

Drugs affecting the CNS

- ▶ Most drugs that affect the CNS act by altering some step in the neurotransmission process
- ▶ Drugs affecting the CNS may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitters
- ▶ Other agents may activate or block postsynaptic receptors

Neurotransmission in the CNS

- ▶ The basic functioning of neurons in the CNS is similar to that of the ANS:
 - Transmission of information in the CNS and in the ANS both involve the release of neurotransmitters that diffuse across the synaptic space to bind to specific receptors on the postsynaptic neuron
 - The recognition of the neurotransmitter by the membrane receptor of the postsynaptic neuron triggers intracellular changes

Neurotransmission in the CNS

- ▶ Differences between neurons in the ANS and those in the CNS
 - The circuitry of the CNS is much more complex
 - The number of synapses in the CNS is far greater
 - The CNS contains powerful networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission
 - The CNS communicates through the use of more than 10 (and up to 50) different neurotransmitters, while the ANS uses only two primary neurotransmitters acetylcholine and norepinephrine

Neurotransmission

1. Synthesis
2. Storage (protection and quantal release)
3. Release
4. Transmitter/Receptor Interactions:
 - A. Postsynaptic
 - B. Presynaptic
5. Inactivation
 - A. Diffusion
 - B. Enzymatic Degradation
 - C. Reuptake

Synaptic potentials

- ▶ In the CNS, receptors at most synapses are coupled to ion channels and binding of the neurotransmitter to the postsynaptic receptors results in a rapid and transient opening of ion channels
- ▶ Open channels allow specific ions inside and outside the cell membrane to flow down their concentration gradients
- ▶ The change in the ionic composition across the membrane of the neuron alters the postsynaptic potential, producing either depolarization or hyperpolarization of the postsynaptic membrane, depending on the ions that move and the direction of their movement

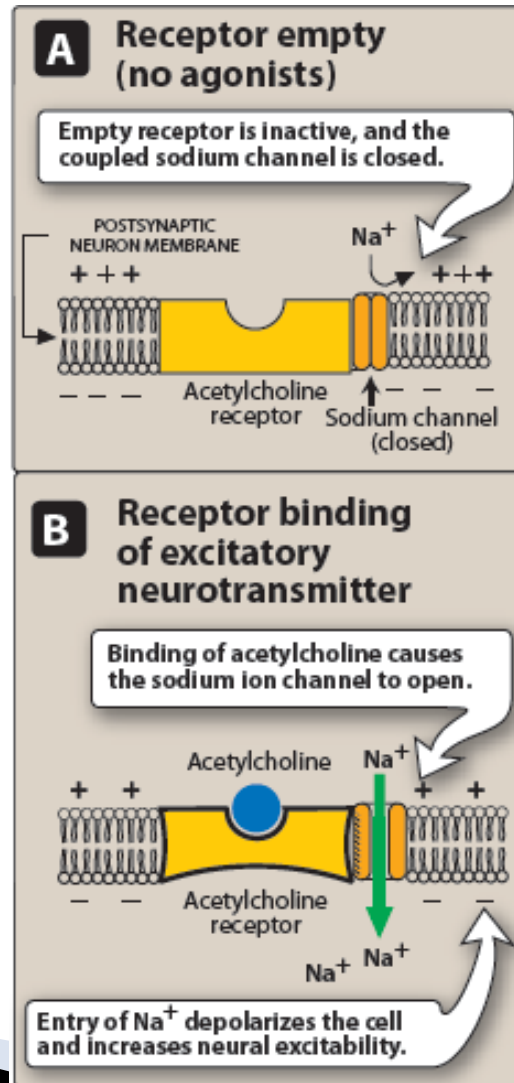
Synaptic potentials

- ▶ Excitatory pathways
- ▶ Inhibitory pathways
- ▶ Combined effects of EPSP and IPSP
- ▶ Neurotransmitters are classified as either excitatory or inhibitory depending on the nature of their action

Excitatory pathways

- ▶ Stimulation of excitatory neurons causes ions movement that results in depolarization of the postsynaptic membrane
- ▶ These excitatory postsynaptic potentials (EPSP) are generated by:
 - 1) Stimulation of an excitatory neuron causes the release of neurotransmitter molecules, such as glutamate or acetylcholine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of sodium (Na^+) ions
 - 2) The influx of Na^+ causes a weak depolarization, or EPSP, that moves the postsynaptic potential toward its firing threshold
 - 3) If the number of stimulated excitatory neurons increases, more excitatory neurotransmitter is released causing the EPSP depolarization of the postsynaptic cell to pass a threshold, thereby generating an all-or-none action potential

Excitatory pathways



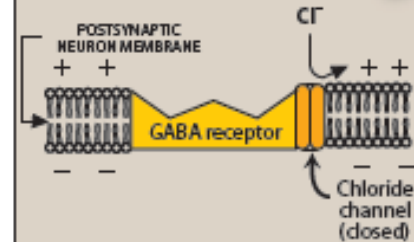
Inhibitory pathways

- ▶ Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane
- ▶ These inhibitory postsynaptic potentials (IPSP) are generated by the following:
 - 1) Stimulation of inhibitory neurons releases neurotransmitter molecules, such as γ -aminobutyric acid (GABA) or glycine, which bind to receptors on the postsynaptic cell membrane causing a transient increase in the permeability of specific ions, such as K^+ and Cl^-
 - 2) The influx of Cl^- and efflux of K^+ cause a weak hyperpolarization, or IPSP, that moves the postsynaptic potential away from its firing threshold which diminishes the generation of action potentials

Inhibitory pathways

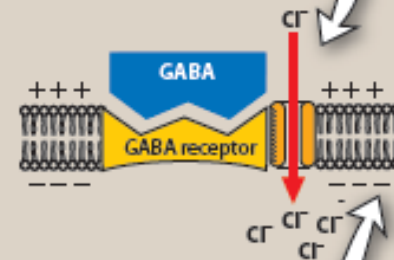
A Receptor empty (no agonists)

Empty receptor is inactive, and the coupled chloride channel is closed.



B Receptor binding of inhibitory neurotransmitter

Binding of GABA causes the chloride ion channel to open.



Entry of Cl^- hyperpolarizes the cell, making it more difficult to depolarize and, thereby, reducing neural excitability.

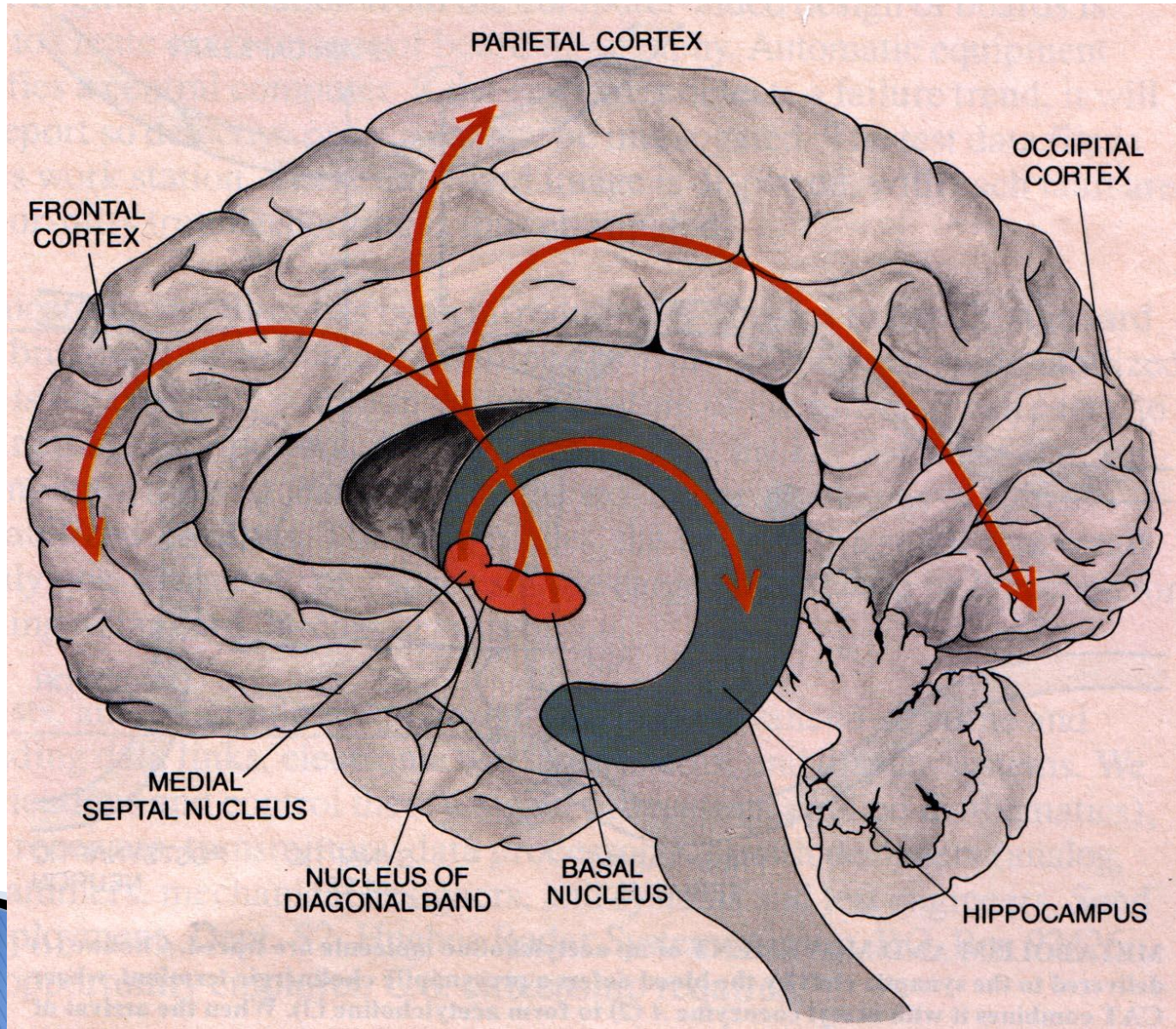
Combined effects of the EPSP and IPSP

- ▶ Most neurons in the CNS receive both EPSP and IPSP input
- ▶ Several different types of neurotransmitters may act on the same neuron but each binds to its own specific receptor
- ▶ The overall resultant action is due to the summation of the individual actions of the various neurotransmitters on the neuron
- ▶ The neurotransmitters are not uniformly distributed in the CNS but are localized in specific clusters of neurons, the axons of which may synapse with specific regions of the brain
- ▶ Many neuronal tracts are chemically coded offering greater opportunity for selective modulation of certain neuronal pathways

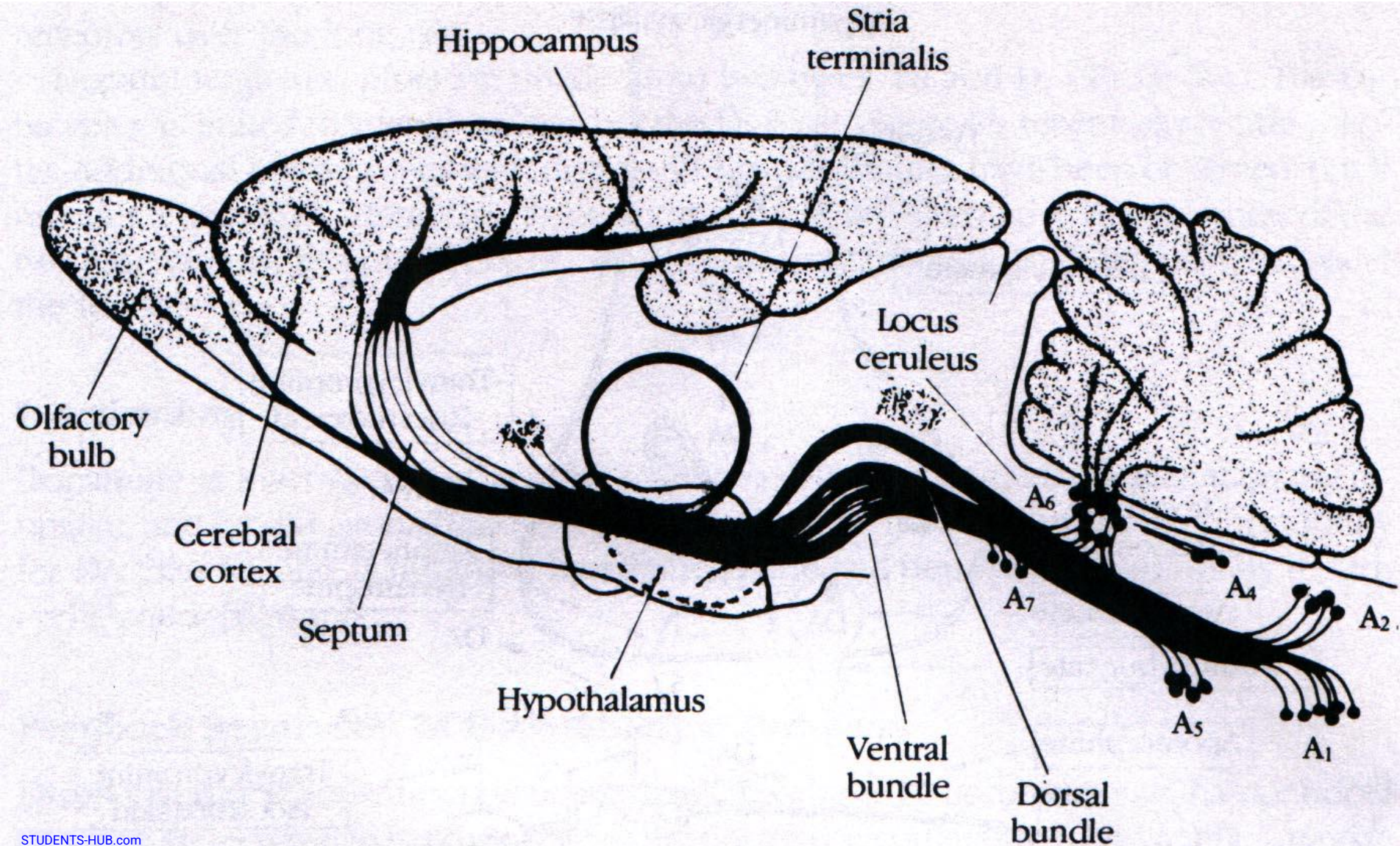
Synaptic pathways

- ▶ Acetylcholine pathways
- ▶ Norepinephrine pathways
- ▶ GABA pathways
- ▶ Dopamine pathways
- ▶ Serotonin pathways
- ▶ Histamine pathways

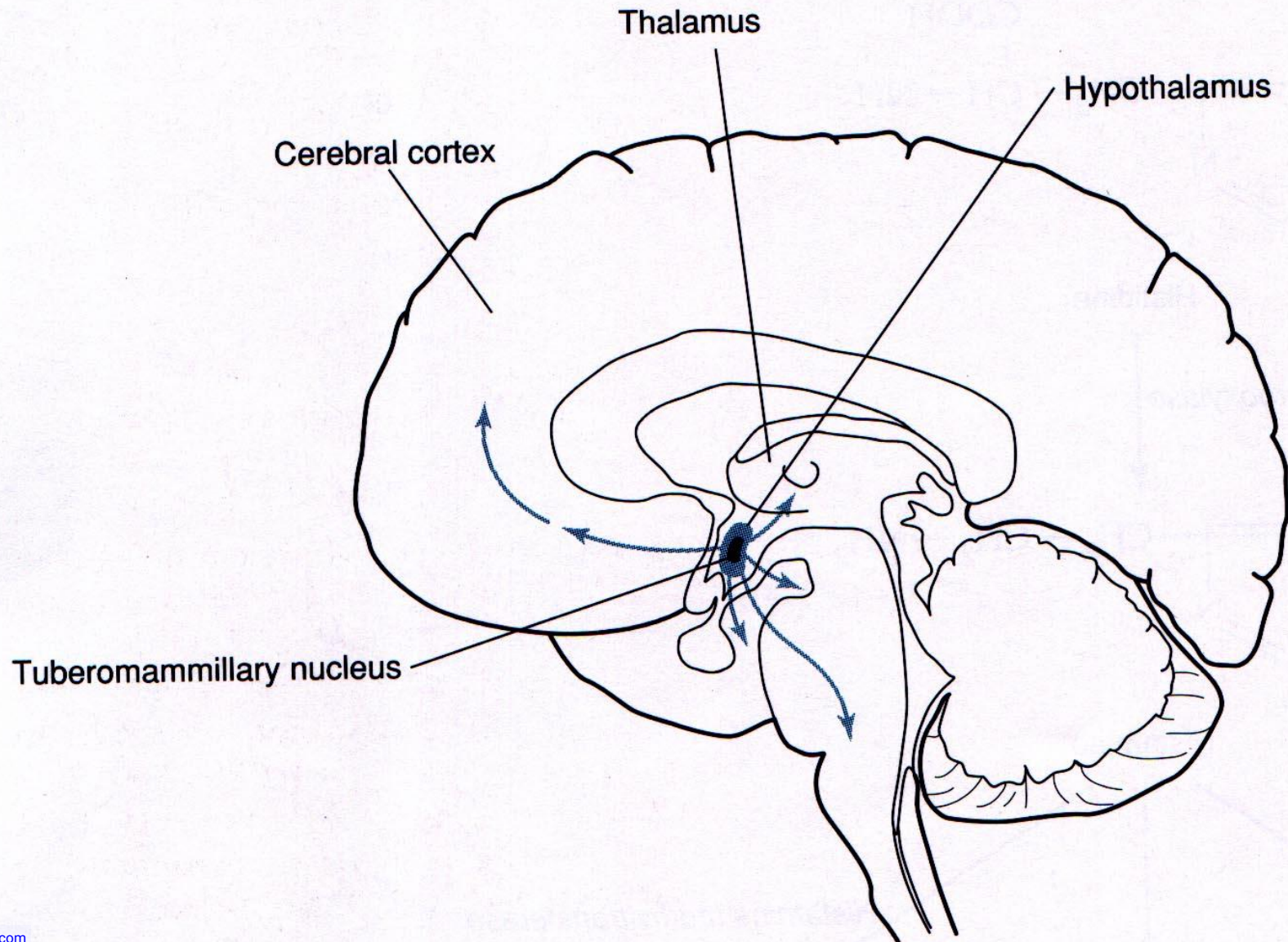
Acetylcholine Pathways



Norepinephrine Pathways



Histamine Pathways



Levels of Complexity

- ▶ Number of brain regions: 100
- ▶ Number of different forms of cells: 1000
- ▶ Number of connections to each cell: 10000
- ▶ Number of nerve cells: 100,000,000,000

Complexity and heterogeneity

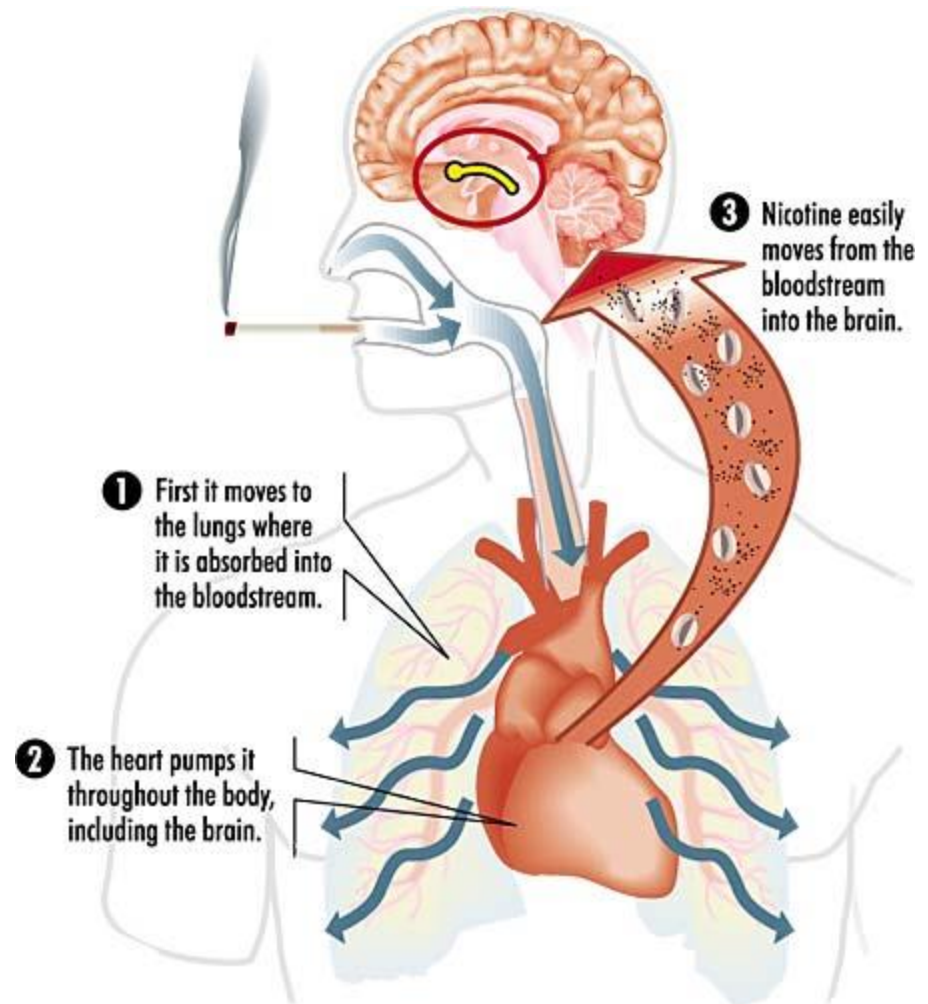
- ▶ In Most organs all cells perform the same function
- ▶ Adjacent cells in the brain may sub serve varied functions and result in different outcomes
- ▶ A lesion in a brain region may affect many other areas that might be connected to it
- ▶ Thus the connectivity of each area has to be taken into consideration when administering drugs so as to avoid un-necessary side effects

Blood brain barrier

- ▶ BBB is laid down within the first trimester of life
- ▶ The BBB denies many drugs from accessing brain tissue
- ▶ Approximately 98% of drugs do not cross the BBB
- ▶ Substances with a molecular weight higher than 500 Daltons can not cross the BBB

Addictive potential of the brain

- ▶ The brain is the information-processing center of the body that determines our behavioral outcome.
- ▶ Reward and punishment pathways
- ▶ The use of powerful and effective drugs may be limited due to their ability to cause addiction or dependence



Neurodegenerative diseases

Neurodegenerative diseases

- ▶ Progressive loss of selected neurons in specific brain areas causing certain disorders in movement or cognition or both
 - Parkinson's disease (PD)
(loss of dopaminergic neurons in the substantia nigra)
 - Alzheimer's disease (AD)
(loss of cholinergic neurons in the nucleus basalis of Maynert)
 - Multiple sclerosis (MS)
 - Amyotrophic lateral sclerosis (ALS)

Parkinson's disease

- ▶ Progressive neurological disorder of muscle movement characterized by:
 - Tremors
 - Muscular rigidity
 - Bradykinesia (slowness in initiating and carrying out voluntary movements)
 - Postural and gait abnormalities
- ▶ Most cases occur after 65 years
- ▶ Incidence is 1%

Parkinson's disease

- ▶ Etiology (cause) is unknown
- ▶ Destruction of dopaminergic neurons in the substantia nigra reducing dopamine actions in corpus striatum, motor control areas of the brain
- ▶ The dopamine influence on cholinergic neurons in the neostriatum is reduced, resulting in overactivity of acetylcholine causing loss of control of muscle movements

Neurotransmitters

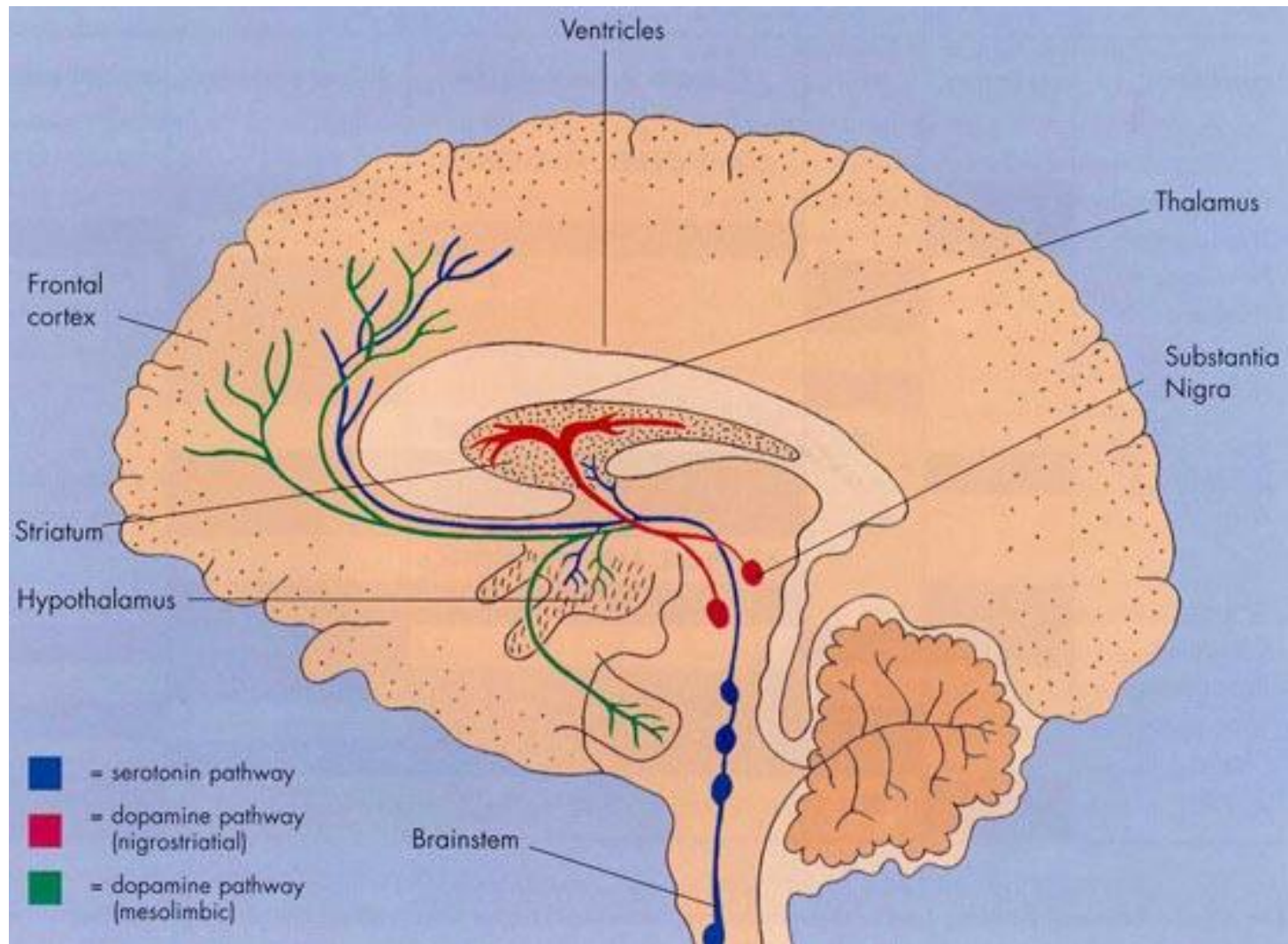
- ▶ Dopamine and acetylcholine in corpus striatum
 - Affect balance, posture
 - Affect muscle tone, involuntary movement
- ▶ Absence of dopamine
 - Allows acetylcholine stimulation

Causes of PD

- ▶ CO or heavy metal poisoning
- ▶ Neurosyphilis
- ▶ Cerebrovascular accidents
- ▶ Brain tumors
- ▶ Head trauma
- ▶ MPTP
- ▶ Post-encephalitic
- ▶ Idiopathic: paralysis agitans

▶ Secondary parkinsonism

- Parkinsonian symptoms infrequently follow viral encephalitis or multiple small vascular lesions
- Drugs such as the phenothiazines and haloperidol may also produce parkinsonian symptoms



Parkinson's disease

- ▶ Strategy of treatment
 - Restoring dopamine in substantia nigra
 - Antagonizing the excitatory effects of cholinergic activity

Parkinson's disease

- ▶ Drugs used in Parkinson's disease offer temporary relief from the symptoms of the disorder, but they do not arrest or reverse the neuronal degeneration
 - Levodopa and carbidopa
 - MAOB inhibitors
 - COMT inhibitors
 - Dopamine receptor agonists
 - Amantadine
 - Antimuscaranic agents

Levodopa and carbidopa

- ▶ Levodopa is a metabolic precursor of dopamine. It restores dopaminergic neurotransmission in the corpus striatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra.
- ▶ Relief provided by levodopa is only symptomatic, and it lasts only while the drug is present in the body.
- ▶ The effects of levodopa on the CNS can be greatly enhanced by coadministering carbidopa, a dopa decarboxylase inhibitor that does not cross the BBB.

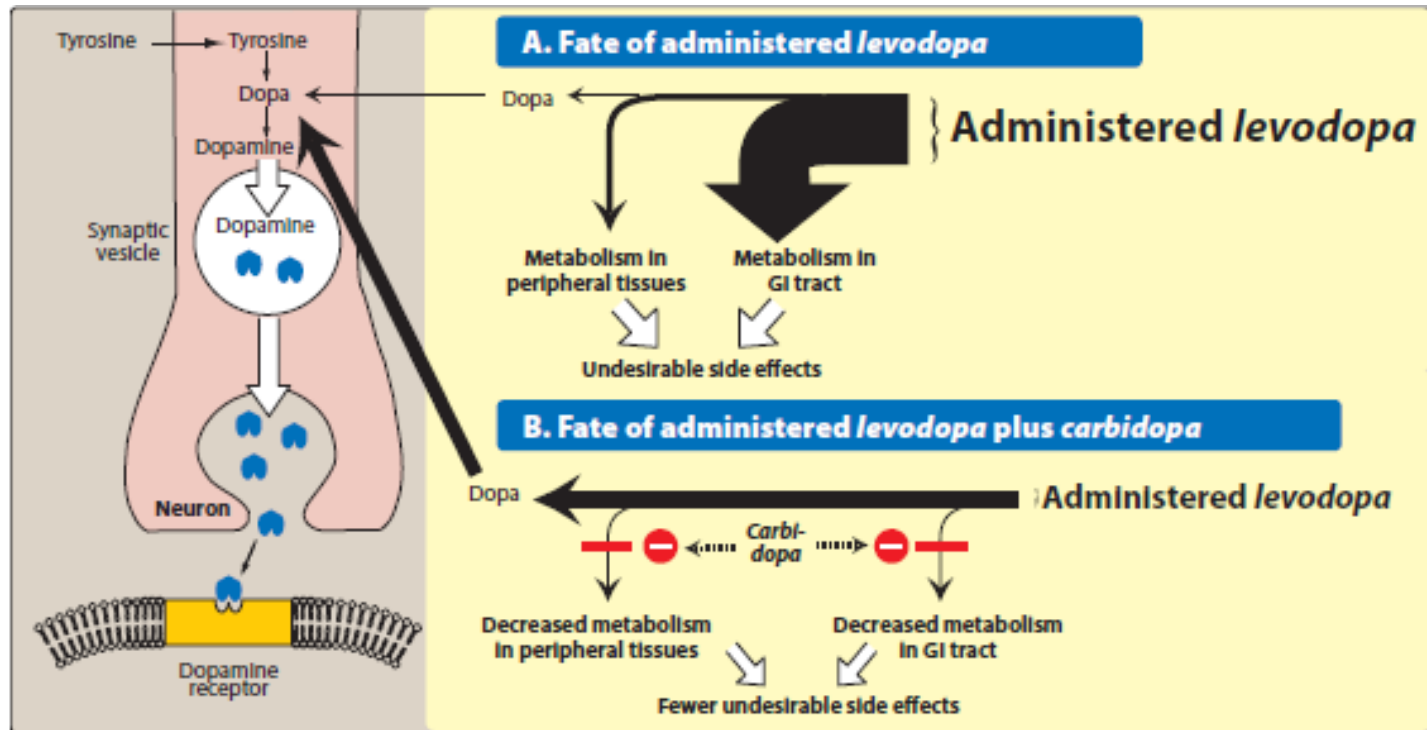


Figure 8.5

Synthesis of dopamine from *levodopa* in the absence and presence of *carbidopa*, an inhibitor of dopamine decarboxylase in the peripheral tissues. GI = gastrointestinal.

Levodopa and carbidopa

▶ Mechanism of action:

◦ Levodopa:

- Parkinsonism results from insufficient dopamine in specific regions of the brain
- Dopamine itself does not cross the blood–brain barrier, but its precursor, levodopa does and is converted to dopamine
- Large doses of levodopa are required, because much of the drug is decarboxylated to dopamine in the periphery, resulting in side effects that include nausea, vomiting, cardiac arrhythmias, and hypotension

◦ Carbidopa:

- Dopa decarboxylase inhibitor, diminishes the metabolism of levodopa in the gastrointestinal tract and peripheral tissues,
- Increases the availability of levodopa to the CNS
- Lowers the dose of levodopa needed by four- to fivefold
- Decreases the severity of the side effects arising from peripherally formed dopamine

Levodopa and carbidopa

- ▶ Actions: Levodopa decreases the rigidity, tremors, and other symptoms of parkinsonism
 - In approximately two-thirds of patients with Parkinson disease, levodopa-carbidopa treatment reduces the severity of the disease for the first few years of treatment
 - Patients then typically experience a decline in response during the third to fifth year of therapy
- ▶ Levodopa should be taken on an empty stomach, typically 45 minutes before a meal

Levodopa and carbidopa

▶ Adverse effects

- Anorexia, Nausea, vomiting
- Abnormal involuntary movements (dyskinesias)
- Tachycardia
- CNS effects: hallucination, psychosis, anxiety

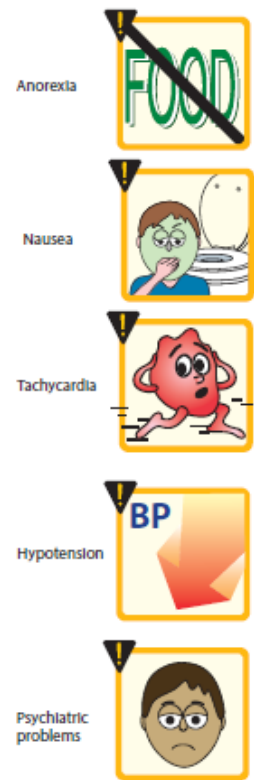


Figure 8.6
Adverse effects of
levodopa.

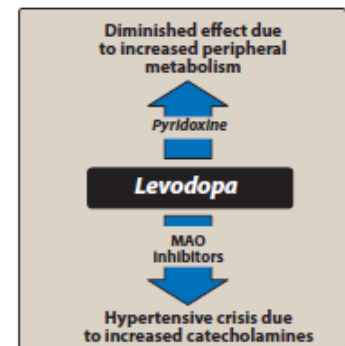
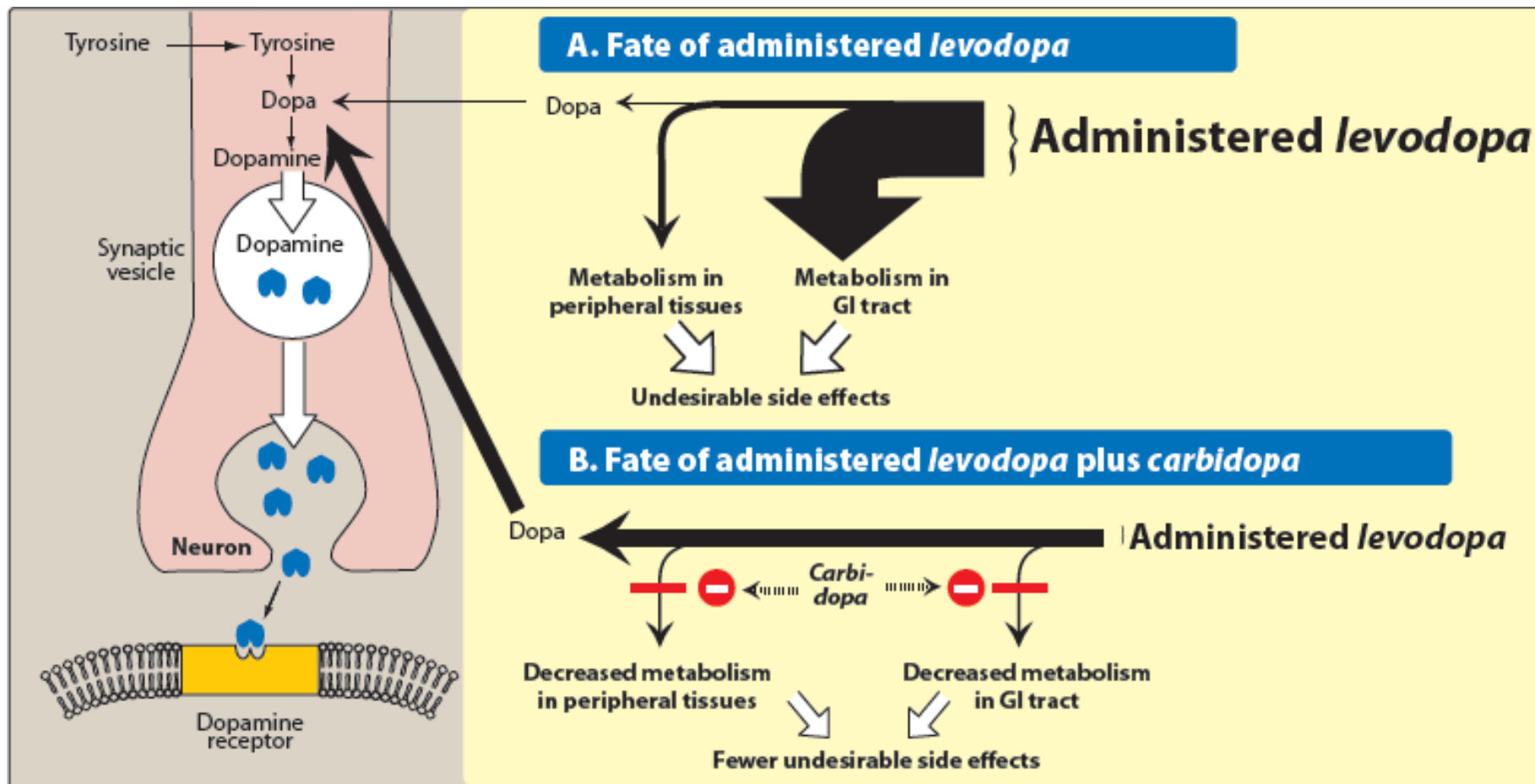
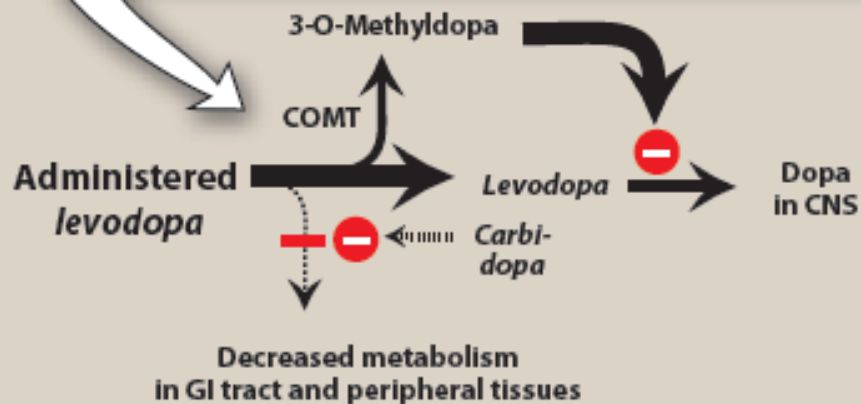


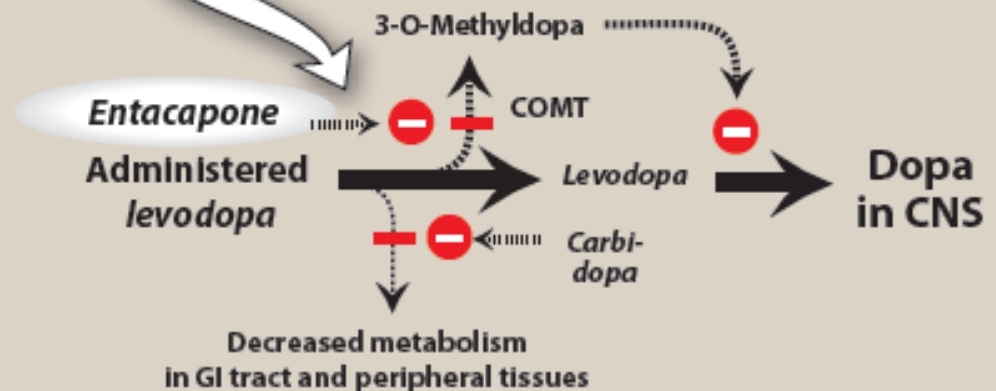
Figure 8.7
Some drug interactions observed
with *levodopa*. MAO = monoamine
oxidase.



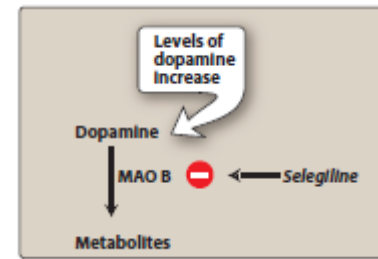
A When peripheral dopamine decarboxylase activity is inhibited by *carbidopa*, a significant concentration of 3-O-methyldopa is formed, which competes with *levodopa* for active transport into the CNS.



B Inhibition of COMT by *entacapone* leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of *levodopa*, and greater concentrations of brain dopamine.



Selegiline and rasagiline



- ▶ Selectively inhibit MAO Type B decreasing the metabolism of dopamine and increasing dopamine levels in the brain
- ▶ Can be co-administered with levodopa and carbidopa
- ▶ Rasagiline is an irreversible and selective inhibitor of brain MAO Type B, has five times the potency of selegiline

COMT inhibitors

- ▶ Catechol-O-methyltransferase metabolizes levodopa to 3-O-methyldopa which competes with levodopa for active transport into the CNS
- ▶ Entacapone or tolcapone selectively inhibit COMT enzyme leading to decreased plasma 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine

Entacapone, tolcapone

- ▶ Can be given in combination with levodopa and carbidopa
- ▶ Both entacapone or tolcapone educe the symptoms of “wearing-off ” phenomena in patients on levodopa-carbidopa
- ▶ Adverse effects
 - Diarrhea, nausea, anorexia
 - Postural hypotension
 - Dyskinesias, hallucinations
 - Tolcapone can cause hepatic necrosis

Dopamine receptor agonists

- ▶ Bromocriptine
 - ▶ Apomorphine
 - ▶ Ropinirole
 - ▶ Pramipexole
 - ▶ Rotigotine
-
- ▶ Effective in patients with advanced Parkinson disease complicated by motor fluctuations and dyskinesias

Dopamine–receptor agonist

Bromocriptine

▶ Ergot alkaloid

▶ Adverse effects:

- Nausea
- Hallucinations, confusion, delirium
- Orthostatic hypotension
- Can cause pulmonary fibrosis

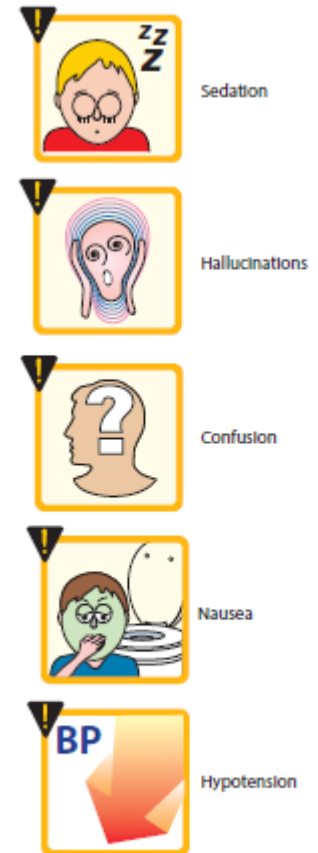


Figure 8.10

Some adverse effects of dopamine agonists.

Dopamine receptor agonists

- ▶ Apomorphine, pramipexole, ropinirole, and rotigotine
- ▶ Apomorphine is parenterally used for the acute management of the hypomobility “off” phenomenon
- ▶ Adverse effects:
 - Nausea
 - Constipation
 - Hallucinations, insomnia, dizziness
 - Orthostatic hypotension

Amantadine

- ▶ Antiviral drug
- ▶ Mechanism of action:
 - Increase release of dopamine
 - Block cholinergic receptors
 - Inhibit N-methyl-D-aspartate (NMDA) glutamate receptors
- ▶ Adverse effects
 - Restlessness
 - Confusion
 - Hallucinations

Antimuscarinic drugs

- ▶ Benztropine
- ▶ Trihexyphenidyl
- ▶ Procyclidine
- ▶ Biperiden
- ▶ Mechanism of action: block cholinergic transmission to restore the balance between acetylcholine and dopamine
- ▶ Less efficacious than levodopa, used as adjuvant in antiparkinsonism therapy
- ▶ Adverse effects (antimuscarinic side effects)
 - Tachycardia
 - Urinary retention
 - Dry mouth
 - Constipation
 - Confusion, hallucination

Summary of Treatment by Stage

- ▶ Mild PD: anticholinergic only
- ▶ Moderate PD: l-dopa, carbidopa, and an anticholinergic
- ▶ Severe PD: add on dopamine agonist, MAO-B inhibitor, or COMT inhibitor as required

Alzheimer's disease

- ▶ Progressive neurodegenerative disorder characterized by progressive loss of brain function
 - Memory loss, confusion, dementia
- ▶ The most prevalent neurodegenerative disease
- ▶ The number of cases is expected to increase as the proportion of elderly people in the population increases
- ▶ Characterized by:
 - Accumulation of plaque and tangle deposits in the brain
 - Loss of cortical neurons, particularly cholinergic neurons

Alzheimer's disease

- ▶ Pharmacologic intervention is only palliative and provides modest short-term benefit
- ▶ None of the currently available therapeutic agents alter the underlying neurodegenerative process
- ▶ Current therapies aim at:
 - Improving cholinergic transmission within the CNS
 - Preventing excitotoxic actions resulting from overstimulation of NMDA–glutamate receptors in selected brain areas

Alzheimer's disease

- ▶ Alzheimer's has three distinguishing features:
 - 1) accumulation of senile plaques (β -amyloid)
 - 2) formation of numerous neurofibrillary tangles
 - 3) loss of cortical cholinergic neurons

Alzheimer's Disease (AD)

- ▶ Unknown cause
- ▶ Possible causes
 - Genetic defects
 - Chronic inflammation
 - Excess free radicals
 - Environmental factors

Alzheimer's disease

- ▶ Treatment strategies
 - Acetylcholineesterase inhibitors
 - NMDA receptor antagonists

Acetylcholinesterase inhibitors

- ▶ Donepezil
- ▶ Galantamine
- ▶ Rivastigmine
- ▶ Tacrine
- ▶ Inhibit acetylcholinesterase (AChE) within the CNS which improves cholinergic transmission, at least at those neurons that are still functioning
- ▶ Provide a modest reduction in the rate of loss of cognitive functions in Alzheimer patients

Acetylcholinesterase inhibitors

▶ Adverse effects

- Nausea, diarrhea, vomiting, anorexia
- Tremors
- Bradycardia
- Muscle cramps
- Tacrine is hepatotoxic

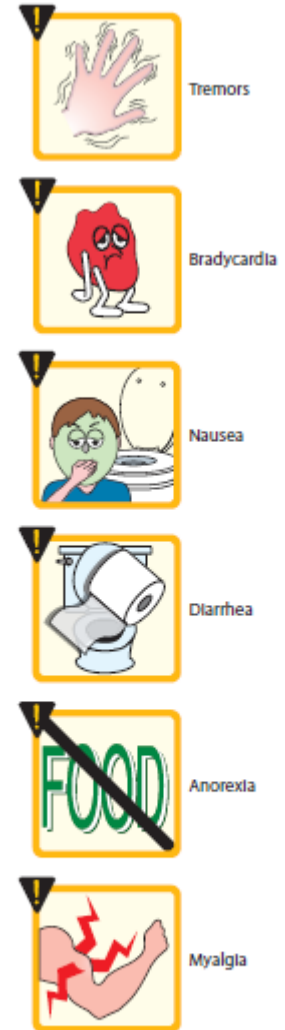


Figure 8.13
Adverse effects of AChE inhibitors.

NMDA receptor antagonist

- ▶ Overstimulation of NMDA glutamate receptors is excitotoxic on neurons and is suggested as a mechanism for neurodegenerative or apoptotic (programmed cell death) processes
- ▶ Binding of glutamate to the NMDA receptor assists in the opening of an associated ion channel that allows Na^+ and, particularly, Ca^{2+} to enter the neuron, excess intracellular Ca^{2+} can activate a number of processes that ultimately damage neurons and lead to apoptosis
- ▶ Antagonists of the NMDA–glutamate receptor are neuroprotective preventing the loss of neurons following ischemic and other injuries

NMDA receptor antagonist

- ▶ Memantine
- ▶ Mechanism of action:
 - Acts as neuroprotective, preventing the neuron loss by blocking NMDA glutamate receptor-associated ion channel, limiting Ca^{2+} influx into the neuron, so that toxic intracellular levels are not achieved during NMDA-receptor overstimulation and preventing its and excitotoxic effects on neurons
- ▶ Memantine slows the rate of memory loss

Multiple sclerosis

- ▶ Autoimmune inflammatory demyelinating disease of the CNS
- ▶ Progressive weakness, visual disturbances
- ▶ Mood alterations, cognitive deficits
- ▶ Symptoms may be mild, such as numbness in the limbs, or severe, such as paralysis or loss of vision

Drugs used for multiple sclerosis

- ▶ Corticosteroids like prednisone and dexamethasone
(For acute attacks of the disease)
- ▶ Azathioprine: Immunosuppressant
- ▶ Interferon $\beta 1a$ and interferon $\beta 1b$: immune system modulators of interferons and T-helper cell response that contribute to inflammatory processes causing demyelination of axons

Drugs used for multiple sclerosis

▶ Mitoxantrone:

- Cytotoxic, kills T cells
- Modifies the body's immune response through inhibition of white blood cell-mediated inflammatory processes that eventually lead to myelin sheath damage and a decreased or inappropriate axonal communication between cells
- Adverse effects
 - Depression
 - Local injection or infusion reactions
 - Hepatic enzyme increases
 - Flu-like symptoms, such as fever and myalgias
 - Leukopenia

Drugs used for multiple sclerosis

- ▶ Fingolimod (oral)
 - Alters lymphocyte migration, resulting in sequestration of lymphocytes in lymph nodes
 - Risk of life-threatening infection
- ▶ Dalfampridine (oral)
 - Blocks potassium channels, increases conduction of action potentials in demyelinated axons
 - Improves walking speeds vs placebo
- ▶ Glatiramer
 - Synthetic polypeptide that resembles myelin protein and may act as a “decoy” to T-cell attack

Amyotrophic lateral sclerosis

- ▶ Progressive neurological disease that attacks the neurons responsible for controlling voluntary muscles
- ▶ Progressive weakness and wasting of muscles
- ▶ Destruction of motor neurons
- ▶ Causes muscle weakness, disability and death
- ▶ Drugs for ALS
 - Riluzole
 - NMDA receptor antagonist
 - Blocks glutamate, sodium channels, and calcium channels
 - Improve the survival time and delay the need for ventilator support in patients suffering from ALS