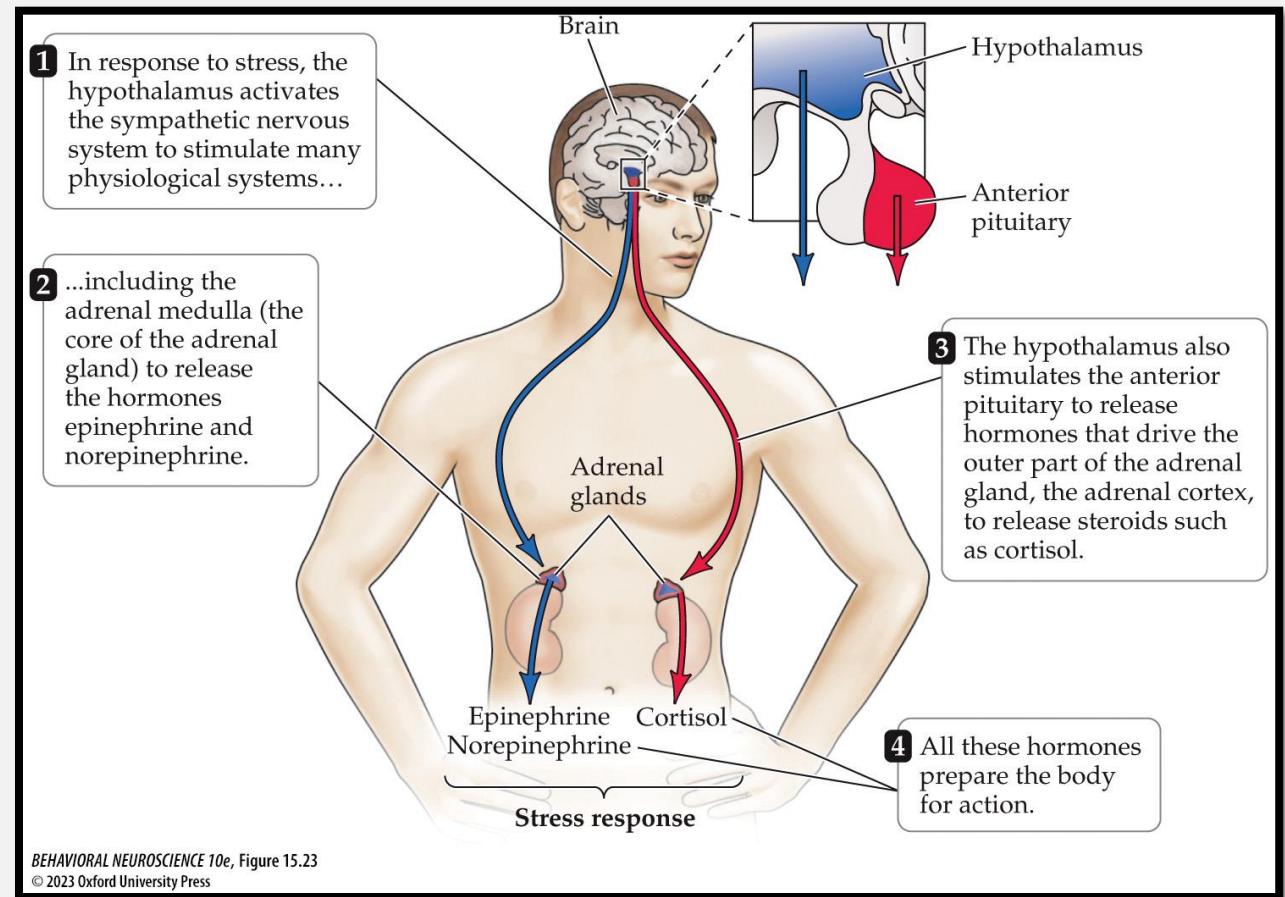
“Fight or flight” system:

- hypothalamus activates the sympathetic nervous system which stimulates the **adrenal medulla** to release **epinephrine** and **norepinephrine**.
- These hormones increase heart rate and breathing; prepare body for action.

Stress - Bodily Responses

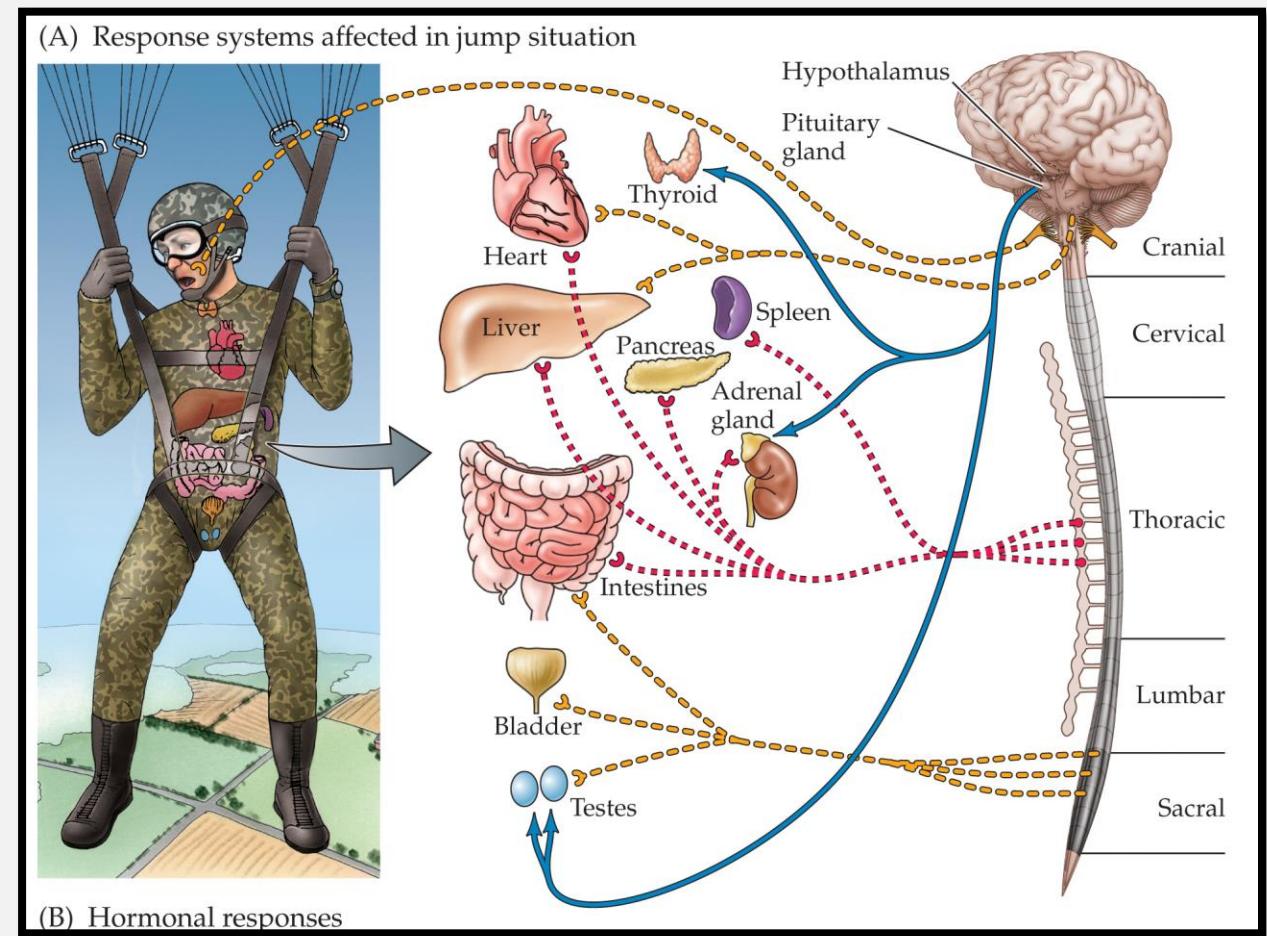
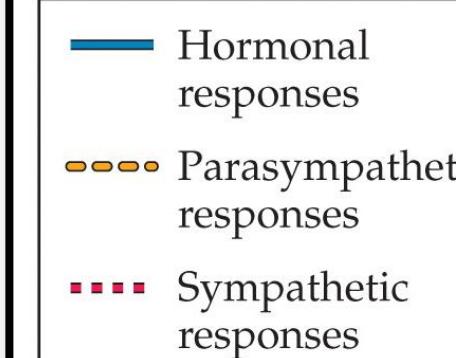
The hypothalamus

- also stimulates the anterior pituitary to release a hormone that causes the **adrenal cortex** to release **adrenal steroids** such as **cortisol**.
- These hormones act more slowly but also prepare the body for action by releasing stores of energy.



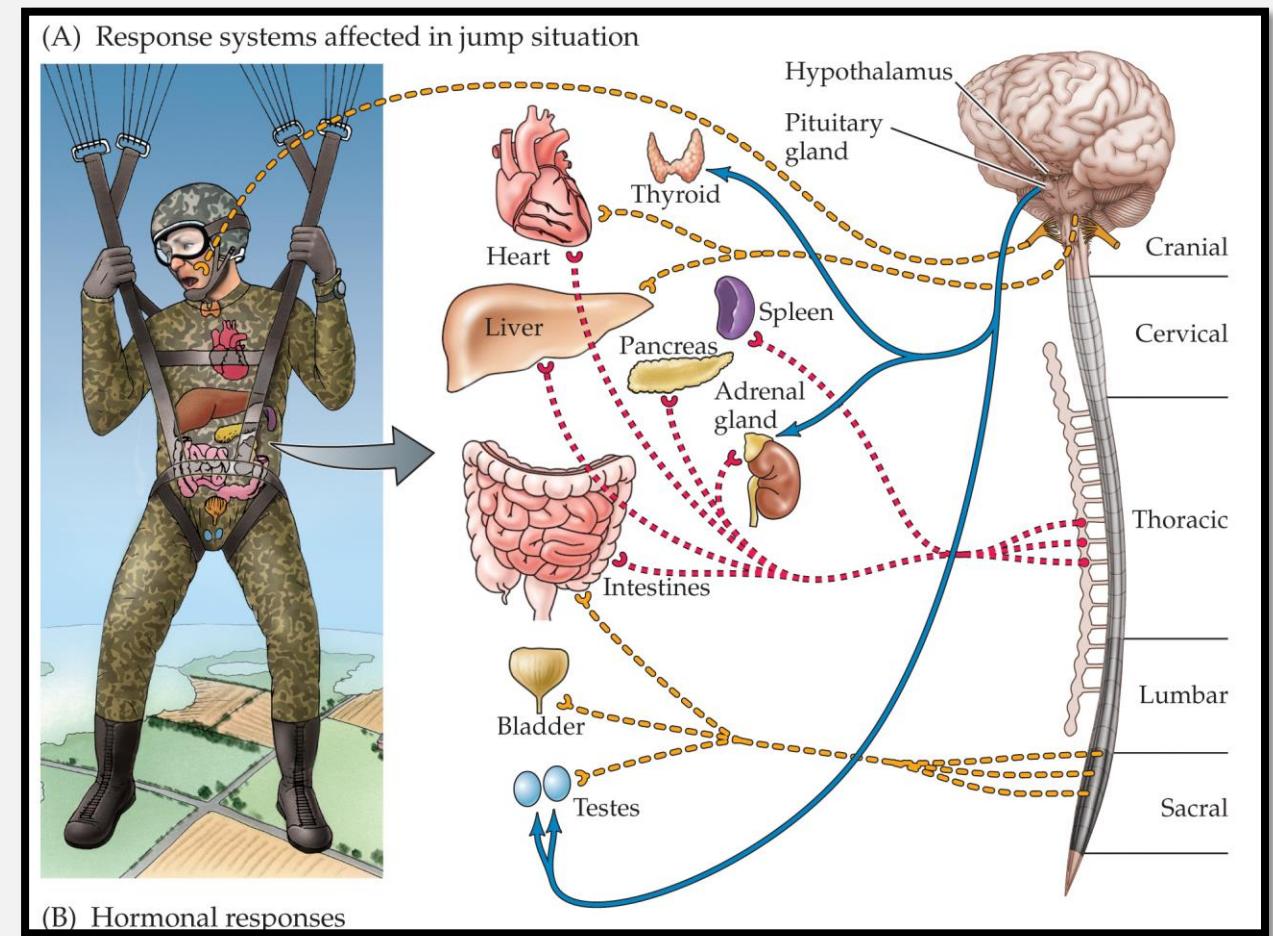
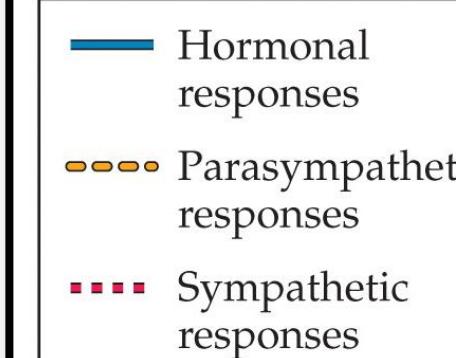
Stress - Bodily Responses

- Hormonal responses to stress were studied in military recruits learning to parachute.



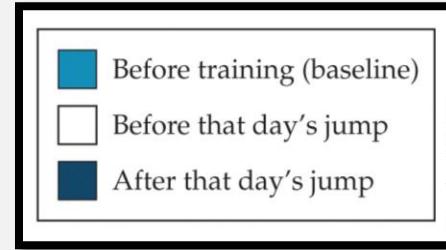
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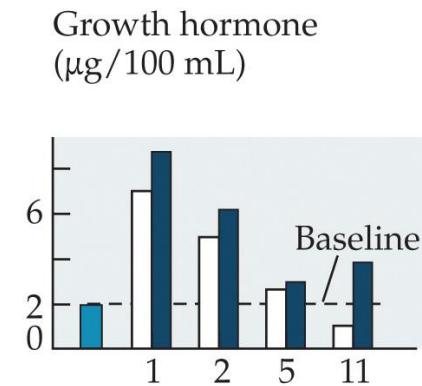
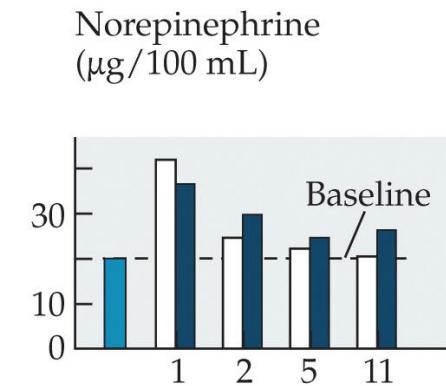
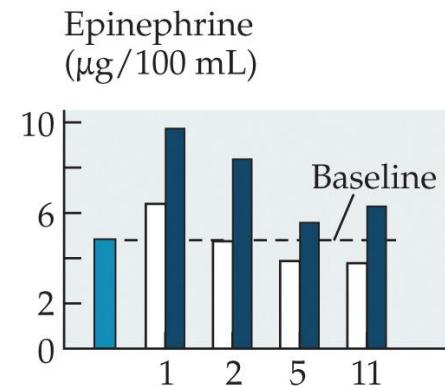
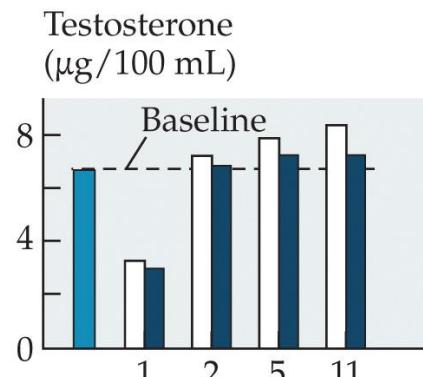
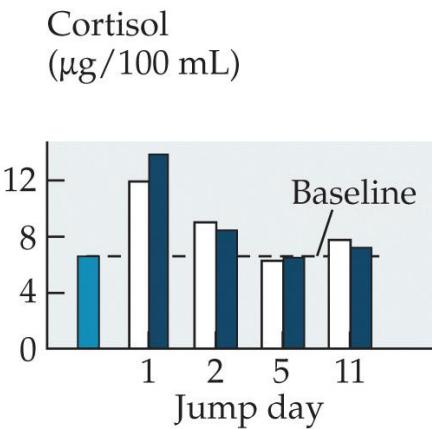


Stress - Bodily Responses

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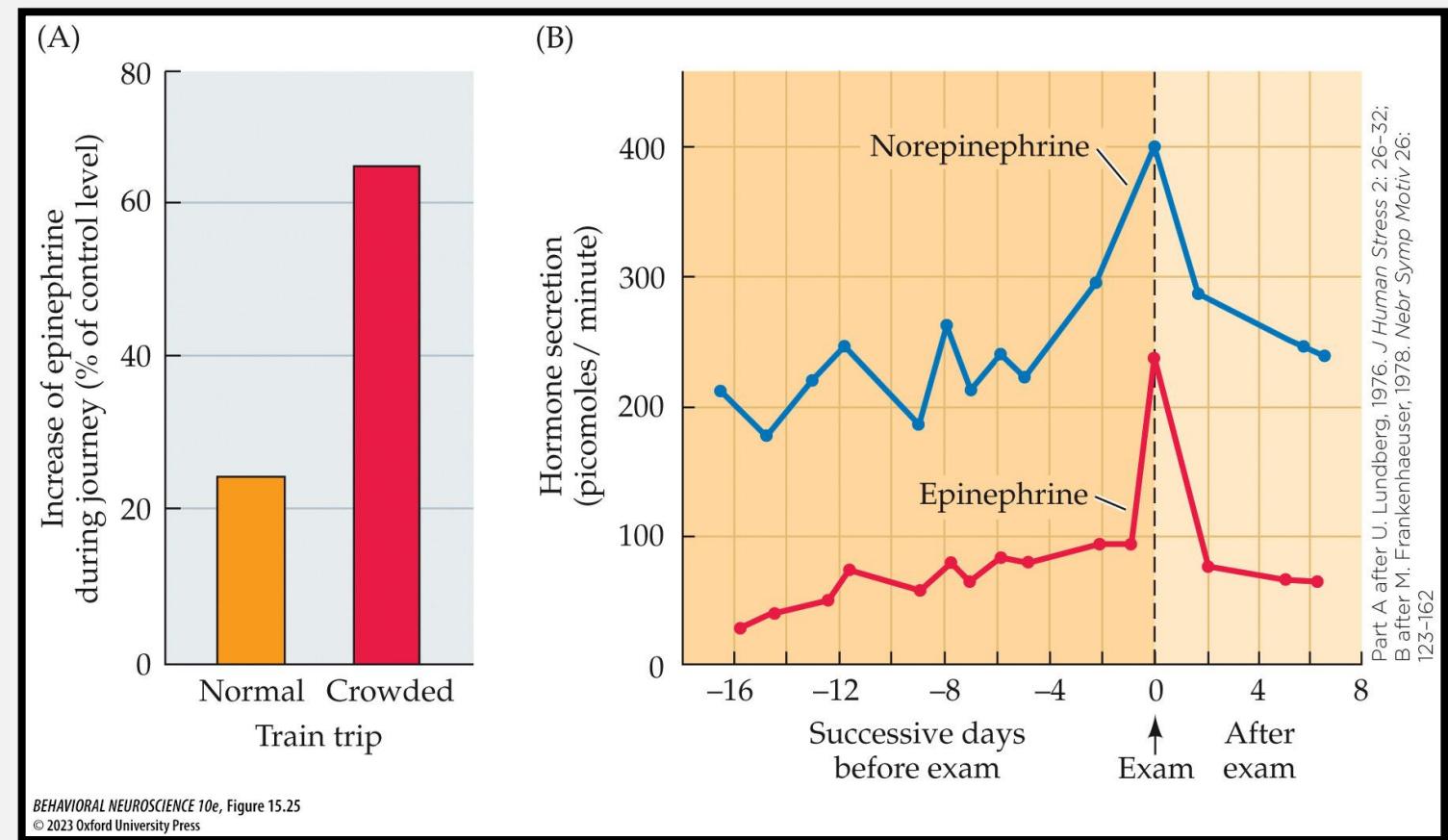


(B) Hormonal responses



Stress - Bodily Responses

- Hormonal responses to stress have also been shown in work, school and social situations such as riding commuter trains and taking exams.
- Sustained stress can have lasting effects.



Stress - investigated

Why do individuals differ in their response to stress?

- Levine et al. 1967
- One hypothesis: **stress immunization**: Mild stress early in life makes one more capable of handling stress later in life.
- In experiments with rats, pups handled briefly had less response to adult stresses than pups that were left alone.

Stress - investigated

- But the pups benefited because their mothers *comforted* them *after* the stress.
- Rat pups separated for long periods and received little maternal attention exhibited increased stress response as adults, had trouble learning mazes, and had reduced neurogenesis in the hippocampus.
- Immunizing effects of maternal grooming behaviour on stress response seen in undisturbed litters too!

Stress - investigated

Epigenetic regulation:

- maternal deprivation exerts this negative effect on adult stress responses by causing long-lasting changes in the expression of genes for adrenal steroid receptors in the brain.
- This has also been found in humans, e.g., suicide victims that were abused or neglected as children.
 - Early epigenetic modifications can make a person less able to handle stress and more likely to develop significant psychiatric disturbances, like mood and anxiety disorders.
 - McGowen et al., 2009, *Nature Neuroscience* – decreased expression of glucocorticoid receptors in the hippocampus of abused/neglected children → decreased monitoring of the body's stress response by the brain → prolonged stress response

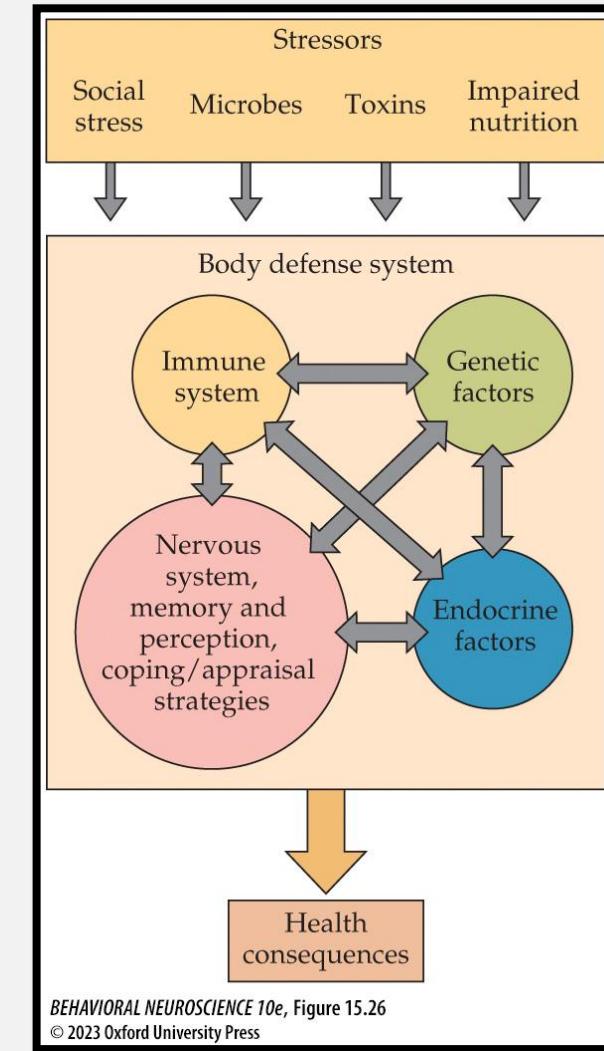
Stress - investigated

Psychosomatic medicine

- explores the role of psychological, behavioral, and social factors in disease.

Health psychology

- (or behavioral medicine) studies psychological influences on health and illness.
- Several factors interact to affect human health and disease.



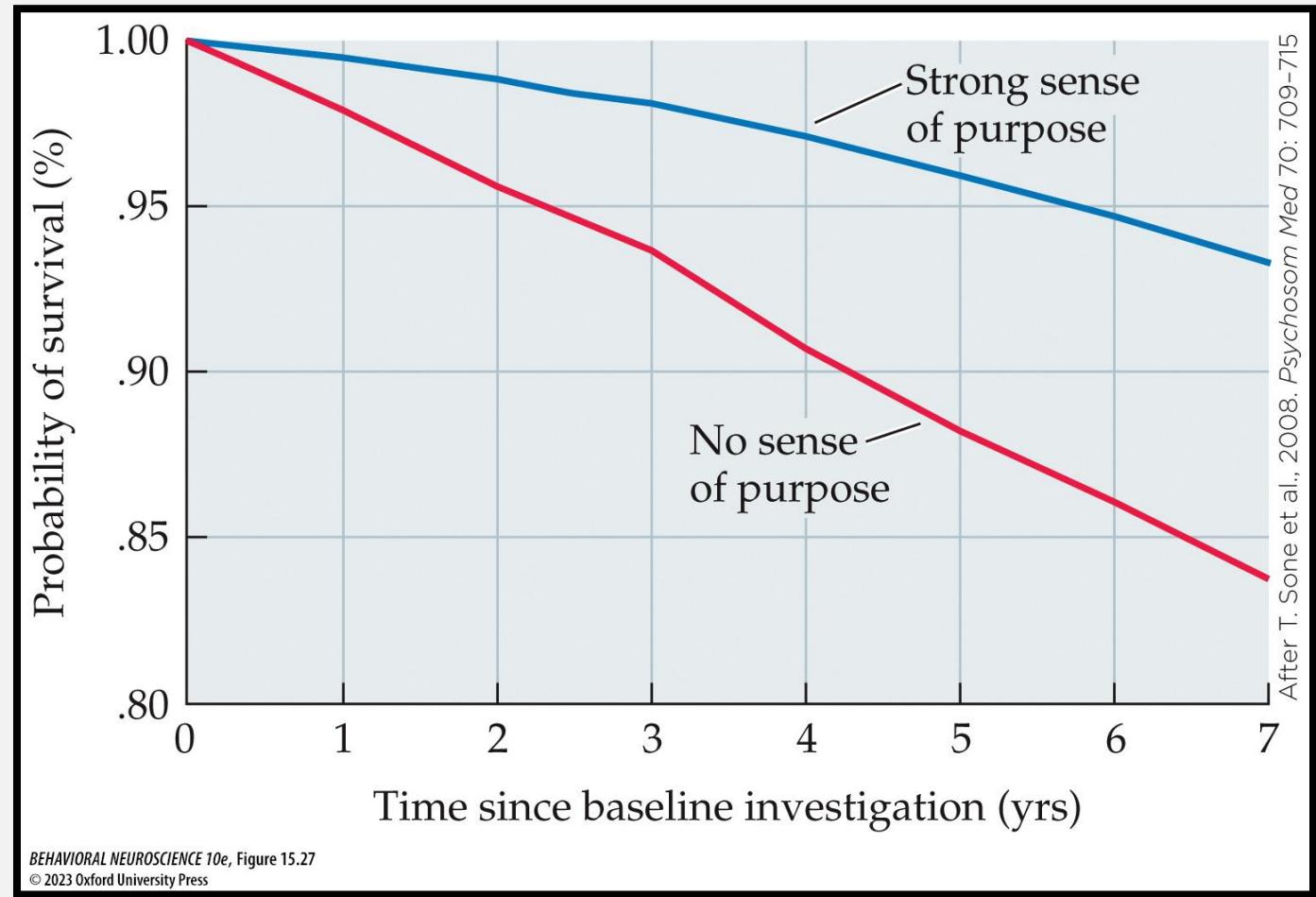
Stress - investigated

- Links between strong emotions and heart attacks:
 - **Type A vs Type B personality** – What do you think?
-
- Other risk factors for dying of heart disease include poor sleep, depression, stressful jobs and/or relationships, social isolation, and lack of life purpose.

Stress - investigated

Other risk factors

- include poor sleep, depression, stressful jobs and/or relationships, social isolation,
- Lack of life purpose.



Stress and illness

Psychoneuroimmunology

- studies interactions of the immune, endocrine, and nervous systems.
- People who are more stressed, are more likely to become sick when exposed to common viruses.
- **Cohen et al., 2015, *New England Journal of Medicine***
- **Methods –**
 1. Complete a questionnaire on behaviour, psychological stress (graded), personality, health practices and get blood taken.
 2. Get nasal drops of either rhinovirus type 2, 9 or 14, respiratory syncytial virus (RSV), or coronavirus (394 healthy adults and 26 controls received saline)
 3. Monitor immune response (quarantined day -2 to +6 from exposure)
- **Findings –**
 1. Positive correlation between psychological stress and cold symptoms
 2. Positive correlation between psychological stress and infection rates

Findings

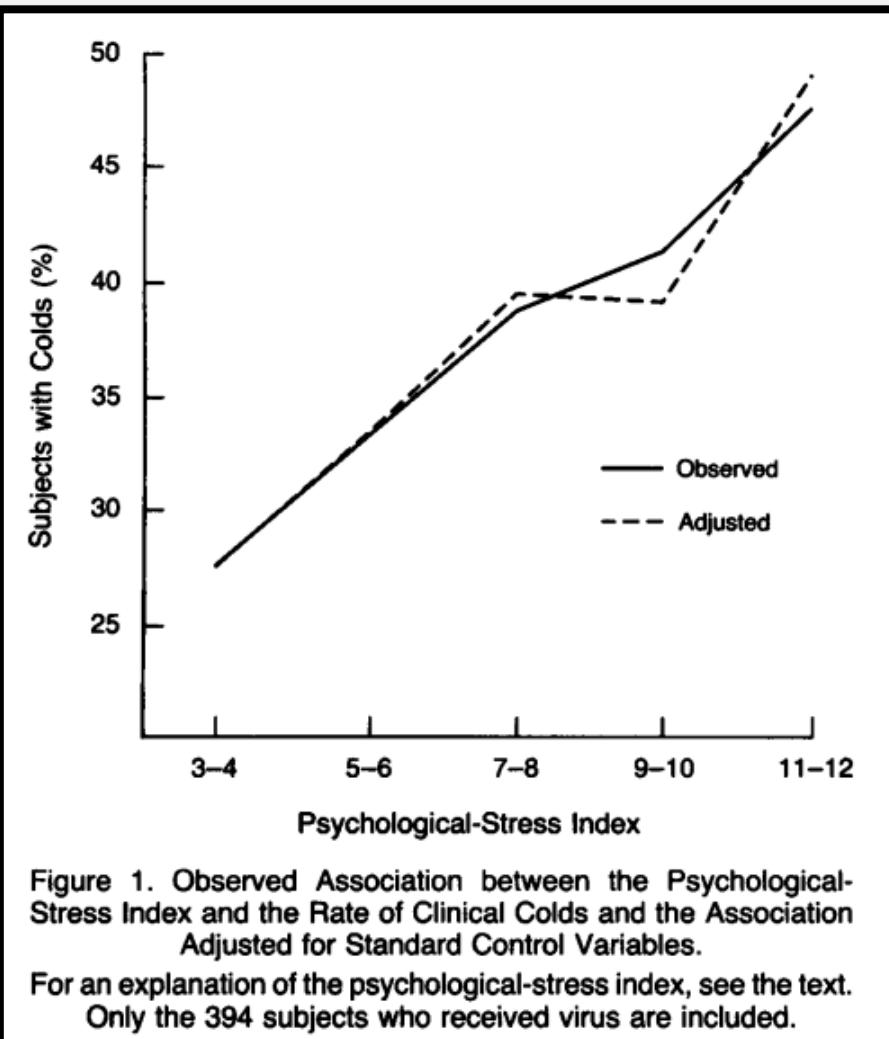


Figure 1. Observed Association between the Psychological-Stress Index and the Rate of Clinical Colds and the Association Adjusted for Standard Control Variables.

For an explanation of the psychological-stress index, see the text.
Only the 394 subjects who received virus are included.

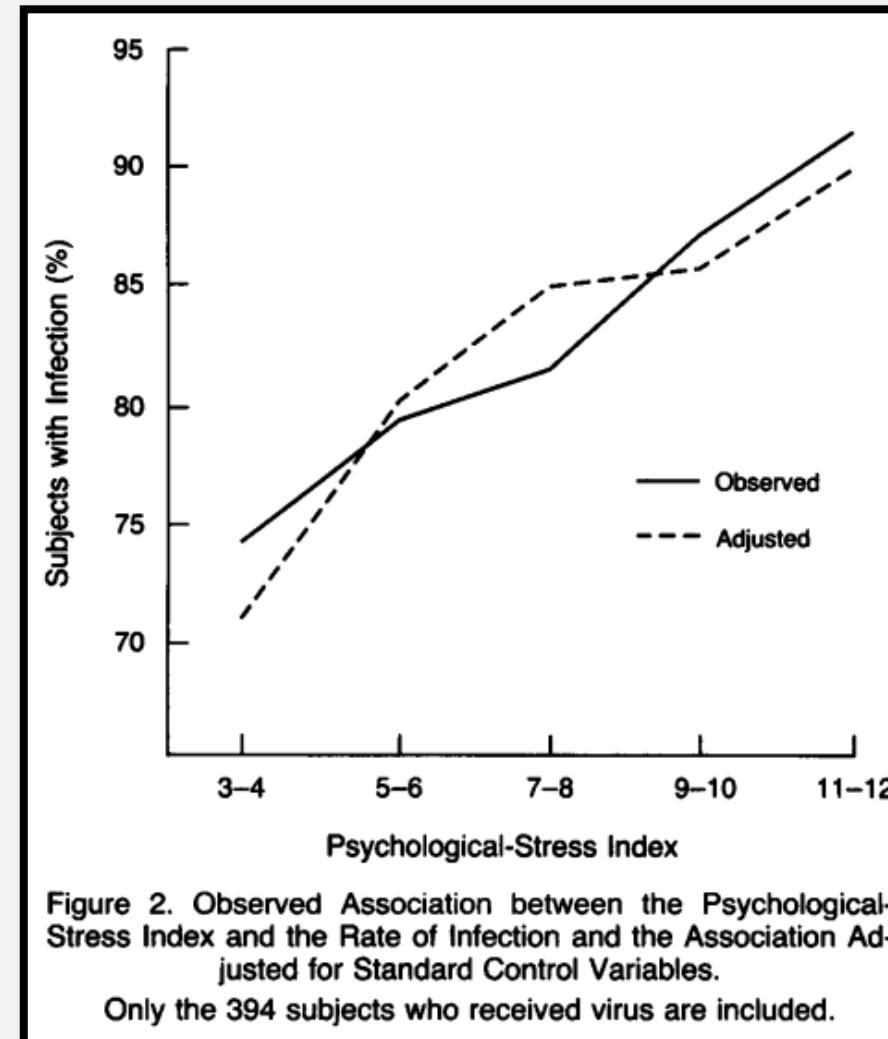


Figure 2. Observed Association between the Psychological-Stress Index and the Rate of Infection and the Association Adjusted for Standard Control Variables.

Only the 394 subjects who received virus are included.

Stress and illness

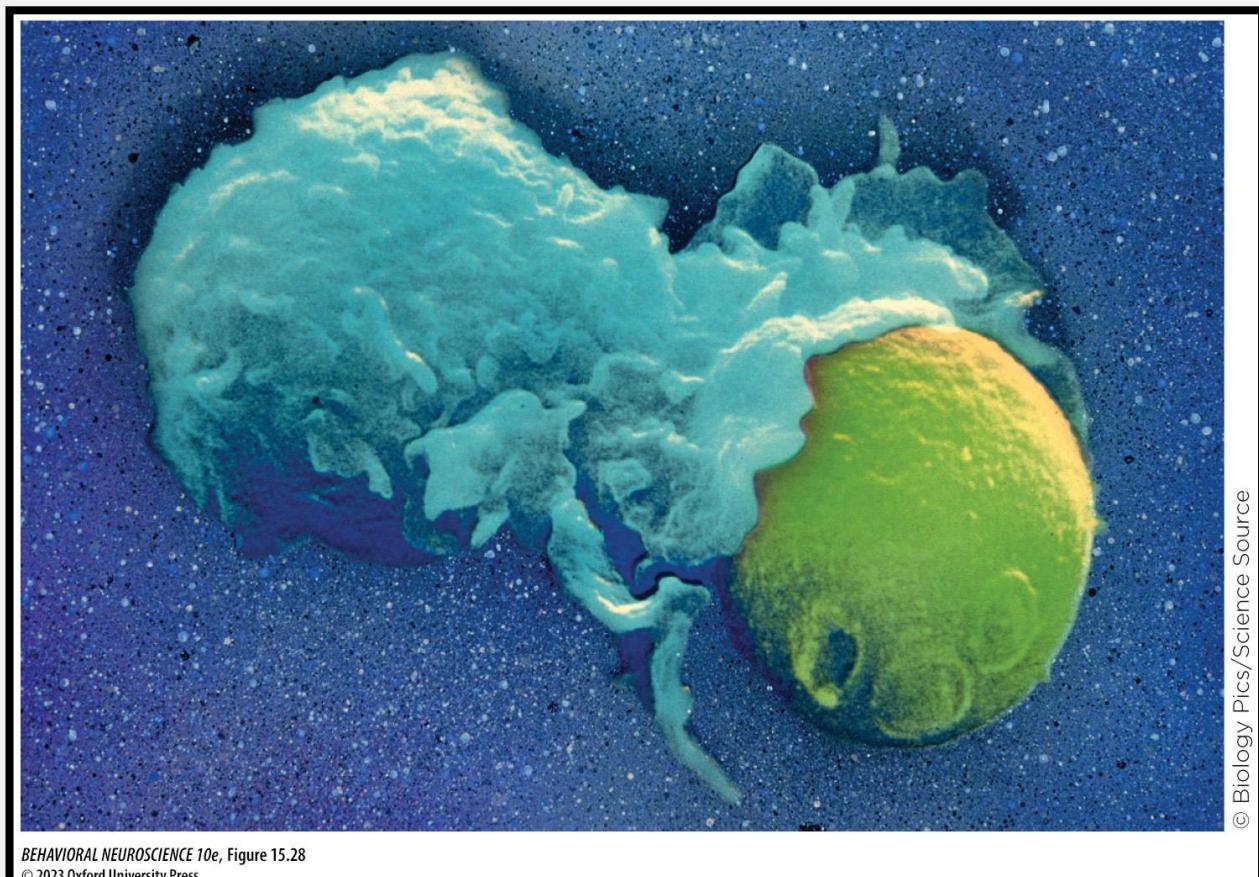
Psychoneuroimmunology

- studies interactions of the immune, endocrine, and nervous systems.
- People who have happy social lives and social support—such as hugs—are less likely to develop a cold, even when exposed to a virus.
- **Cohen et al., 2015, *New England Journal of Medicine***
- *Methods* –
 1. Complete a physical exam (including blood draws), questionnaire regarding demographics and social support, 2-week evening interview protocol (daily interpersonal interactions).
 2. Viral challenge trial (prequarantine, inoculation with challenge virus)
 3. Monitor immune response (quarantined day -2 to +6 from exposure)
- *Findings* –
 1. More conflict = more symptoms
 2. More social support (and more hugs) = less severe symptoms

Stress and illness

White blood cells:

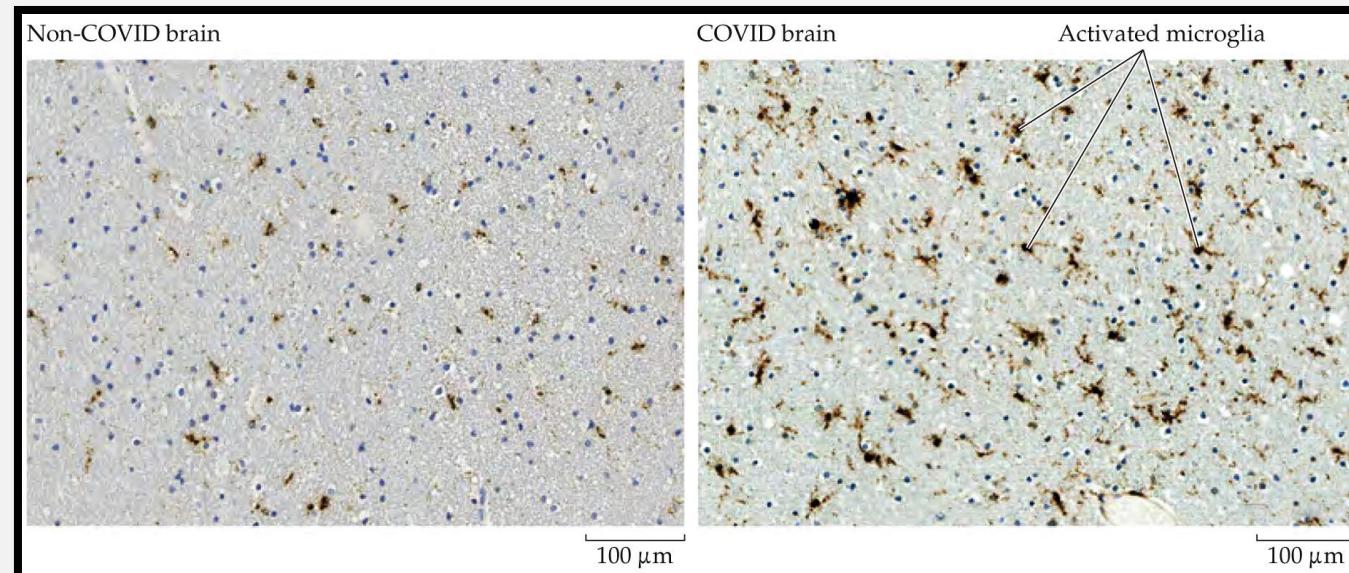
- **Phagocytes** engulf and destroy microbes.
- **B lymphocytes** (B cells) produce **antibodies** against foreign molecules.
- **T lymphocytes** (T cells), some act as killer cells, attacking microbes.
- Helper T cells secrete **cytokines**, proteins that induce cell proliferation in the immune system.



Stress and illness

Resident immune cells of the nervous system

- **Microglia** – kind of macrophage (type of phagocyte)
- Neuroprotective – clear debris and maintain tissue integrity
- Also – mediate inflammatory responses – can be harmful when prolonged
- Brain fog and fatigue from COVID-19 thought to be a product of overactive microglia



Stress and illness

The brain impacts immune function

- Seeing photographs of sick people can trigger the release of cytokines (regulation of B-cells; Schaller et al. 2010)

The brain monitors immune function

- Vagus nerve – detects high levels of cytokines, leads to release of acetylcholine which inhibits cytokine release from immune organs
- The immune system acts as a sensory receptor system, informing the brain.

Stress and illness

- The immune system is compromised during depression.
- Stress can produce a decline in the number of immune cells and in levels of cytokines.

The dental experience

- *Experiment* – two small wounds placed in the mouths of dental students
 1. *First wound – during summer vacation*
 2. *Second wound – during first major examination*
- *Result* - healing took 40% longer during exam period. No student healed faster during exams
- *Take away* - The perception of stress can decrease the number of antibodies produced to fight illness, e.g., if a student perceives an academic program to be stressful.

Stress and illness

Immediate stress response

- Adrenal steroid hormones released during stress directly suppress the immune system.
- Why would the you suppress immune function when you might be more likely to sustain an injury or get an infection?

Sustained stress

- Any animal that is stressed for a prolonged period dies
- Humans – unique ability to be stressed for prolonged periods (analytical minds and highly social lives)

Prolonged stress

TABLE 15.1 The Stress Response and Consequences of Prolonged Stress

Principal components of the stress response	Common pathological consequences of prolonged stress
Mobilization of energy at the cost of energy storage	Fatigue, muscle wasting, steroid diabetes
Increased cardiovascular and cardiopulmonary tone	Hypertension (high blood pressure)
Suppression of digestion	Ulcers
Suppression of growth	Psychogenic dwarfism, bone decalcification
Suppression of reproduction	Suppression of ovulation, impotence, loss of libido
Suppression of immunity and of inflammatory response	Impaired disease resistance
Analgesia	Apathy
Neural responses, including altered cognition and sensory thresholds	Neural degeneration in hippocampus and prefrontal cortex

Stress and illness

Mindfulness-based stress reduction (MBSR)

- A therapy inspired by meditation that has been shown to
- Reduce activity in the amygdala
- Prevent relapses of anxiety disorder or depression



Break

Learning objectives

1. Summarize the criteria for establishing that a substance acts as a neurotransmitter.
2. Name the major chemical families of transmitters, and give examples of each
3. Identify major behavioral functions associated with each type of transmitter.
4. Distinguish between agonist, antagonist, inverse agonist, and partial agonist drug actions.
5. Explain the distinction between competitive and noncompetitive ligands.
6. Summarize the key events that occur when a ligand interacts with a receptor.
7. Define and distinguish between binding affinity and efficacy.
8. Define the dose-response curve and explain ways in which it is useful in studies of pharmacodynamics.
9. Summarize the routes of drug administration and the ways in which the brain and body adapt to the presence of drugs over time

Neurochemistry

Neurochemistry

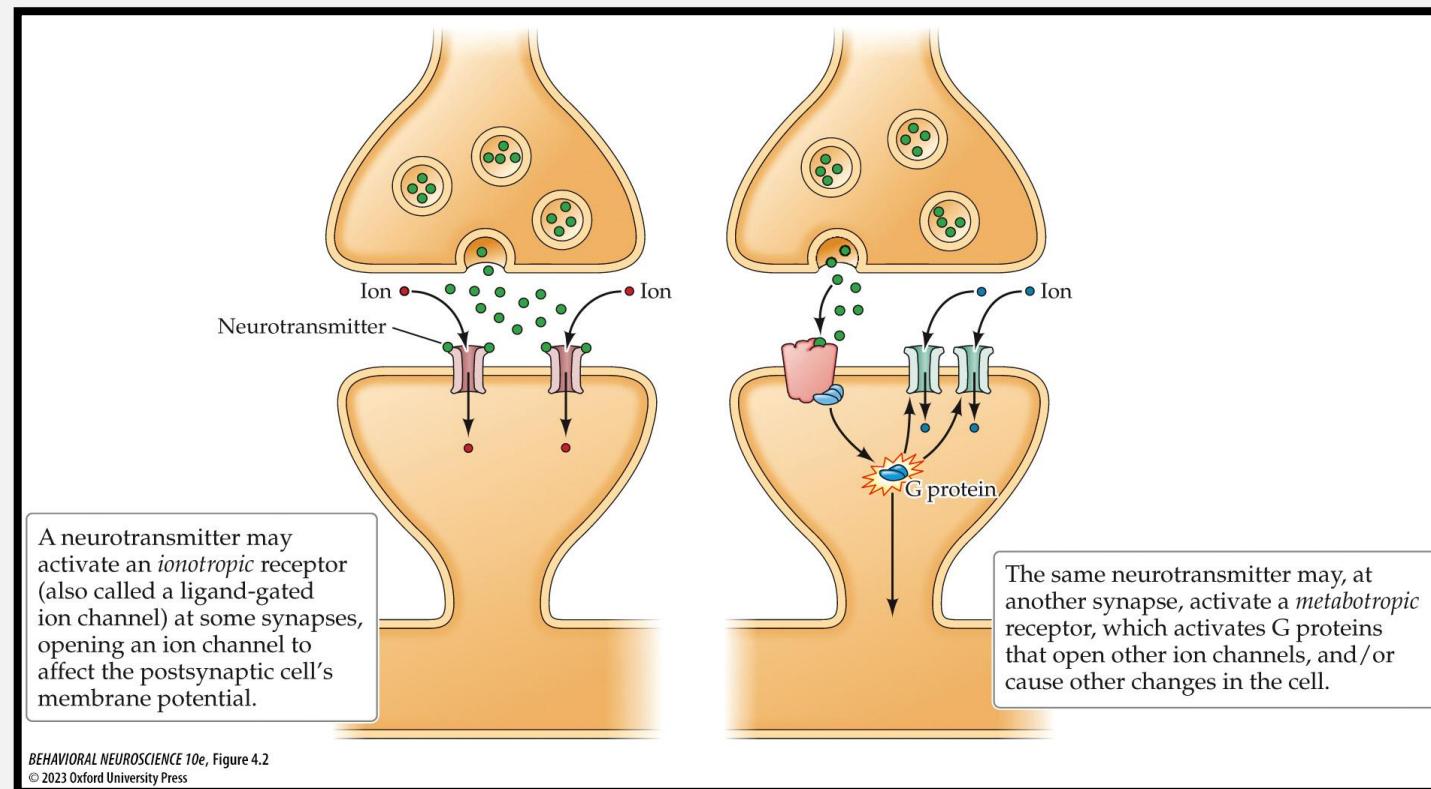
- focuses on the basic chemical composition and processes of the nervous system.

Neuropharmacology

- is the study of compounds that selectively affect the nervous system.

Neurochemistry

- A diversity of **receptor subtypes** adds an important layer of complexity in neural signaling: any given transmitter may affect various kinds of receptors.
- Different receptor subtypes may trigger very different responses in target cells.



Neurochemistry

Neurotransmitters

- **Endogenous substance** – Made within the body
- exists in presynaptic axon terminals
- Presynaptic cell has the right enzyme to make the substance
- Substance is released with APs reach the axon terminal
- Receptors recognize the release of the substance and exist on the postsynaptic membrane
- Application of the substance experimentally produces changes in the post synaptic cell
- Blocking the release, prevents presynaptic activity from impacting post synaptic activity

Neurochemistry

Types of neurotransmitters:

- **Amine**—acetylcholine, dopamine, serotonin
- **Amino acid**—GABA, glutamate
- **Peptide**—short chain amino acids (neuropeptides)
- **Gas**—soluble gases; nitric oxide, carbon dioxide

Neurochemistry

Main excitatory NTs

- in the brain are **glutamate** and **aspartate**.

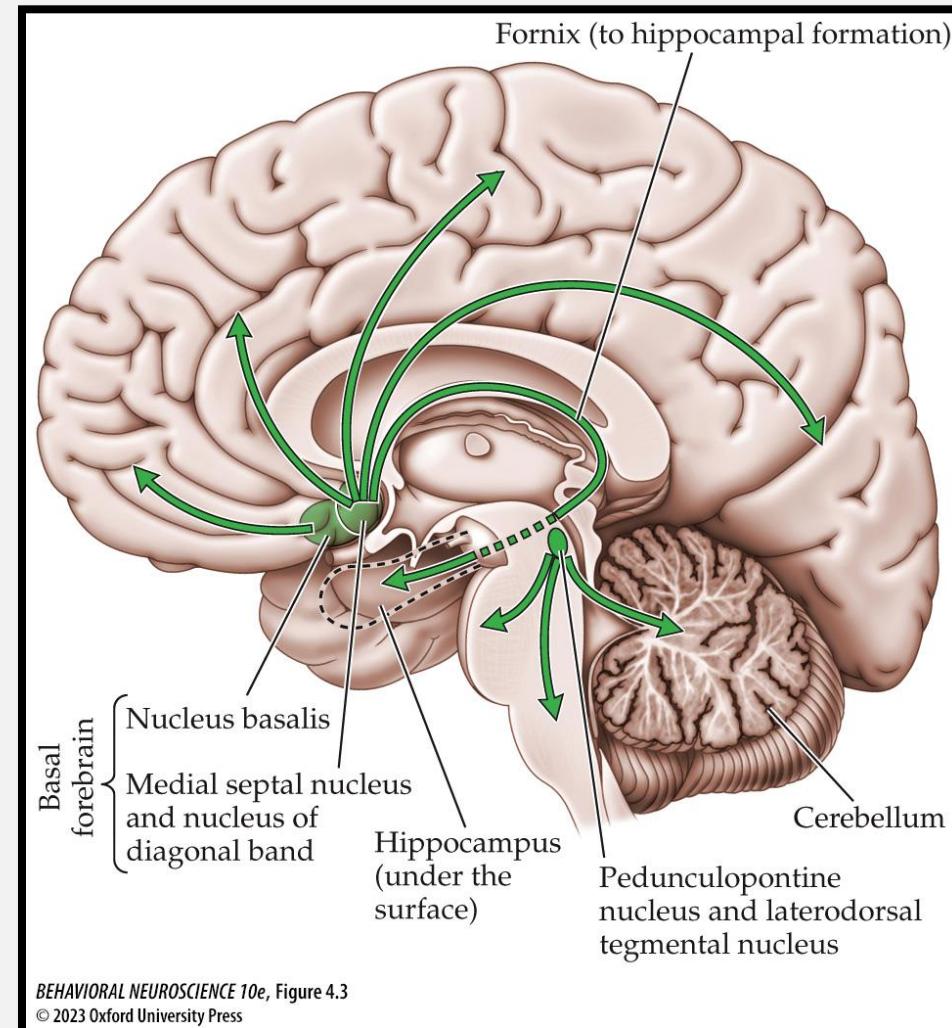
Main inhibitory NTs

- **Gamma-aminobutyric acid (GABA)** and **glycine** are inhibitory.
- There are several classes of GABA receptors.

Neurotransmitters

Acetylcholine (ACh)

- was the first neurotransmitter to be identified.
- Neurons that use Ach are called **cholinergic**.
- In Alzheimer's disease: widespread loss of cholinergic neurons suggest involvement with learning and memory.



Neurotransmitters

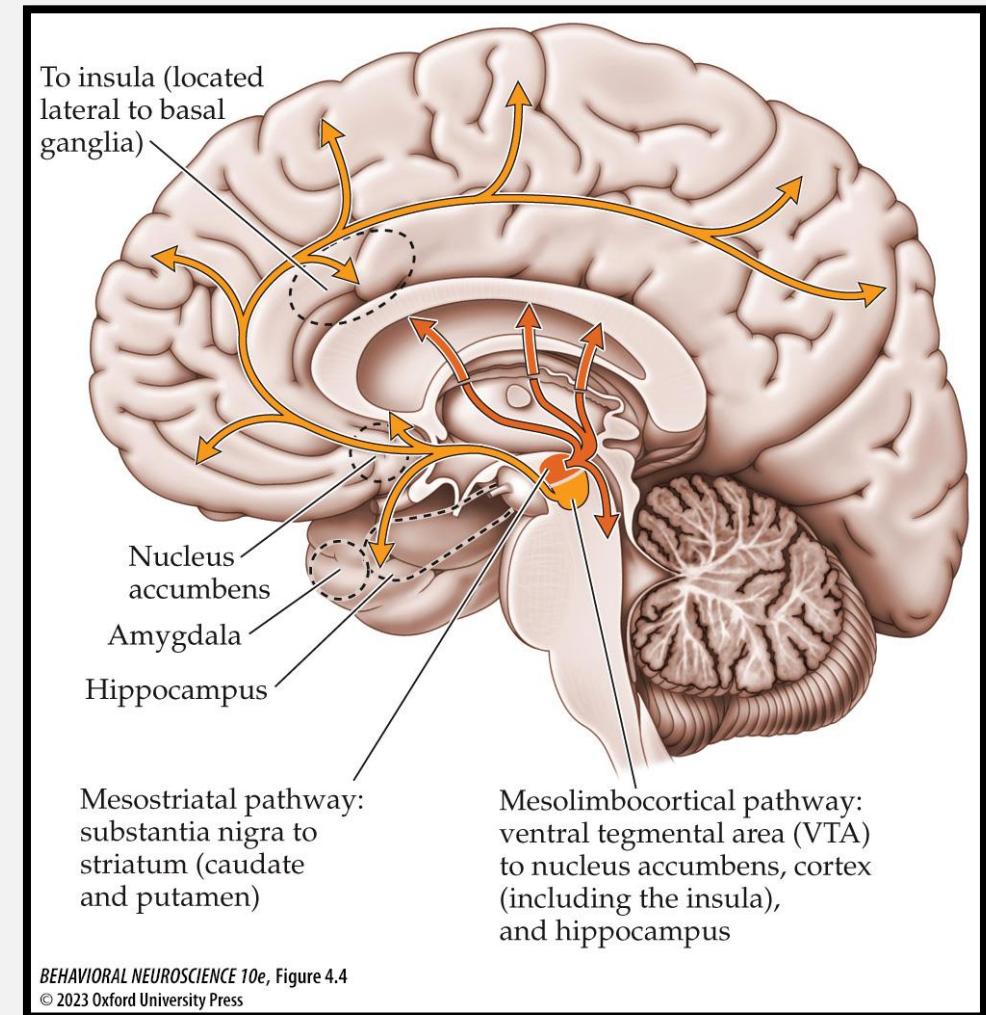
Monoamine neurotransmitters:

- **Catecholamines**—dopamine, epinephrine, norepinephrine
- **Indoleamines**—melatonin, serotonin

Neurotransmitters

Dopamine (DA) is found in neurons in:

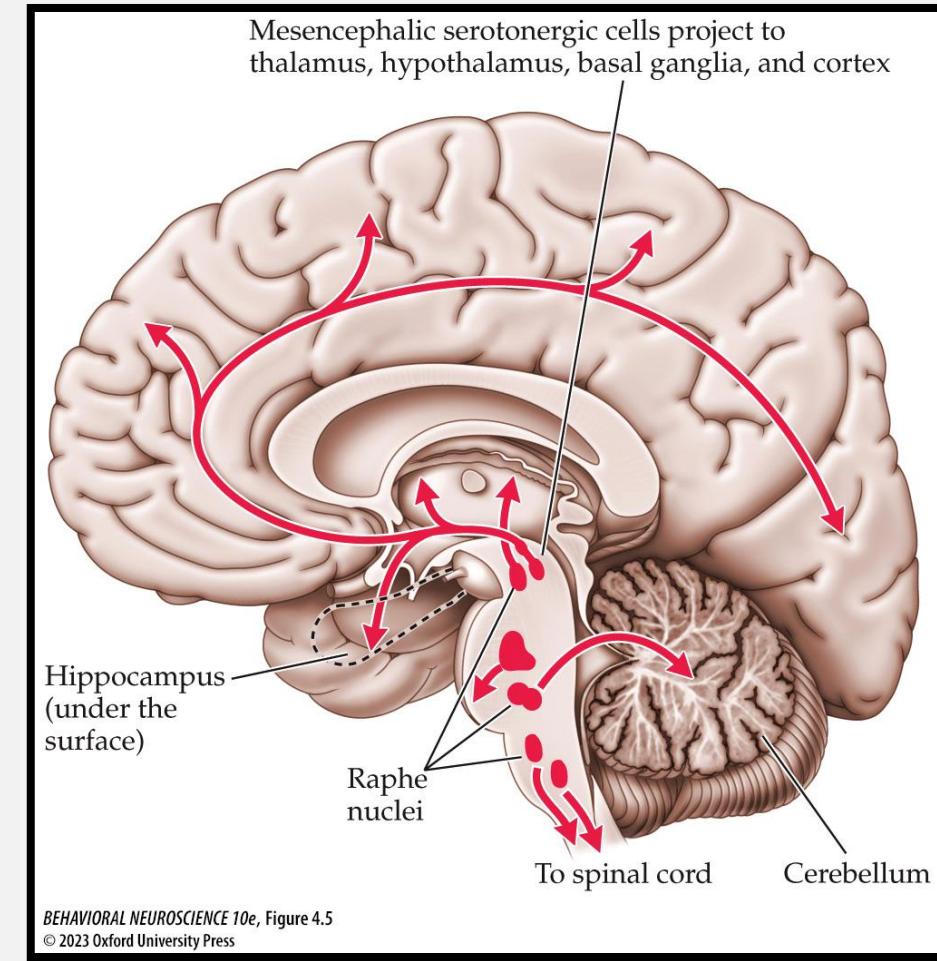
- **Mesostriatal pathway**—important in motor control; neuronal loss is a cause of Parkinson's disease.
- **Mesolimbocortical DA pathway**—involved in reward, reinforcement, and learning; abnormalities are associated with schizophrenia.



Neurotransmitters

Serotonin

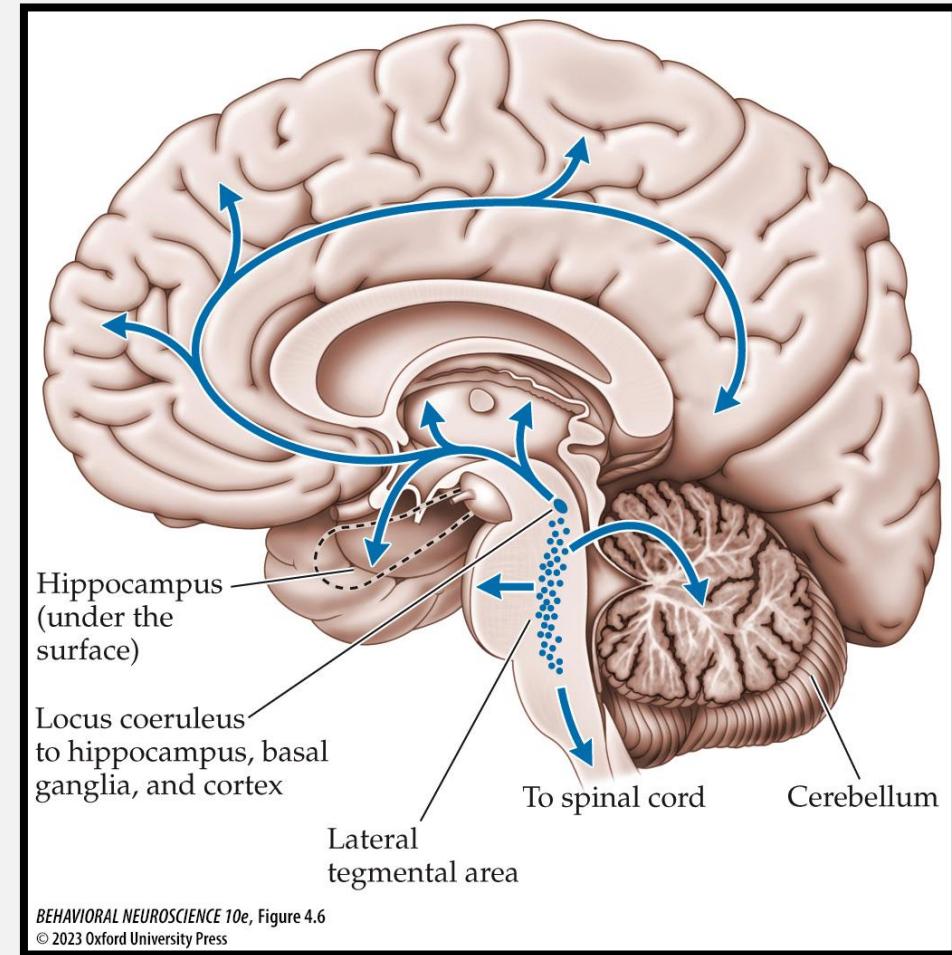
- **5-HT (5-hydroxytryptamine)**: most cell bodies are in **raphe nuclei**; their **serotonergic** fibers project widely.
- Serotonin is implicated in sleep states, mood, sexual behavior, and anxiety.
- Antidepressants, such as Prozac, increase 5-HT activity—effects depend on which receptor subtypes are affected.



Neurotransmitters

Norepinephrine, NE (*noradrenaline*):

- Released from the **locus coeruleus** in the pons and lateral tegmental system in the midbrain
- Cells producing it are **noradrenergic**.
- NE systems modulate processes including mood, arousal, and sexual behavior.



BEHAVIORAL NEUROSCIENCE 10e, Figure 4.6
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Neurotransmitters

Many peptides act as neurotransmitters :

- **Opioid peptides**—mimic opiate drugs such as morphine (enkephalins and endorphins)
- Peptides in gut, spinal cord, or brain
- Pituitary hormones—oxytocin and vasopressin

Neurotransmitters

Nitric oxide (NO) is a gas neurotransmitter:

- Produced in locations other than axons
- Not held in vesicles
- Does not interact with membrane-bound receptors; diffuses out of and into cells
- Can act as a **retrograde transmitter** diffuses from postsynaptic neuron back to the presynaptic neuron
 - Synaptic plasticity
 - Neurovascular coupling
 - Vasodilation
 - Hair growth and penile erection

Drug action

Ligand:

- a substance that binds to a receptor.

Agonist:

- initiates normal effects of the transmitter on that receptor.

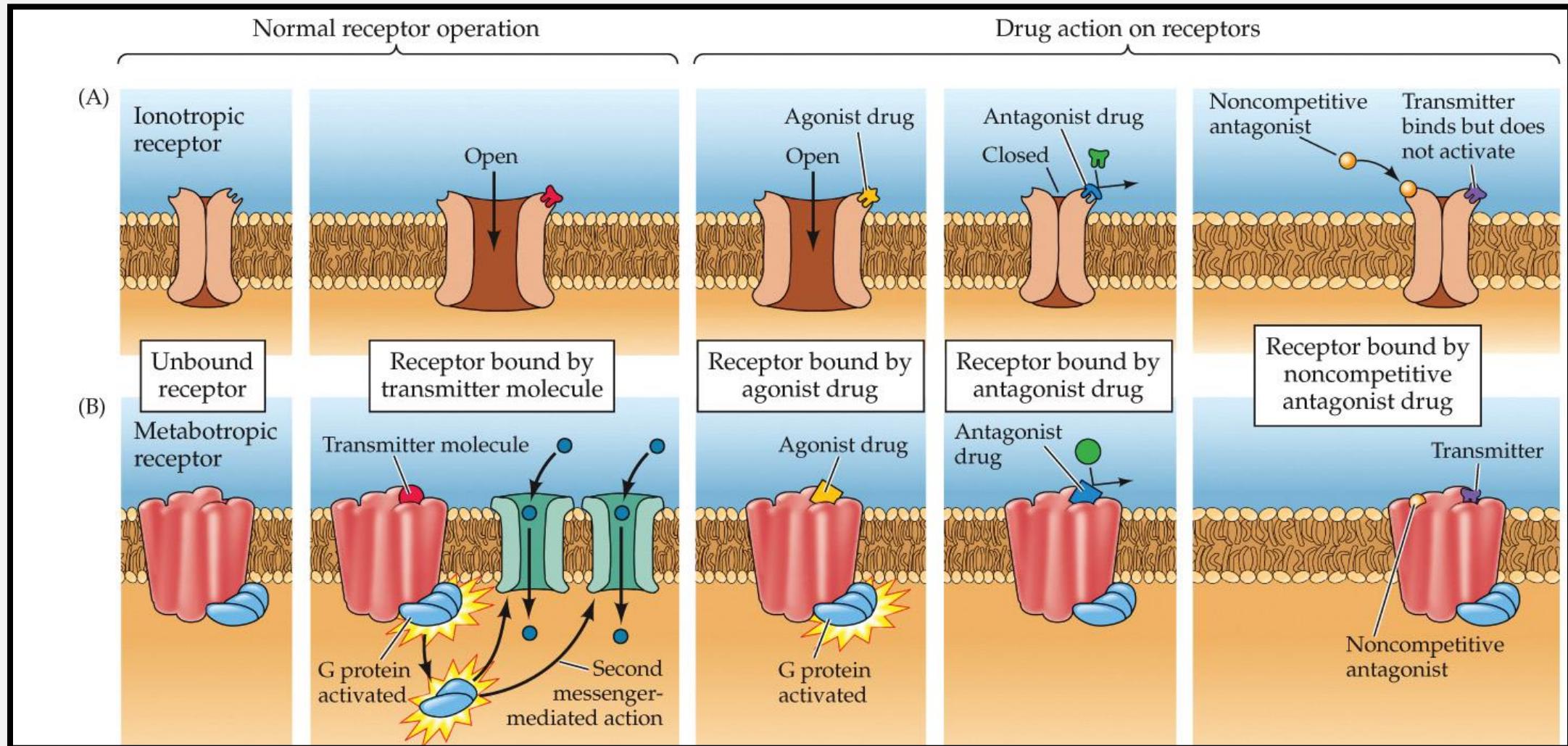
Antagonist:

- binds to a receptor and does not activate it, prevents binding by other ligands.

Inverse agonist:

- initiates the reverse of the normal effect.

Drug action



Drug action

Drugs are competitive ligands:

- they bind to the same part of receptor molecule as an endogenous ligand.
Can be agonists, antagonists, or inverse agonists.

Noncompetitive ligands:

- bind to **modulatory** sites that are not part of the receptor complex.

Drug action

Drugs

- can be developed to bind to just one or a few receptor subtypes.
- Because receptor subtypes have different localizations and functions, drug actions can have widely varying effects.
- Binding of drug on receptor is usually temporary, and afterward, the receptor returns to its normal function.

Drug action

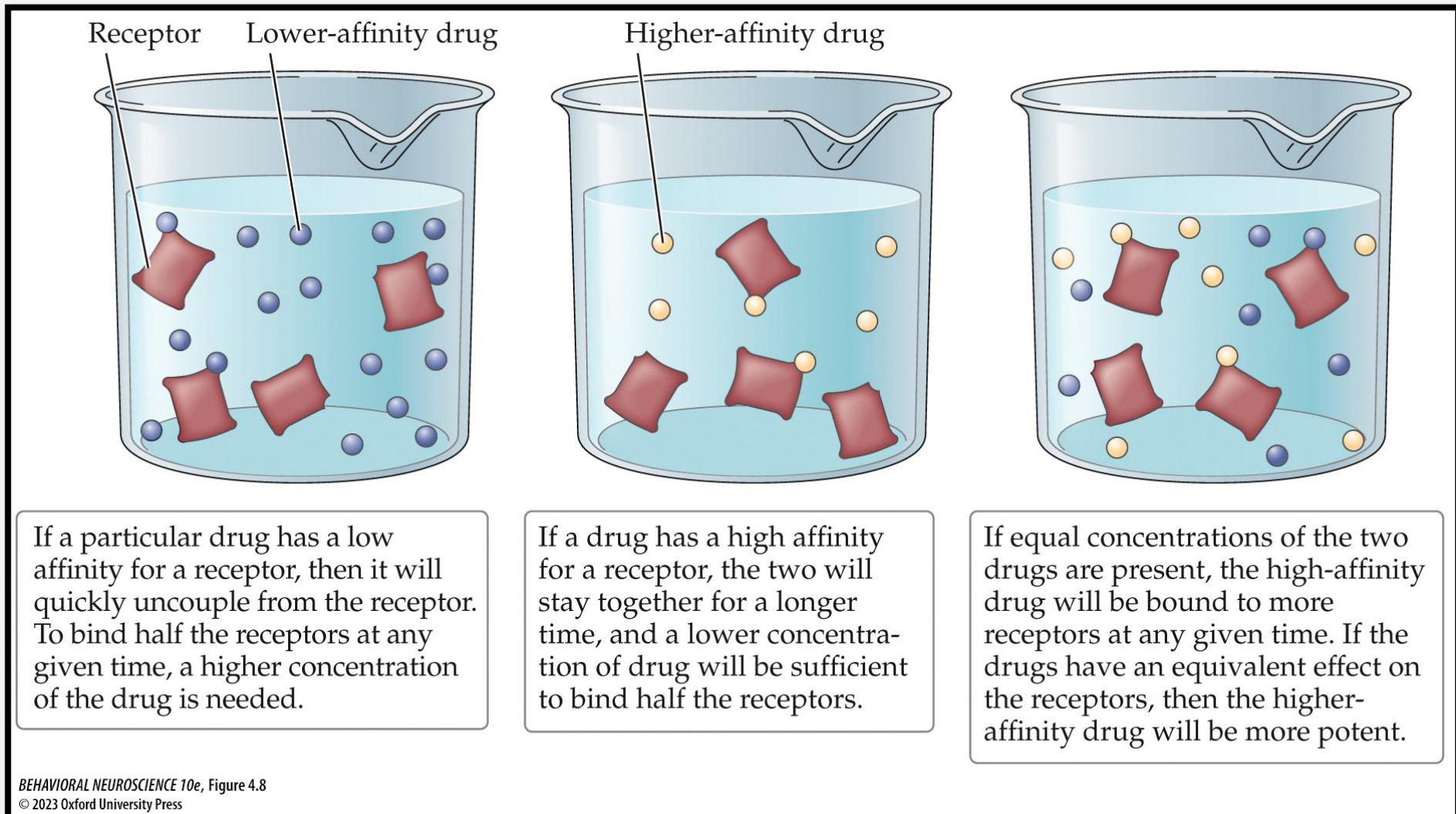
Binding affinity:

- degree of chemical attraction between ligand and receptor.
- A drug with a high affinity for its receptor will be effective at very low doses.

Neurotransmitters

- are low-affinity ligands; can rapidly dissociate from receptors.

Drug action



Drug action

Efficacy:

- ability of a bound ligand to activate the receptor.
- Agonists have high efficacy; antagonists have low efficacy.
- **Partial agonists** produce a medium response regardless of dose.
- Combination of affinity and efficacy determines the overall action of a drug.

Drug action

- The amount of drug that is **bioavailable**—free to act on the target—varies with route of ingestion.
- Duration of a drug's effect is determined by how it is metabolized.
- **Biotransformation** produces active metabolites that may produce side effects.

Drug action

Pharmacokinetics:

- factors that affect movement of a drug through the body.

Blood-brain barrier:

- tight junctions within the CNS prevent the movement of large molecules—can limit drug availability.
- Many drugs that might be useful are too large to pass the blood-brain barrier to enter the brain.

Drug action

Drug tolerance:

- successive exposures have decreasing effects.

Metabolic tolerance:

- organ systems become more effective at eliminating the drug.

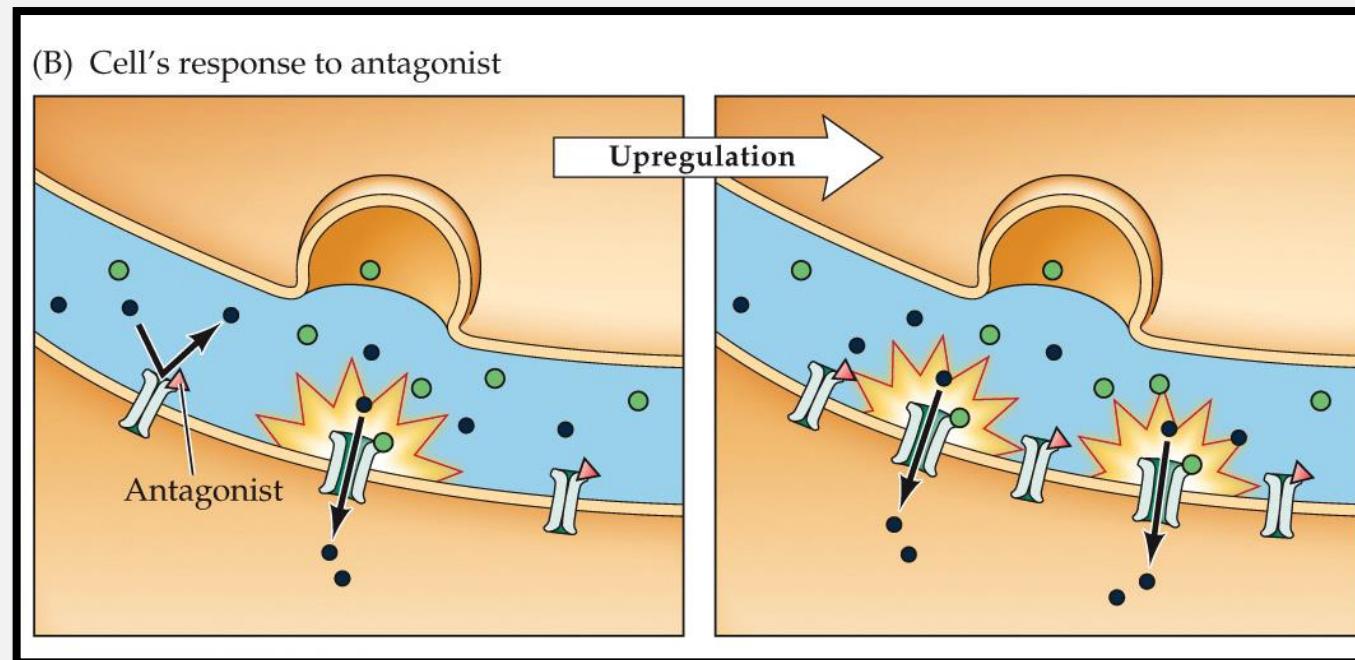
Functional tolerance:

- target tissue may show altered sensitivity to the drug.

Drug action

Receptor regulation

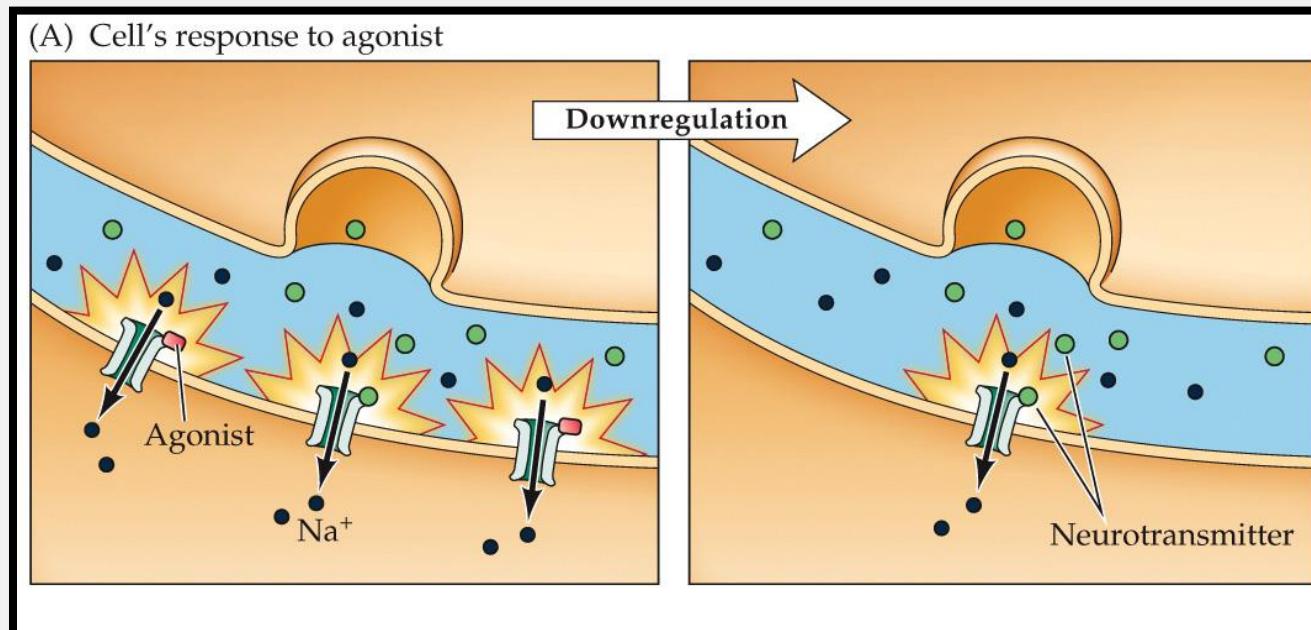
- contributes to functional tolerance—changes in receptor numbers can alter sensitivity in the direction opposite to the drug's effects:
- They **up-regulate** in response to an antagonist.



Drug action

Receptor regulation

- contributes to functional tolerance—changes in receptor numbers can alter sensitivity in the direction opposite to the drug's effects:
- Neurons **down-regulate** in response to an agonist drug—fewer receptors available.



Drug action

Cross-tolerance:

- tolerance to a whole class of chemically similar drugs.

Withdrawal symptoms

- may be caused by drug tolerance.

Sensitization:

- drug effects become stronger with repeated treatment.

Learning objectives

1. Summarize the ways in which drugs alter presynaptic processes, with examples.
2. Summarize drug effects on postsynaptic processes, with examples.
3. Define auto-receptors and explain their function, using caffeine as an example.
4. Describe the processes that terminate transmitter action at synapses
5. Summarize the two major types of antipsychotic medications and review their pharmacological actions.
6. Discuss the major types of actions of drugs for treating depression and anxiety, with examples.
7. Review the discovery of opiates and their major actions in the brain. Using the opiate receptors as examples, discuss the significance of the discovery of orphan receptors in the brain

Effects of drugs

Presynaptic events

- CNS drugs may affect transmitter production, release, or clearance.

Production:

- Inhibit enzymes used in transmitter synthesis, block axonal transport, or prevent storage of transmitter.

Effects of drugs

Release:

- block Na^+ or Ca^{2+} channels, prevent release of specific transmitters (various mechanisms) or alter auto-receptor signals.
- Novocain, Tetrodotoxin (TTX) – prevent release of NT via blocking APs
- Botox (bacteria) - goes in cells and prevents release of Acetylcholine – paralysis at the neuromuscular junction
- Tetanus (bacteria) – Blocks exocytosis of inhibitory influences of motor neurons – strong involuntary contractions of muscles

Effects of drugs

Release:

- **Autoreceptors** – Feedback receptors on presynaptic membrane – how much NT has been released
- Stimulation – false feedback – reduce NT release
- Inhibition – trick cell to release more NT
- **Caffeine** – Presynaptic autoreceptor antagonist (normally bound by adenosine) → increased catecholamine (DA, NE, Epinephrine) release = increased alertness

Effects of drugs

Clearance:

- block transporters involved in reuptake or inhibit enzymes that degrade transmitters.
- Block **Transporters** – typically remove NT from cleft for reuse
- Very common for antidepressants
- Inhibition of **degradation** - breaking down of NT into inactive metabolites
- *Acetylcholinesterase* – breaks down Ach – inhibition causes prolonged contraction of muscles and eventually paralysis – found in pesticides and chemical weapons – *Serin*

A Effects on Transmitter Production

1 Inhibition of transmitter synthesis

Example: *Para*-chlorophenylalanine inhibits tryptophan hydroxylase, preventing synthesis of serotonin from its metabolic precursor.

2 Blockade of axonal transport

Example: Colchicine impairs maintenance of microtubules and blocks axonal transport.

3 Interference with the storage of transmitters

Example: Reserpine blocks the packaging of transmitter molecules within vesicles, thereby allowing the transmitter to be broken down by enzymes.

B Effects on Transmitter Release

4 Prevention of synaptic transmission

Example: Tetrodotoxin, found in puffer fish, blocks voltage-gated Na^+ channels and prevents nerve conduction.

5 Alteration of synaptic transmitter release through calcium channel blockade

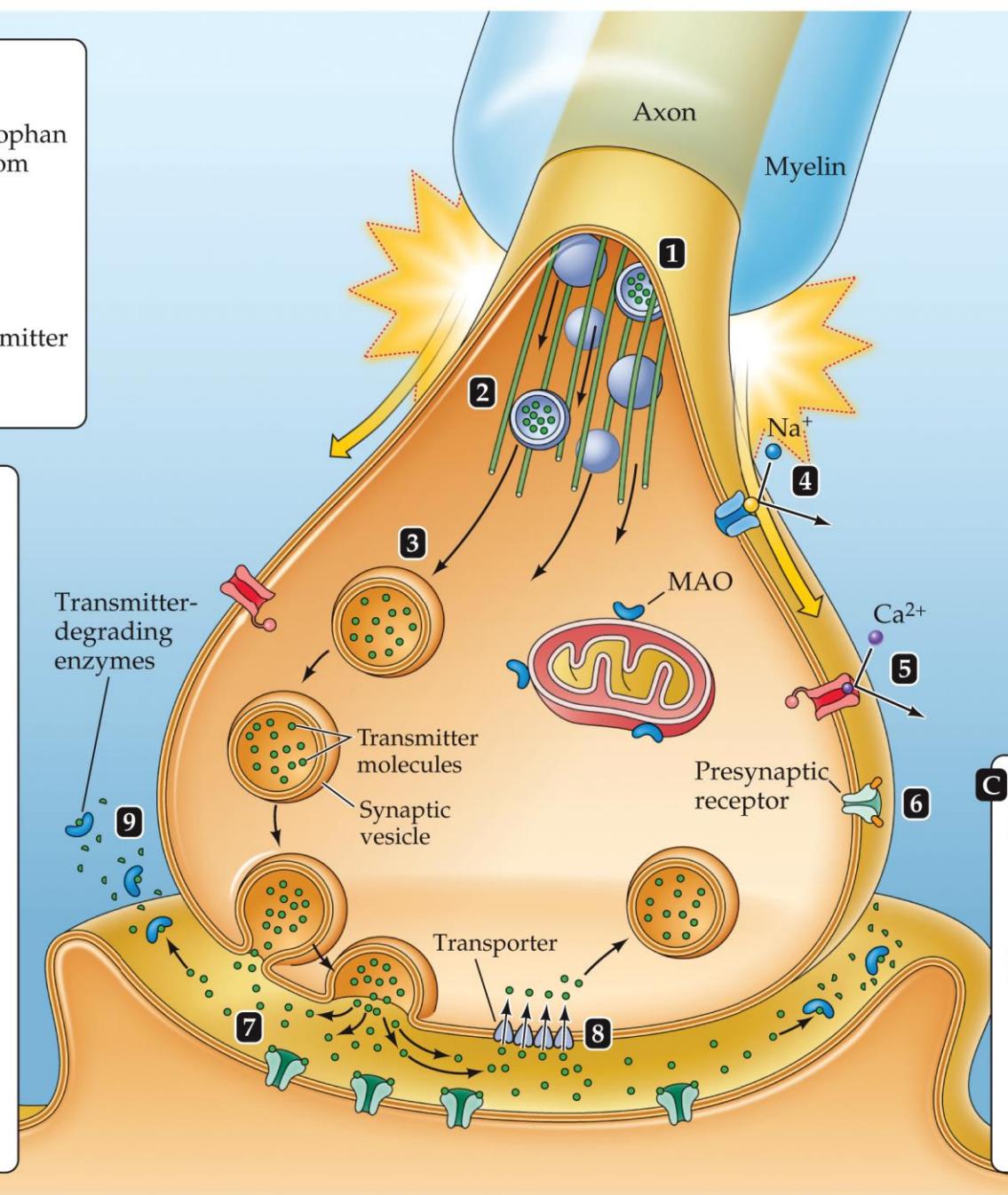
Example: Verapamil, a calcium channel blocker, inhibits transmitter release by reducing the influx of calcium ions that drives vesicles to release transmitter.

6 Alteration of transmitter release through modulation of presynaptic activity

Example: Caffeine competes with adenosine for presynaptic receptors, thus preventing its inhibitory effects.

7 Alteration of synaptic transmitter release through other mechanisms

Examples: Amphetamine stimulates release of catecholamine transmitters, especially DA and NE. Botox (botulinum toxin) disrupts the proteins that allow the vesicles of motor neurons to release ACh, resulting in local paralysis.



C Effects on Transmitter Clearance

8 Inactivation of transmitter reuptake

Examples: Cocaine and amphetamine inhibit reuptake mechanisms, thus prolonging synaptic activity. Certain antidepressants inhibit serotonin or norepinephrine reuptake.

9 Blockade of transmitter degradation

Example: Some drugs (e.g., monoamine oxidase [MAO] inhibitors) inhibit enzymes that normally break down neurotransmitter molecules in the axon terminal or in the synaptic cleft. As a result, transmitter remains active longer and to greater effect.

Effects of drugs

Postsynaptic events

- CNS drugs may affect transmitter receptors or cellular processes in the postsynaptic neuron.
 1. Postsynaptic receptors can be directly blocked or activated by drugs.
 2. Cellular processes: alter receptor numbers, affect second messengers, or alter gene expression.

Effects of drugs

Effects on transmitter receptors

Antagonists

- *Curare* – blocks nicotinic Ach receptors on muscles – immediate paralysis – used as arrow poison

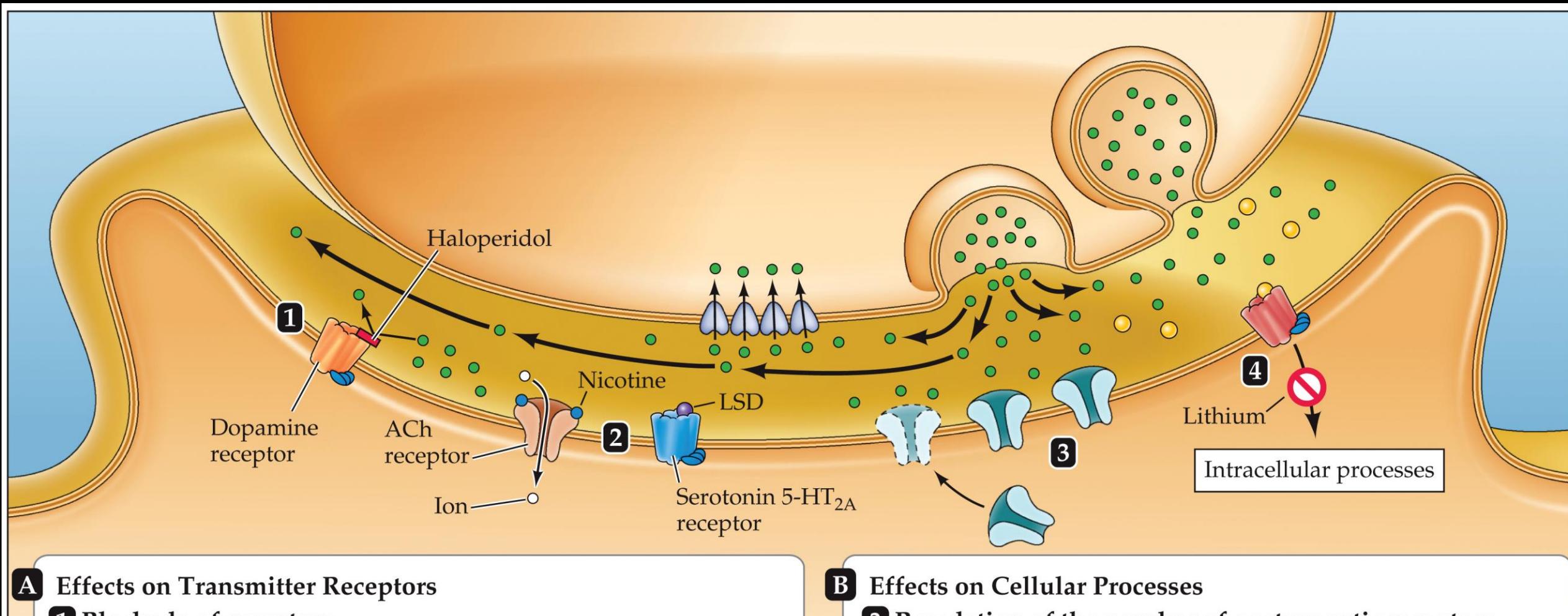
Agonists

- *LSD* – strong stimulation of Serotonin receptor (5-HT_{2A}) found in visual cortex

Effects of drugs

Intracellular processes

- Up/down regulation of receptors
- Impact secondary messenger systems – many effects
- *Lithium Chloride* – Mood stabilizer (helps to control manic and depressive episodes in bipolar disorder (exact mechanism of action unknown)



A Effects on Transmitter Receptors

1 Blockade of receptors

Example: Antipsychotic drugs like haloperidol block dopamine D₂ receptors; curare blocks nicotinic ACh receptors.

2 Activation of receptors

Examples: Nicotine activates ACh receptors. LSD is an agonist at some types of serotonin receptors (such as 5-HT_{2A} receptors).

B Effects on Cellular Processes

3 Regulation of the number of postsynaptic receptors

Example: Alcohol up-regulates (increases) the number of receptors for GABA.

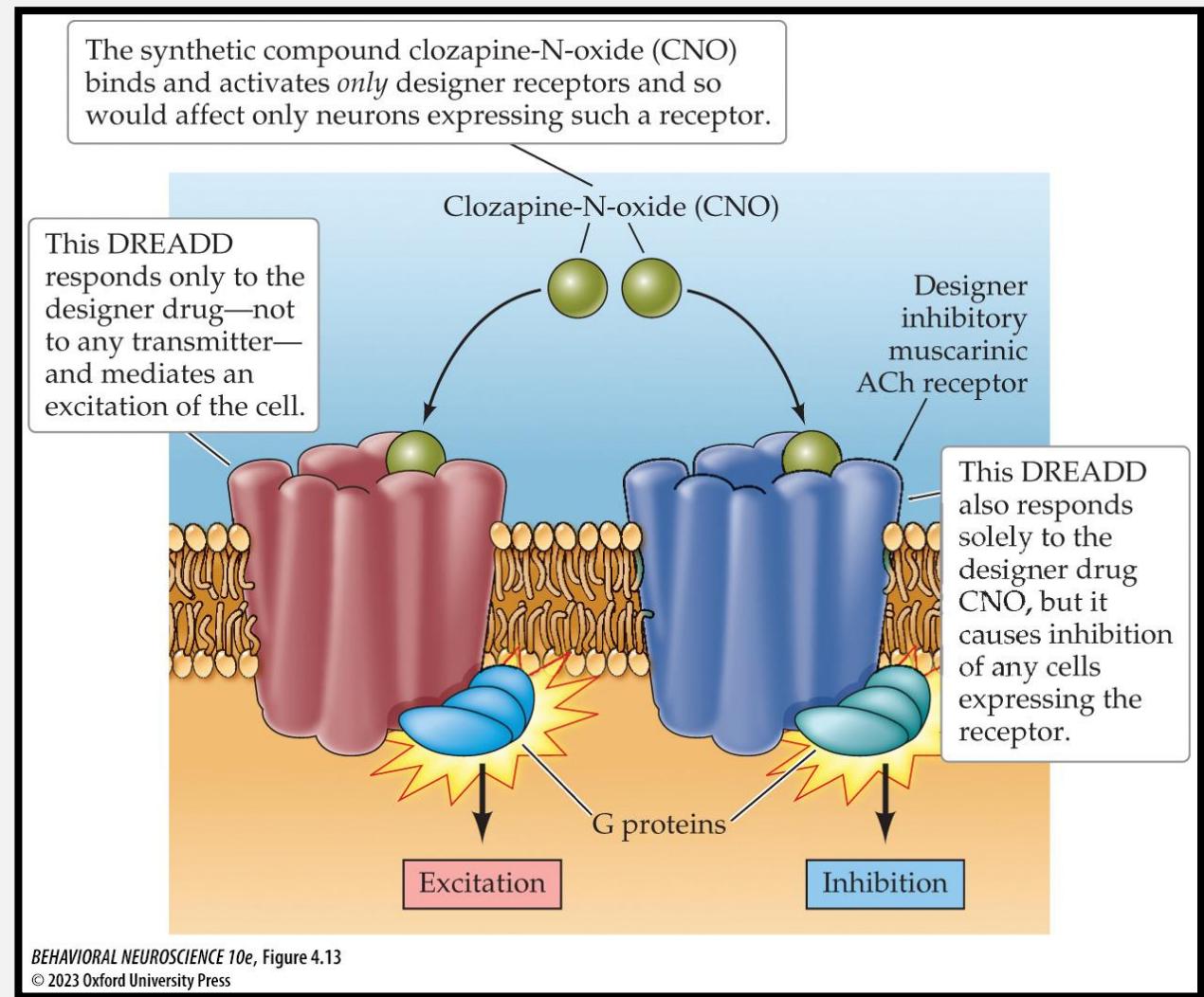
4 Modulation of intracellular signals

Example: Mood stabilizer lithium has many effects, including changes in second messengers, probably leading to changes in gene expression and receptor density.

Neuroactive drugs

Designer receptors exclusively activated by designer drugs (DREADDs):

- receptors expressed *only* by neurons of interest.
- Drugs are designed to selectively activate or inhibit only the targeted cells.
- Used in research to determine the function of the targeted neurons.



Neuroactive drugs

Mental disorders

- Neuroscience breakthroughs over the past 70 years – revolutionized psychiatry and freed millions of people from institutionalized care

Antipsychotics:

- class of drugs used to treat schizophrenia.

First-generation antipsychotics:

- selective dopamine D₂ antagonists.

Second-generation antipsychotics:

- dopaminergic activity; block some serotonin receptors.

Neuroactive drugs

Antidepressants

- treat depression.
- Monoamine oxidase (MAO) inhibitors prevent breakdown of monoamines at the synapses.
- Accumulating monoamines and prolonging their activity is a major feature of antidepressants.

Neuroactive drugs

Tricyclic antidepressants

- increase norepinephrine and serotonin at synapses by blocking their reuptake.

Selective serotonin reuptake inhibitors (SSRIs)

- like Prozac or Zoloft allow serotonin to accumulate in synapses, with fewer side effects than tricyclics.

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

- additionally inhibit reuptake of norepinephrine.

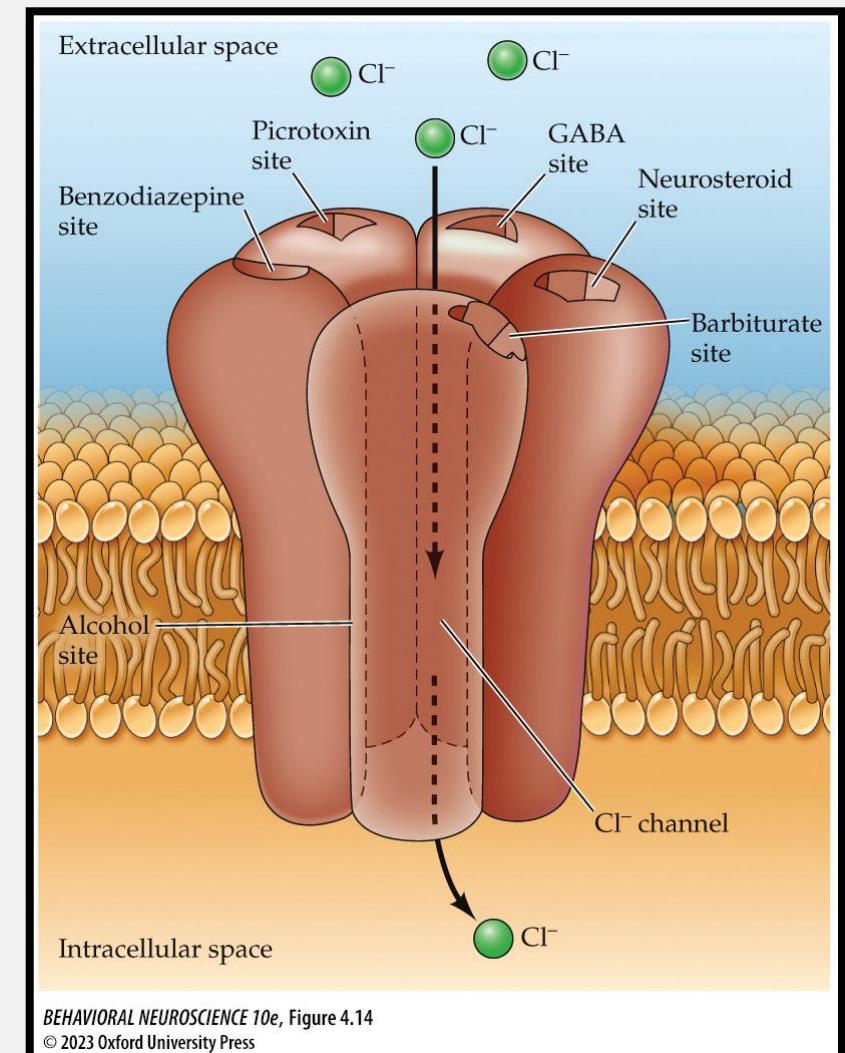
Neuroactive drugs

Depressants

- drugs that reduce nervous system activity.
- **Anxiolytics** (tranquilizers)
- **Barbiturates** – originally developed to reduce anxiety, promote sleep and prevent seizures (but are addictive and easily overdosed)
- **Benzodiazepine agonists** act on GABA_A receptors and enhance the inhibitory effects of GABA (more specific and safer than barbiturates)
- *Alprazolam (Xanax) and Lorazepam (Ativan)* -

Neuroactive drugs

- GABA receptors have several binding sites that enhance or inhibit GABA's effects.
- Benzodiazepines bind at an **orphan receptor**—no known endogenous ligand.
- **Allopregnanolone** acts on a different GABA_A receptor; is elevated during stress and is calming.
- Other **neuro-steroids** may act on GABA_A sites.

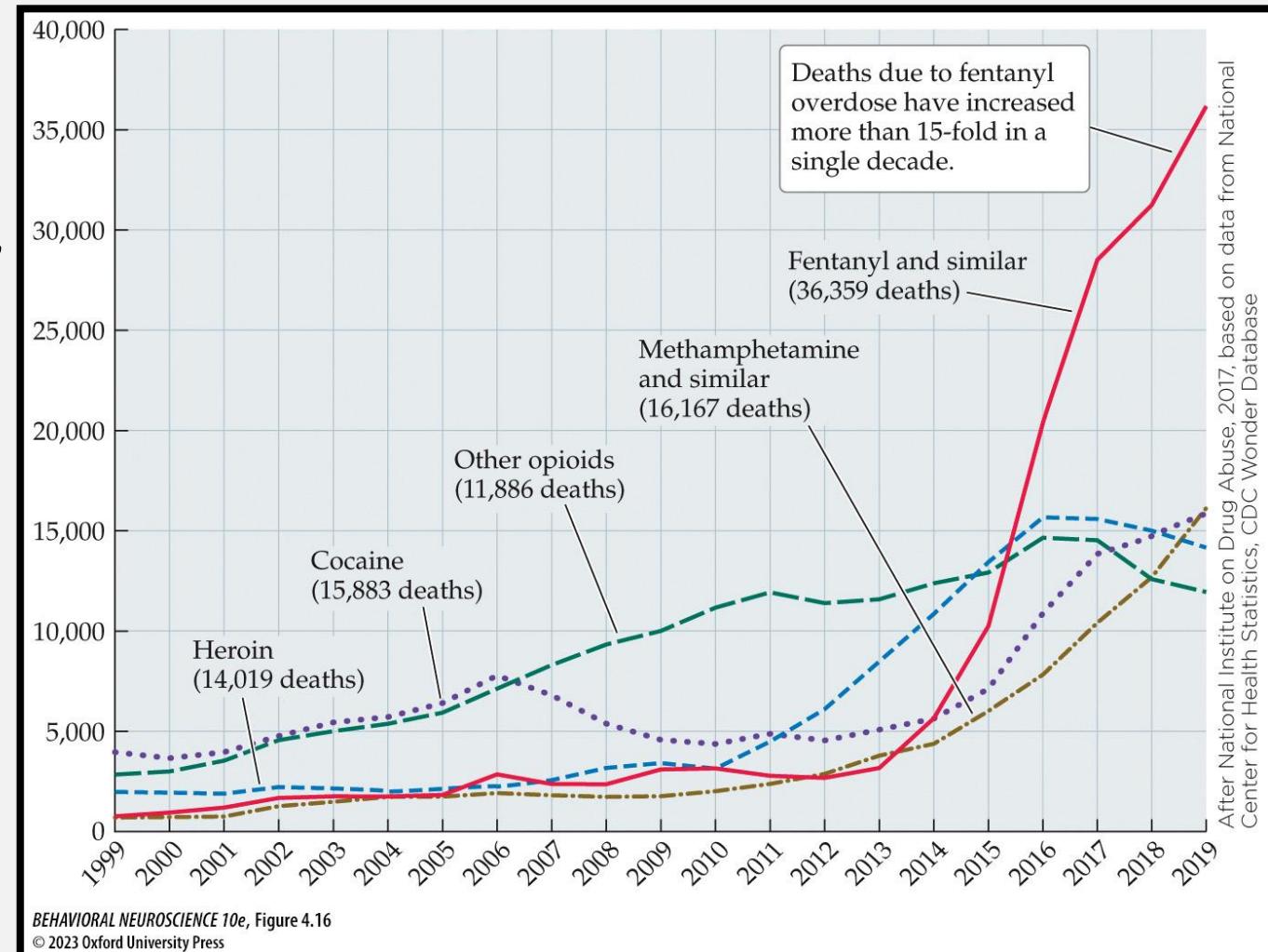


BEHAVIORAL NEUROSCIENCE 10e, Figure 4.14
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Neuroactive drugs

Opiates

- **Opium** (from poppy seedpods) contains **morphine**, an **analgesic** (painkiller).
- Morphine, **heroin**, oxycodone (OxyContin) and fentanyl are all highly addictive.
- Accidental fentanyl overdose is a growing epidemic.



Neuroactive drugs

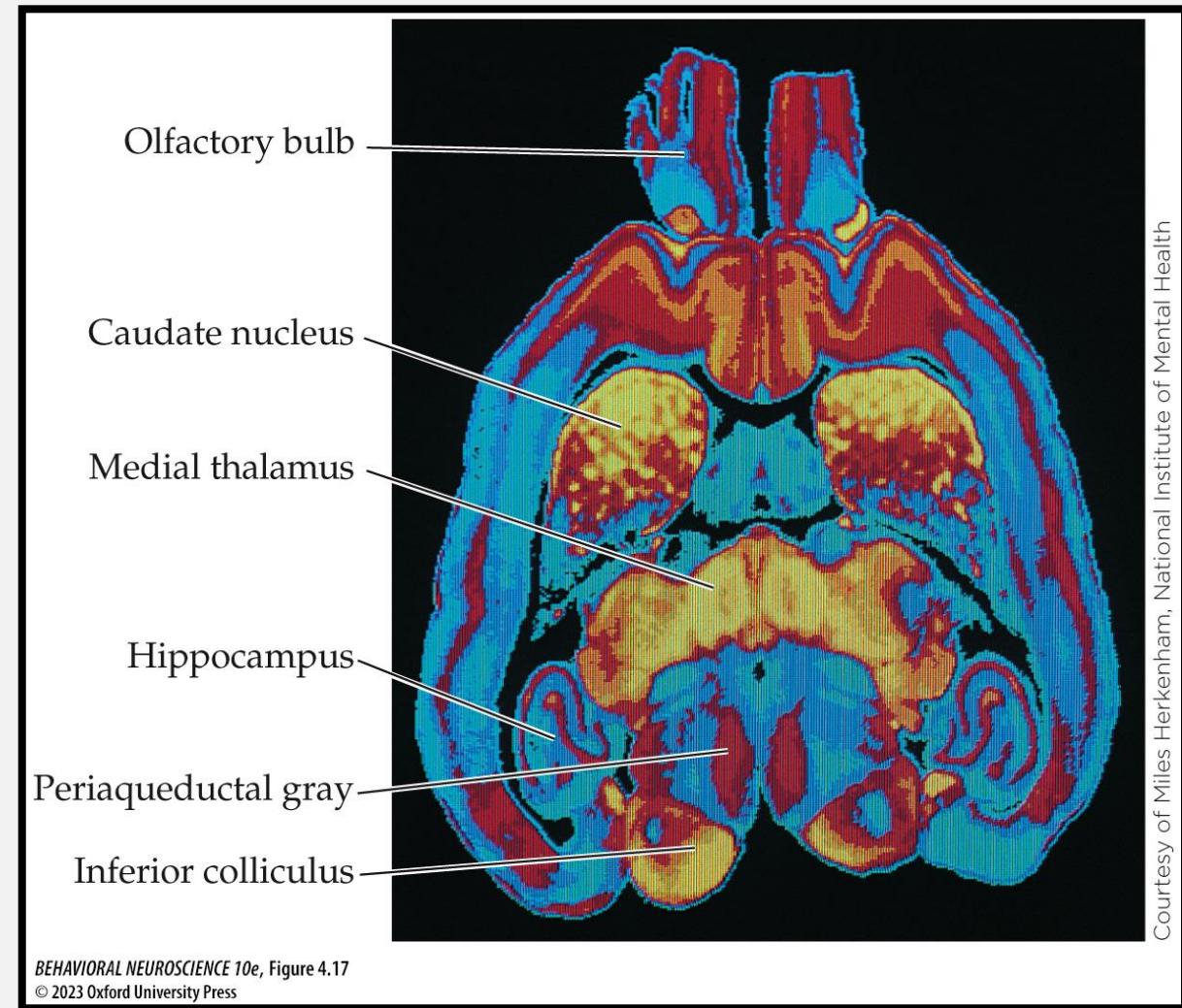
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Opiates

- bind to **opioid receptors** in the brain, especially the locus coeruleus and the **periaqueductal gray**.

Endogenous opioids

- peptides produced in the body that bind to opioid receptors:
- Enkephalins**
- Endorphins**
- Dynorphins**



Neuroactive drugs

Opioids

- 3 main kinds of receptors – all metabotropic
- Antagonists – Naloxone (Narcan), naltrexone – rapidly reverse effects of opiates, rescue people from overdose
- Also blocks rewarding aspects of drugs – helpful to treat addiction
- Naltrexone – approved treatment of alcohol use disorder – blocks the euphoria from alcohol – suggests that alcohol mediates the release of endogenous opioids, which brings pleasure



End
