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 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 than10 (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

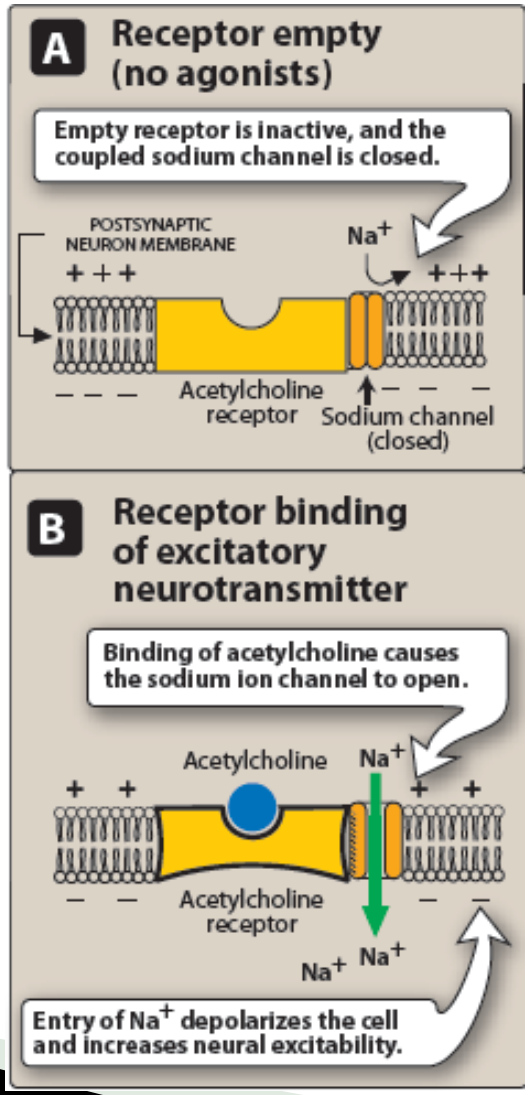
- Stimulation of excitatory neurons causes ions movement that results in depolarization of the postsynaptic membrane
- These excitatory postsynaptic potentials (EPSP) are generated by:

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

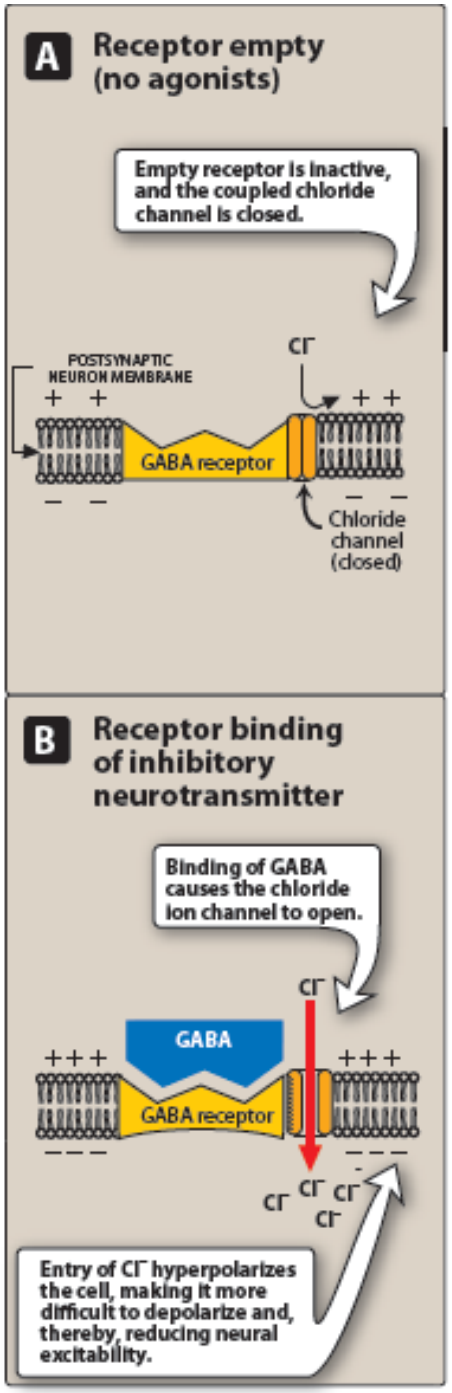
- Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane
- These inhibitory postsynaptic potentials (IPSP) are generated by the following:

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



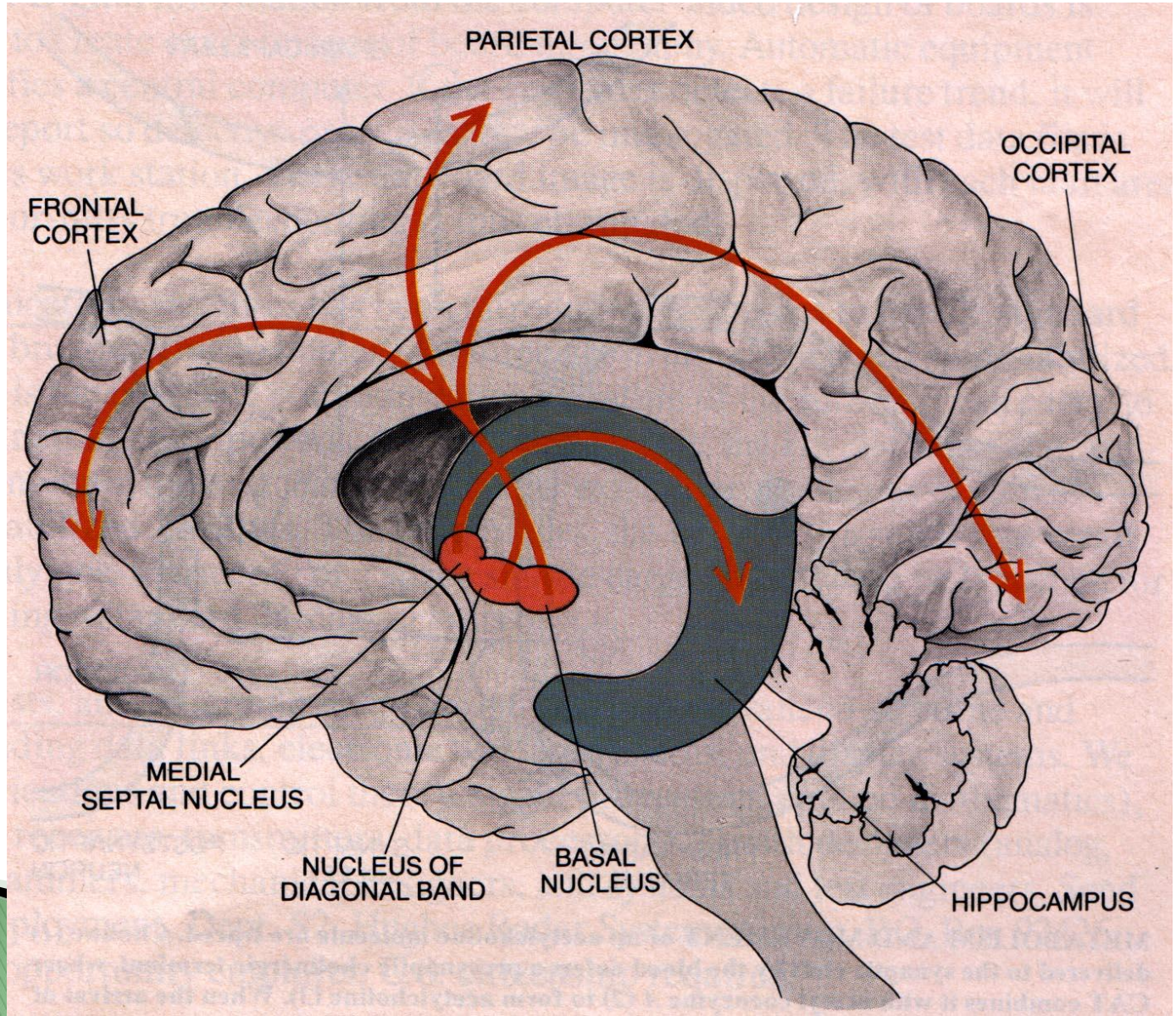
Combined eff ects of the EPSP and IPSP

- 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
- Oerall resultant action is due to the summation of the individual actions of various neurotransmitters on neuron
- Neurotransmitters are not uniformly distributed in the CNS but are localized in specific clusters of neurons
- The axons may synapse with specific regions of the brain
- Many neuronal tracts are chemically coded offering greater opportunity for selective modulation of certain pathways

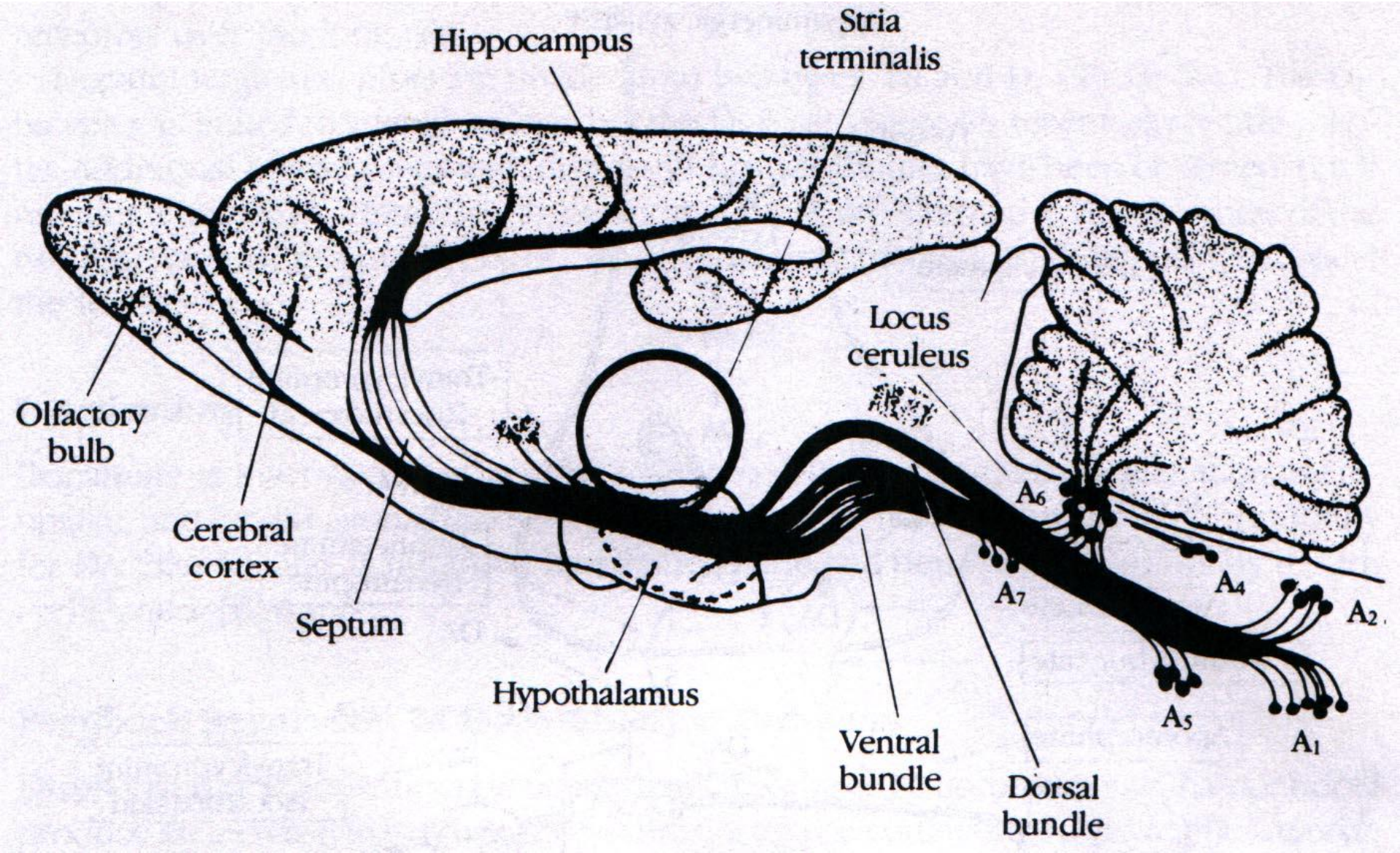
Synaptic pathways

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

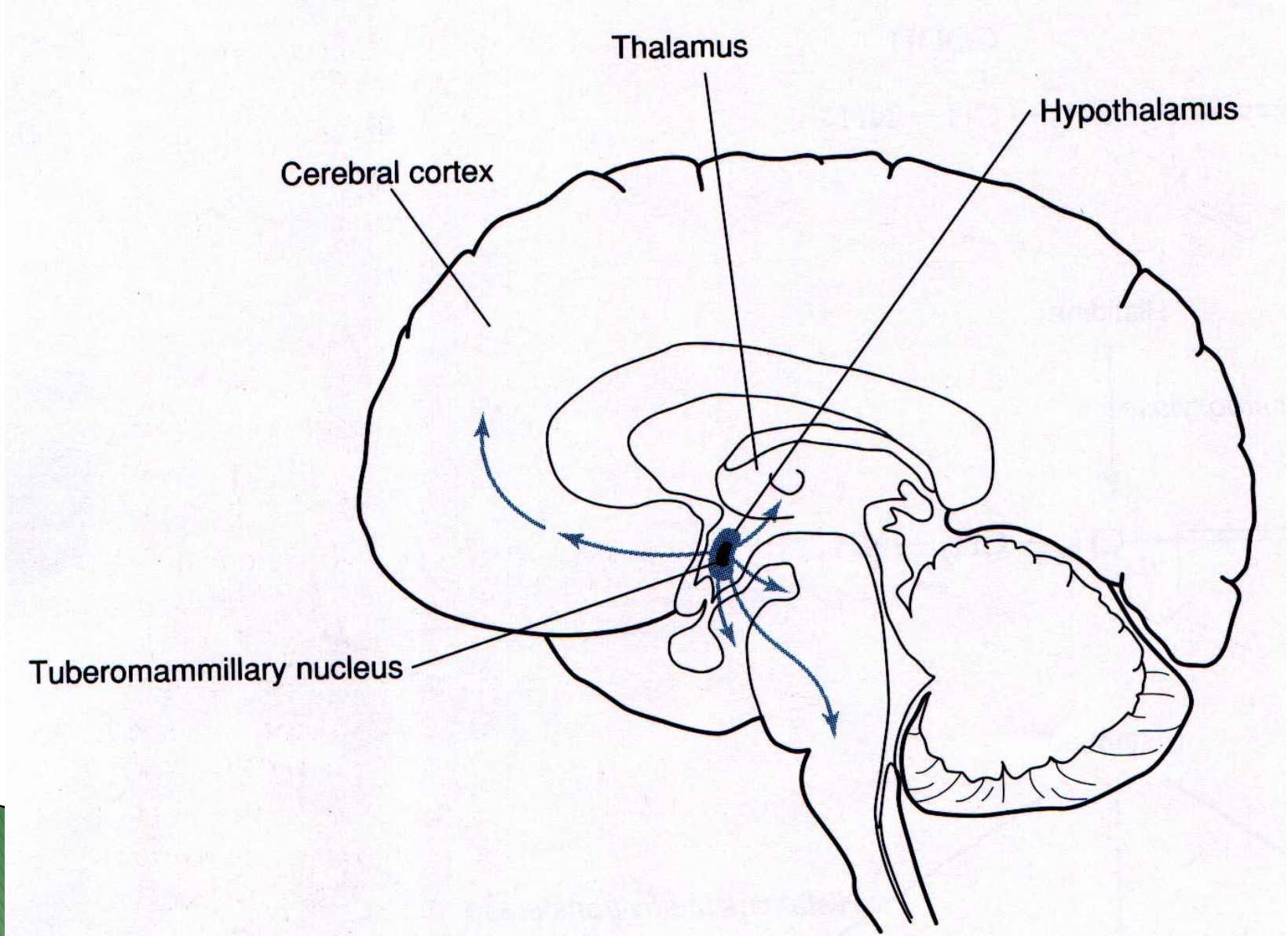
Acetylcholine Pathways



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

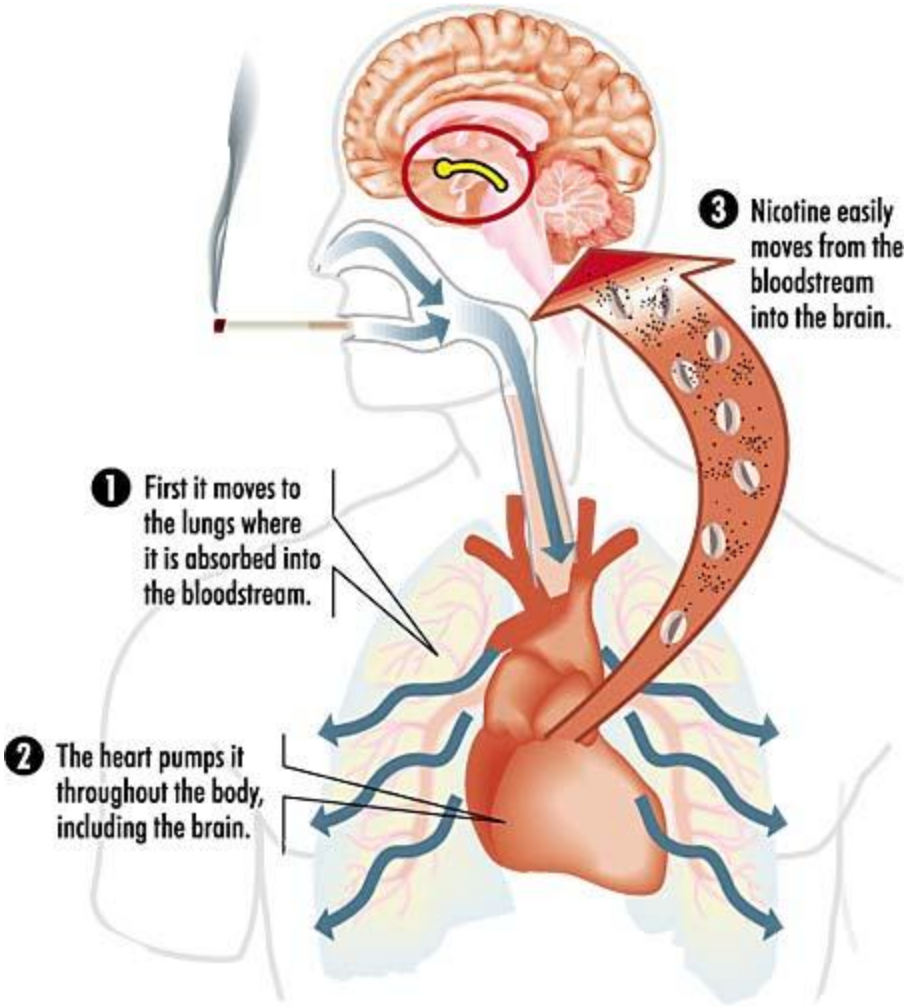
- In Most organs all cells perform the same function
- Adjacent cells in the brain may sub serve varied functions and result in different outcomes
- A lesion in a brain region may affect many other areas that might be connected to it
- Thus the connectivity of each area has to be taken into consideration 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 bnucleus 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 unkown
- 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

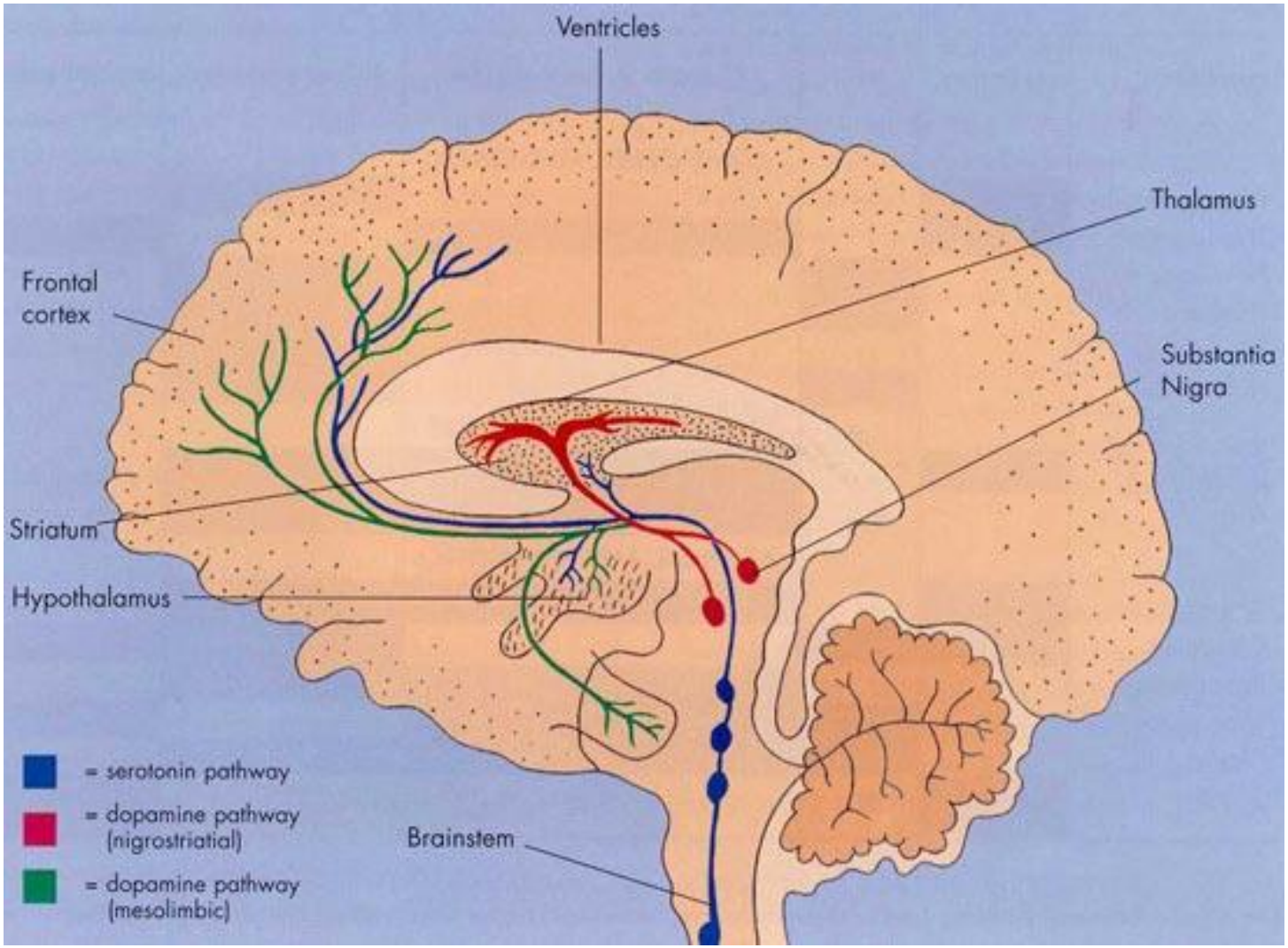
Neurotransmitters

- 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


Ventricles
Thalamus
Frontal cortex
Substantia Nigra
Striatum
Hypothalamus
= seratonin pathway
= dopamine pathway (nigrostriatial)
= dopamine pathway (mesolimbic)
Brainstem

Parkinson's disease

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

Parkinson's disease

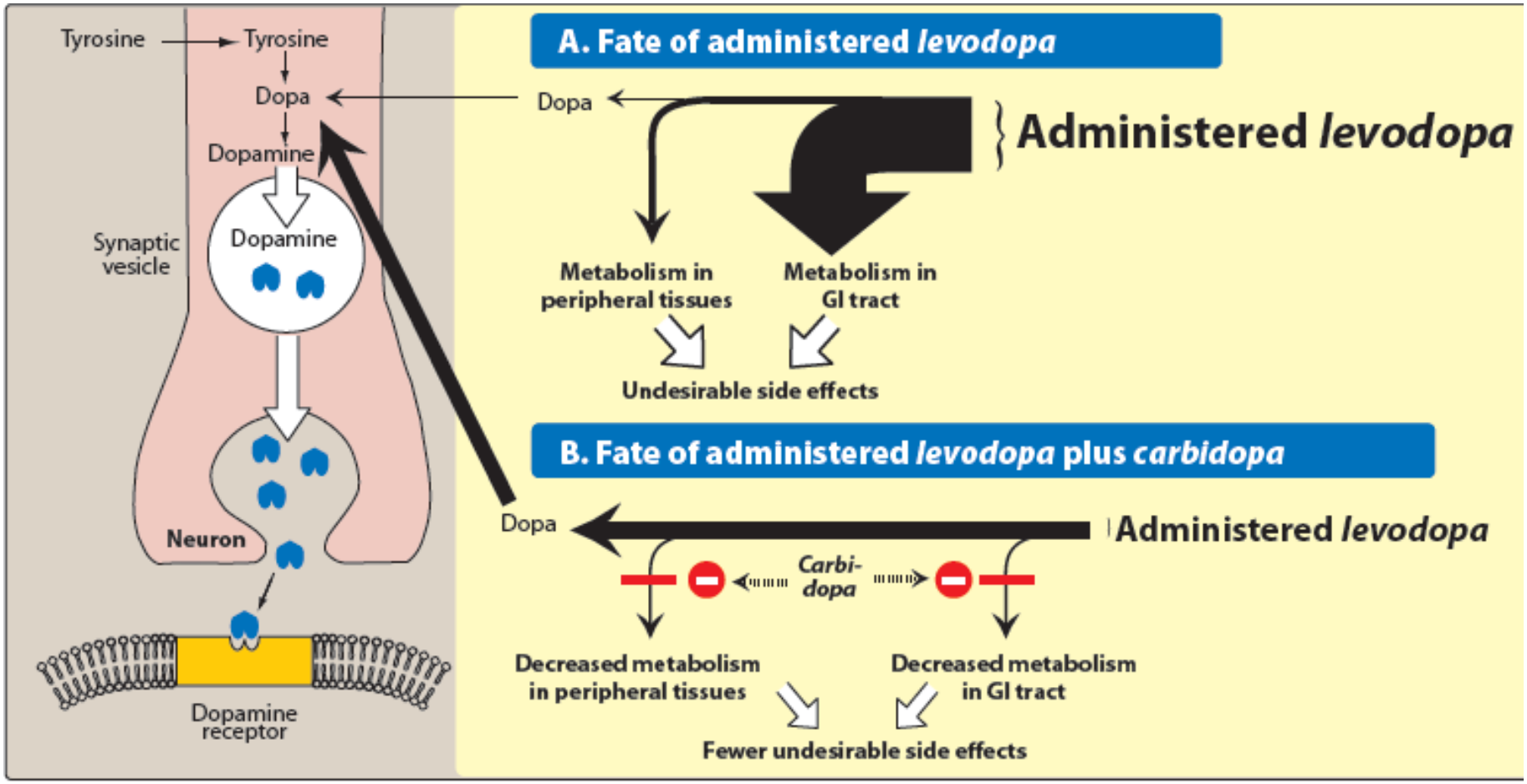
- Drugs used in Parkinson's disease offer temporary relief from the symptoms of the disorder, but they do not arrest or reverse the neuronal degeneration
  - Levodopa and carbidopa
  - MAO_B inhibitors
  - COMT inhibitors
  - Dopamine receptor agonists
  - Amantadine
  - Antimuscaranic agents

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
- The effects of levodopa on the CNS can be greatly enhanced by coadministering carbidopa a dopa decarboxylase inhibitor that does not cross BBB

Levodopa and carbidopa

- Mechanism of action:
  - Levodopa:
    - Parkinsonism results from insufficient dopamine in specific brain regions
    - Dopamine itself does not cross BBB, but its precursor, levodopa does and is converted to DA
    - Large doses of levodopa are required, because much of the drug is decarboxylated to DA 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 GITand peripheral tissues
    - Increases the availability of levodopa to the CNS
    - Lowers the dose of levodopa needed by 4-5 fold
    - Decreases the severity of the side effects arising from peripherally formed dopamine


Tyrosine
Tyrosine
Dopa
Dopamine
Synaptic vesicle
Dopamine
Neuron
Dopamine receptor
A. Fate of administered levodopa
Dopa
Administered levodopa
Metabolism in peripheral tissues
Metabolism in GI tract
Undesirable side effects
B. Fate of administered levodopa plus carbidopa
Dopa
Administered levodopa
Carbi-dopa
Decreased metabolism in peripheral tissues
Decreased metabolism in GI tract
Fewer undesirable side effects

Levodopa and carbidopa

- Actions: Levodopa decreases the rigidity, tremors, and other symptoms of parkinsonism
  - In 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

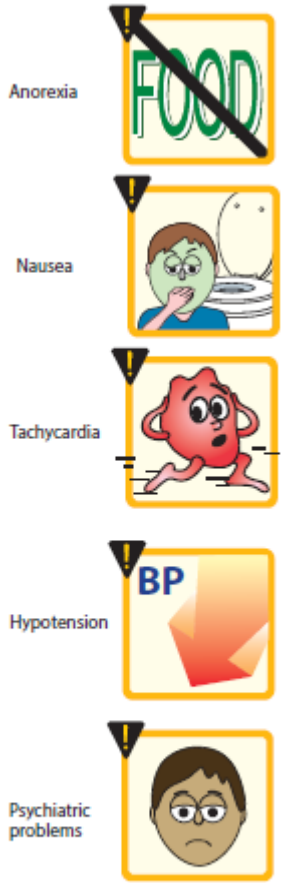


Figure 8.6
Adverse effects of *levodopa*.

Selegiline and rasagiline

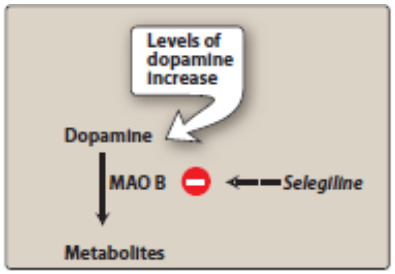


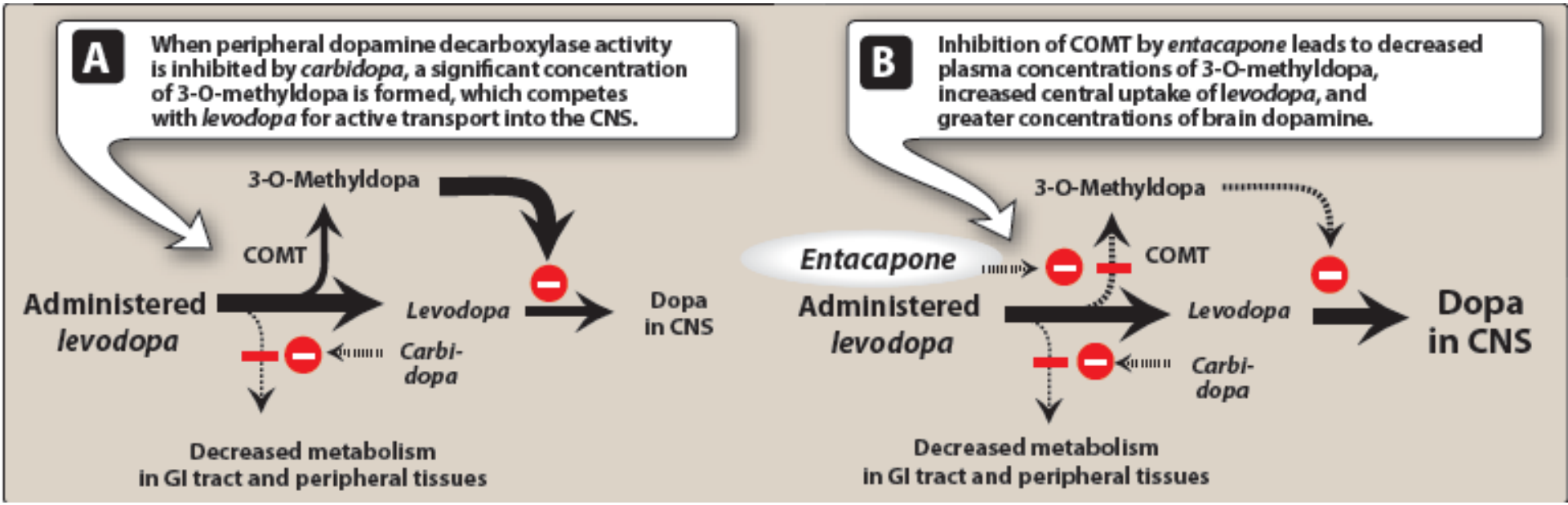
Figure 8.8
Action of *selegiline* (*deprenyl*) in dopamine metabolism. MAO B = monoamine oxidase type B.

- Selectively inhibit MAO B decreasing the metabolism of DA and increasing DA in the brain
- Can be co-administered with levodopa and carbidopa
- Rasagiline is an irreversible and selective inhibitor of brain MAO B, has 5 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 DA


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.
3-O-Methyldopa
COMT
Administered *levodopa*
Levodopa
Dopa in CNS
Carbi-dopa
Decreased metabolism in GI tract and peripheral tissues
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.
3-O-Methyldopa
Entacapone
COMT
Administered *levodopa*
Levodopa
Dopa in CNS
Carbi-dopa
Decreased metabolism in GI tract and peripheral tissues

Entacapone, tolcapone

- Can be given in combination with levodopa and carbidpa
- Both entacapone or tolcapone reduce 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

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

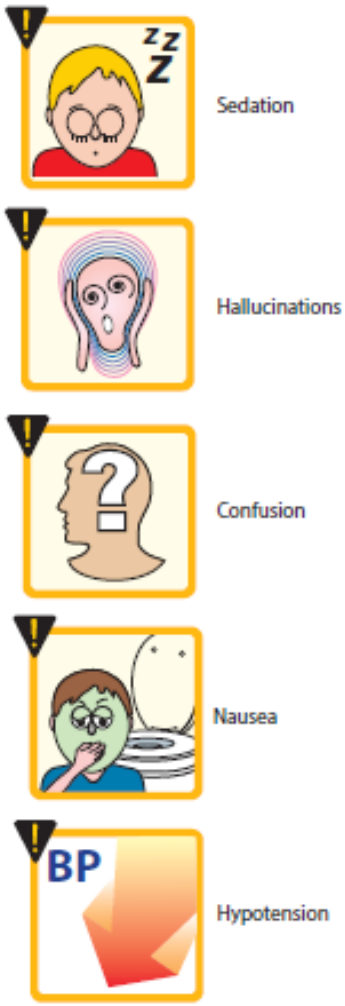


Figure 8.10
Some adverse effects of dopamine agonists.

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 ACh and DA
- Less efficacious than levodopa, used as adjuvant in antiparkinsonism therapy
- Adverse effects (antimuscarinic side effects)
  - Tachycardia
  - Urinary retention
  - Dry moth
  - 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 and is suggested as a mechanism for neurodegenerative or apoptotic processes

- Binding of glutamate to the NMDA receptor assists in the opening of an associated ion channel that allows Na^{+} and 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 β1a and interferon β1b: 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
  - Alters lymphocyte migration, resulting in sequestration of lymphocytes in lymph nodes
  - Risk of life-threatening infection
- Dalfampridine
  - 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