DRUGS AFFECTING THE CENTRAL NERVOUS SYSTEM

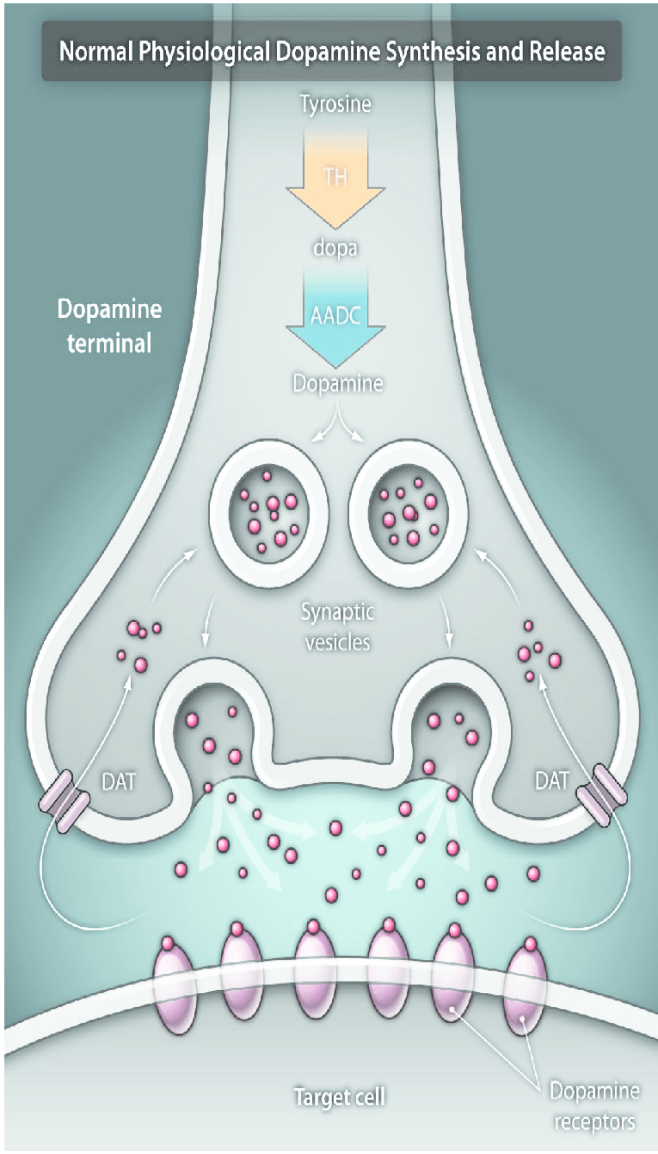
- Most drugs affecting the central nervous system (CNS) act by altering some step in the neurotransmission process
  - Presynaptically by affecting the production, storage, release, or termination of action of neurotransmitters
  - Postsynaptically by activating or blocking postsynaptic receptors

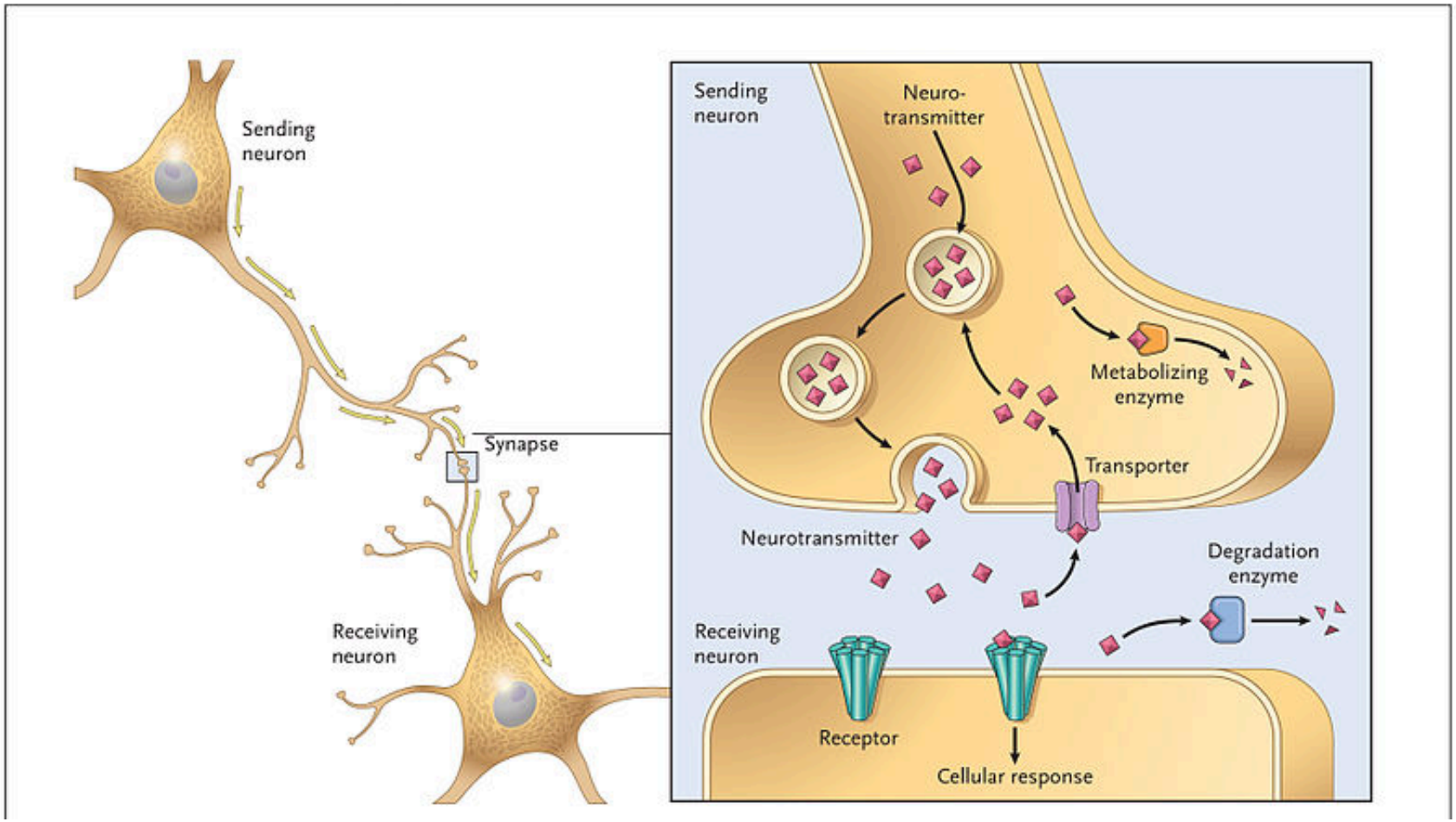
Neurotransmission in the CNS

- Transmission of information in the CNS involves the release of neurotransmitters that diffuse across the synaptic space to bind to specific receptors on the postsynaptic neuron
- The binding of neurotransmitters to membrane receptors on the postsynaptic neuron trigger intracellular changes that lead to a certain response

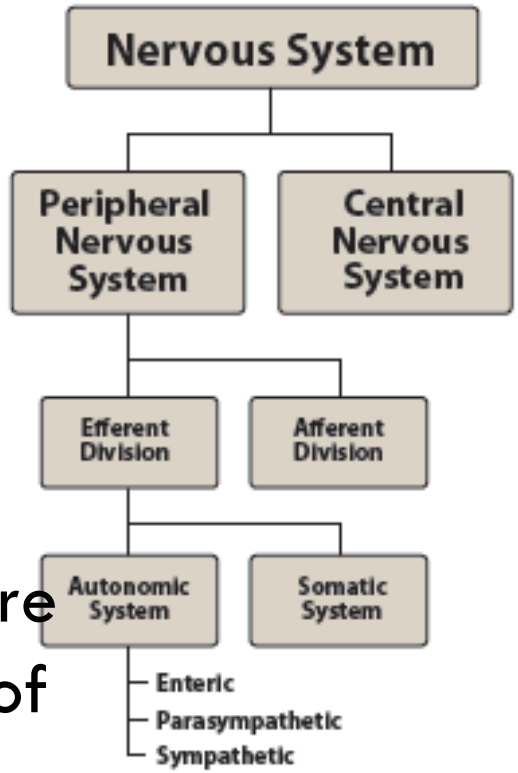
Neurotransmission

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




Sending neuron
Synapse
Receiving neuron
Sending neuron
Neuro-transmitter
Metabolizing enzyme
Transporter
Neurotransmitter
Degradation enzyme
Receiving neuron
Receptor
Cellular response

- CNS is much more complex than ANS
- CNS contains a greater number of synapses
- CNS Includes many more neurotransmitters than ANS
- CNS contains inhibitory neurons that are constantly active to regulate the rate of neurotransmission



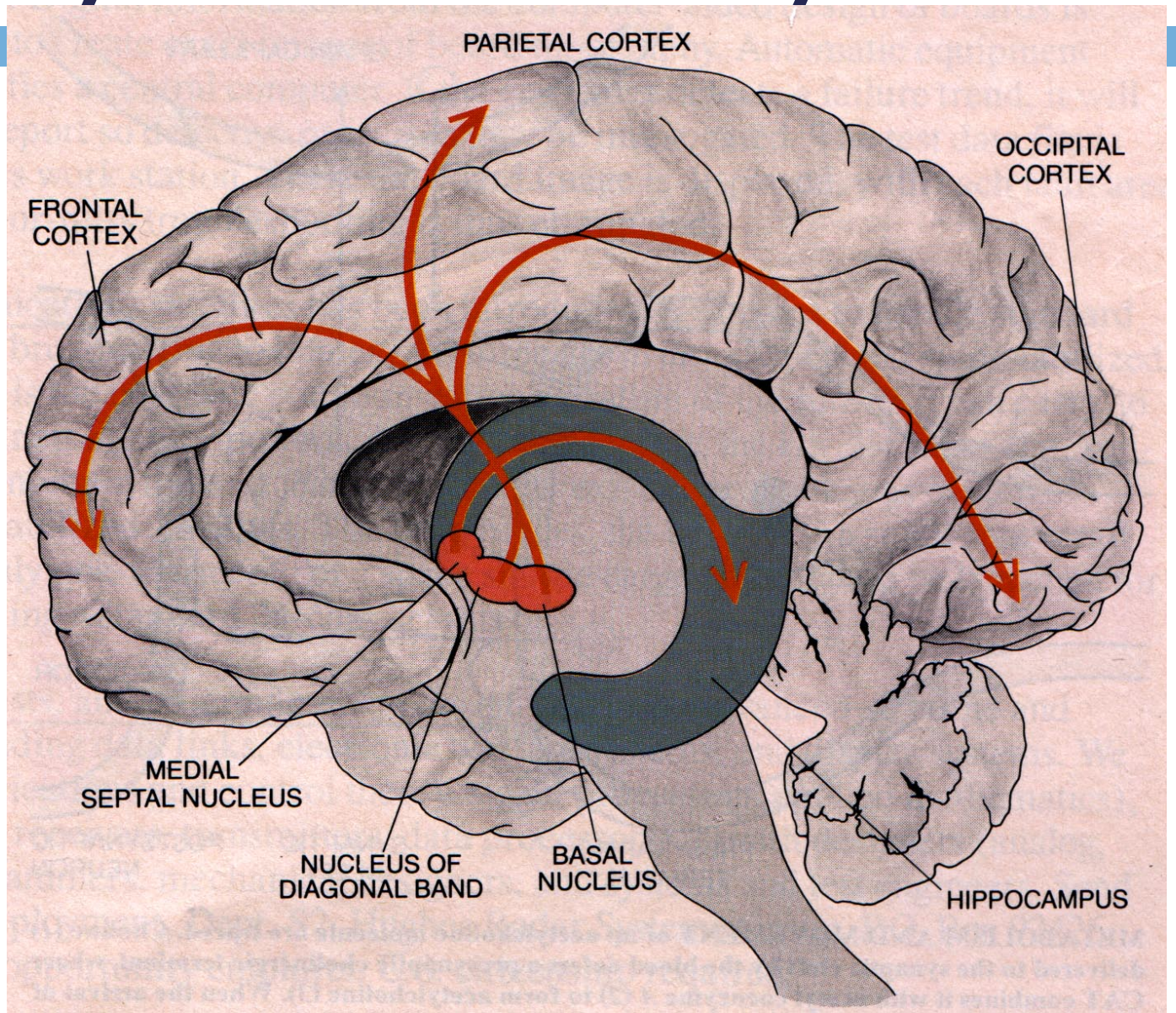
- CNS synaptic receptors are coupled to ion channels
- Binding of the neurotransmitter to the postsynaptic receptor leads to rapid opening of ion channels allowing the flow of ions
- The flow of ions produces depolarization or hyperpolarization of the postsynaptic membrane

- Synaptic pathways:
  - Excitatory
    - Stimulation of excitatory neurons cause a movement of ions that result in depolarization of postsynaptic membranes like with the glutamate neurons and acetylcholine neurons
  - Inhibitory
    - Stimulation of inhibitory neurons cause movement of ions that result in hyperpolarization of postsynaptic membrane. Example γ-aminobutyric acid (GABA) neurons or glycine neurons
  - Combined excitatory and inhibitory effects
    - Most neurons in the CNS receive both excitatory and inhibitory postsynaptic pathways
    - Several neurotransmitters may act on the same neuron but bind to its own specific receptor
    - The neurotransmitters are not uniformly distributed in the CNS but are localized in specific clusters of the axons within specific regions of the brain

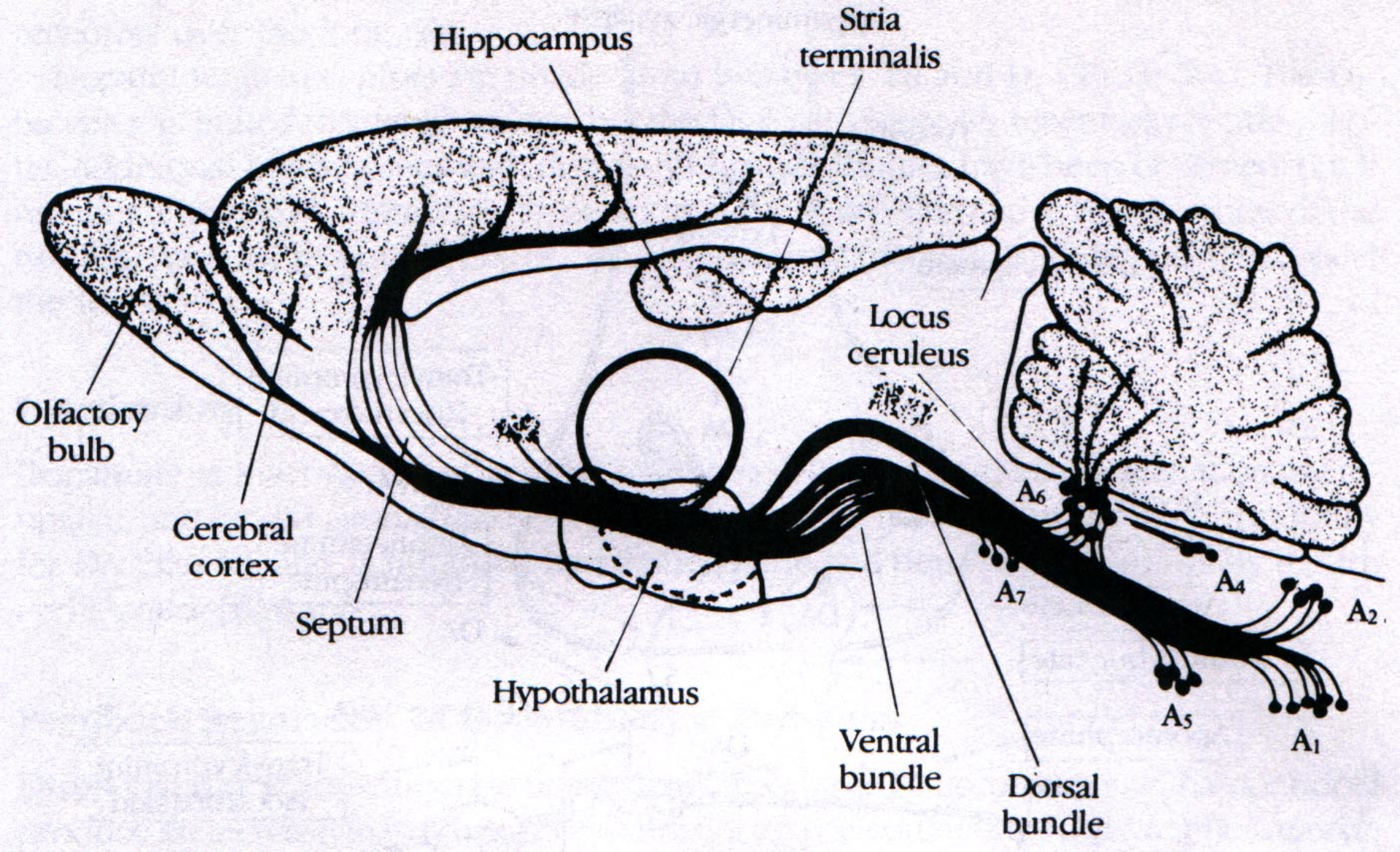
Synaptic pathways

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

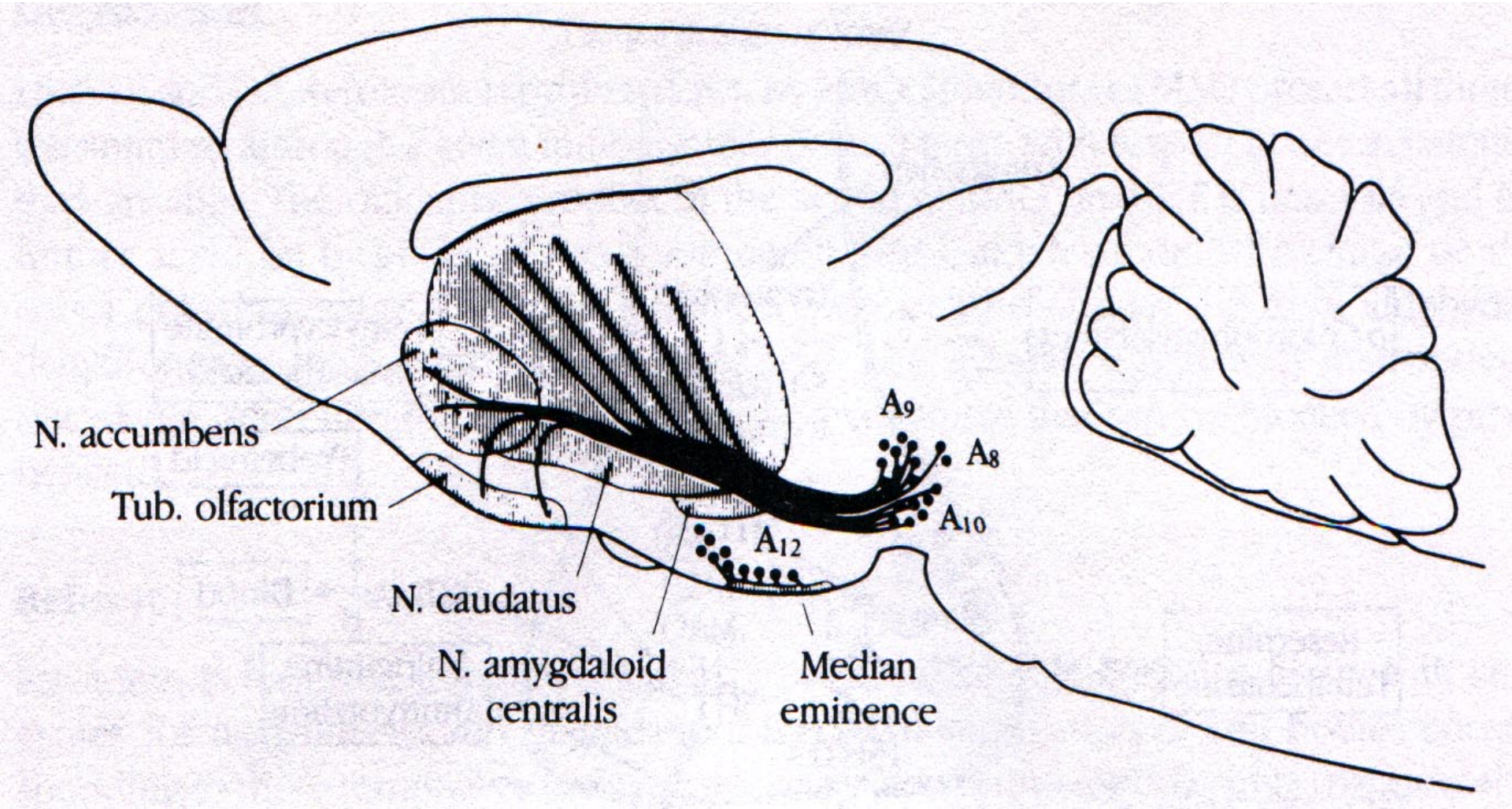
Acetylcholine Pathways



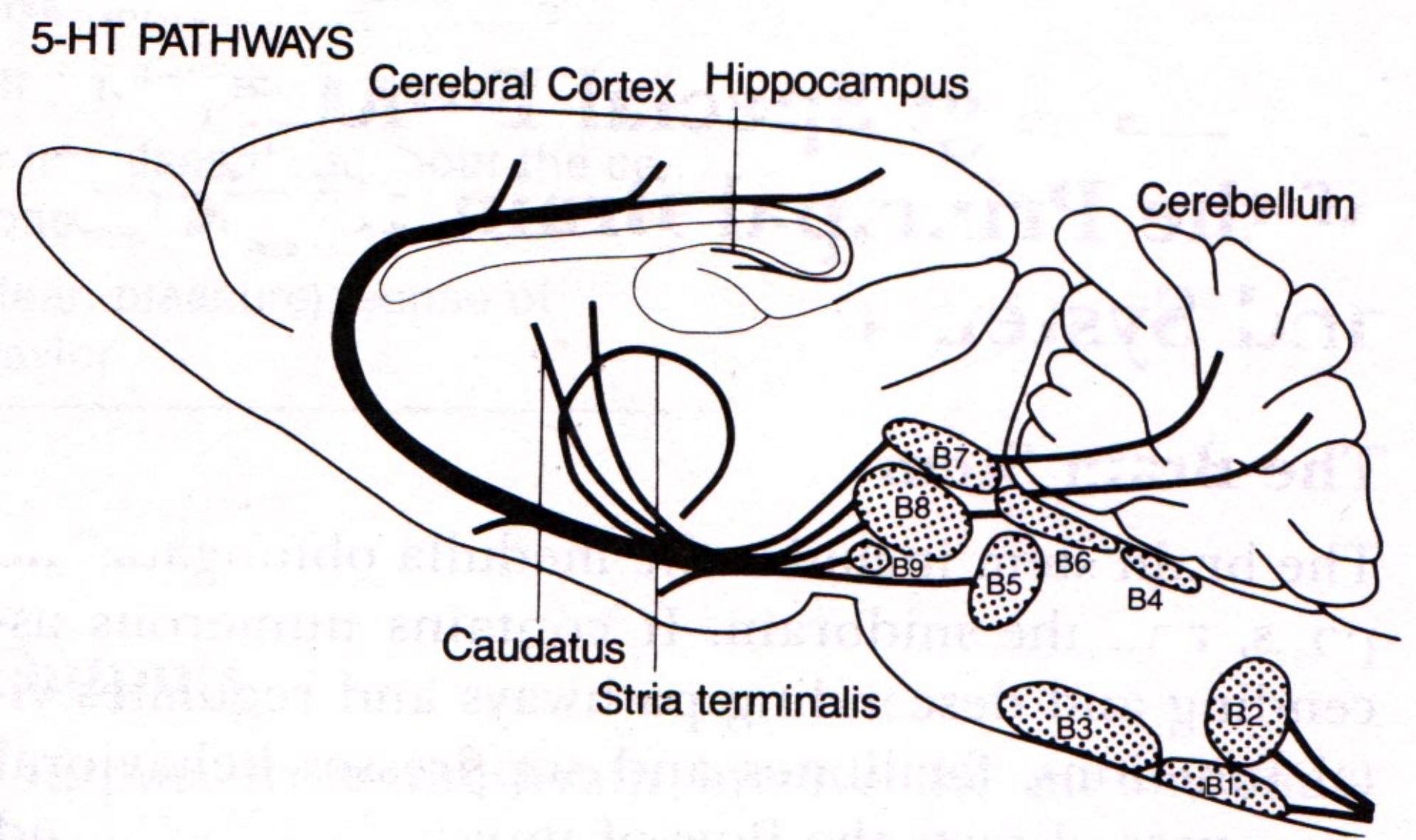
Norepinephrine Pathways



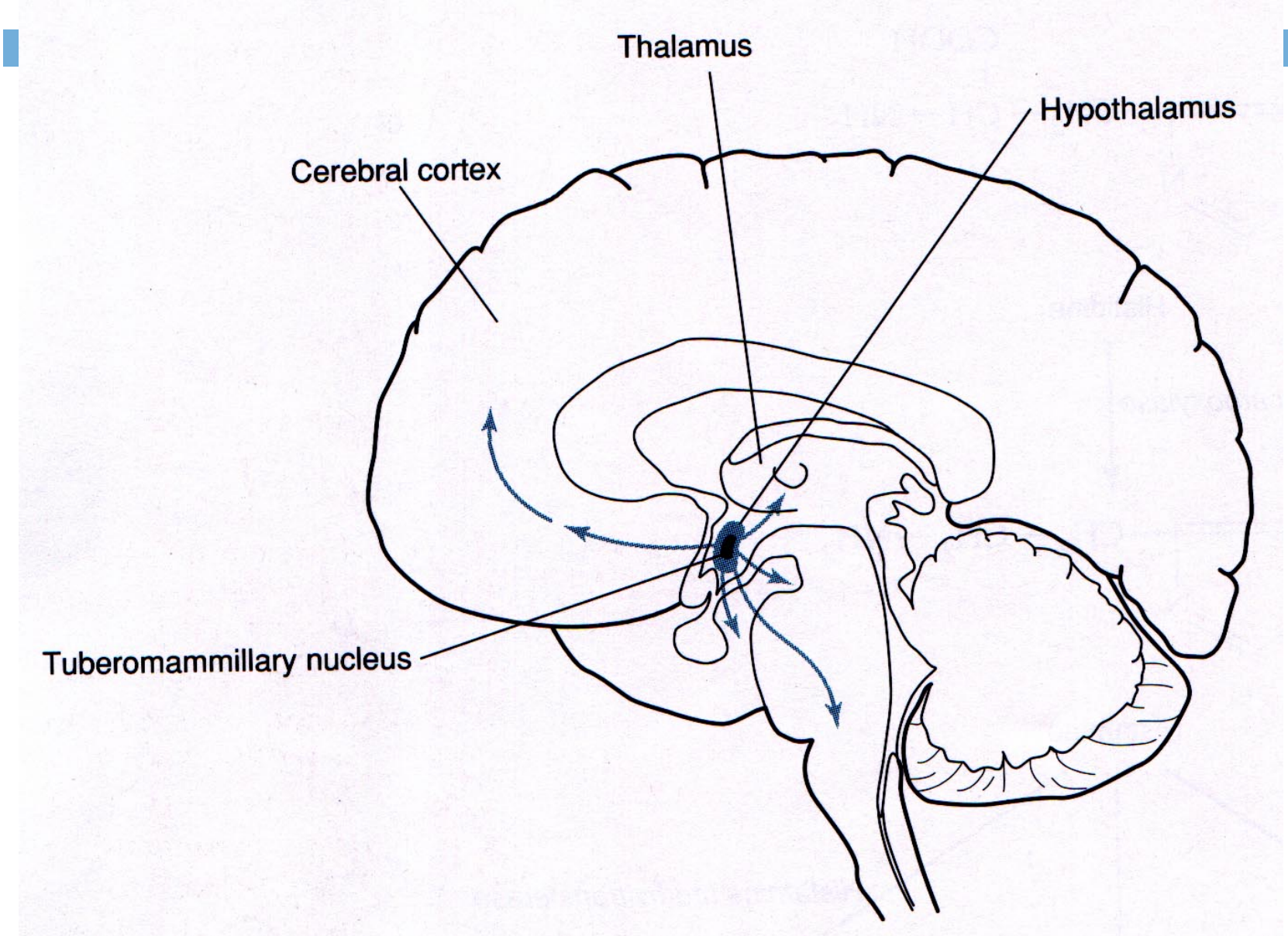
Dopamine Pathways



Serotonin 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

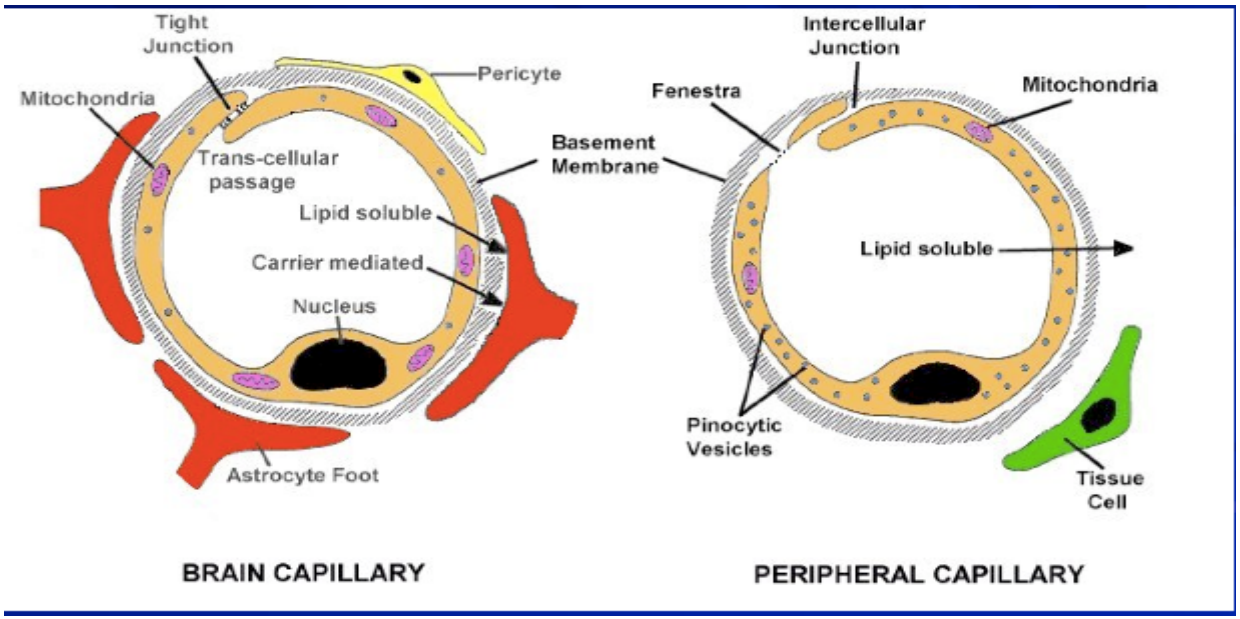
Complexity and heterogeneity

- 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

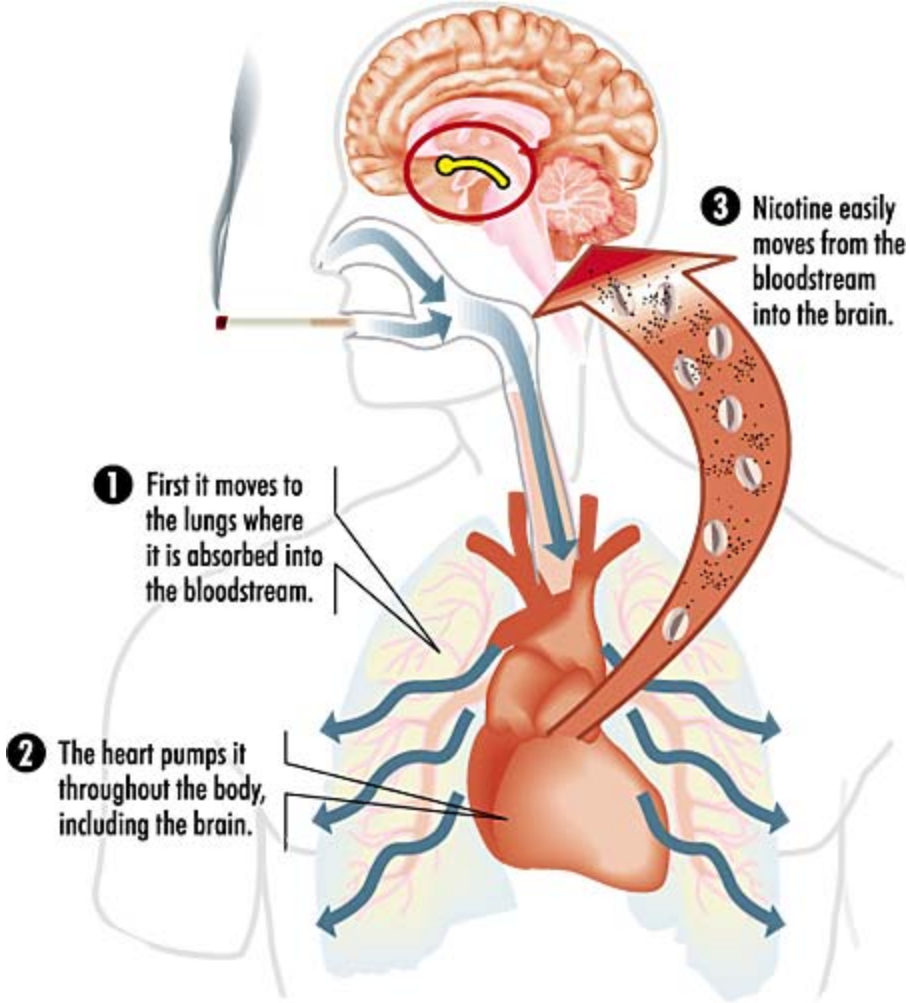
Brain Capillaries



•Endothelial cells are packed together in tight junctions which blocks the movement of all molecules except lipid soluble molecules

Addictive potential of the brain

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



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NEURODEGENERATIVE DISEASES

Neurodegenerative diseases

- Progressive loss of selected neurons in specific brain areas causing certain disorders in movement or cognition
  - Parkinson's disease (PD)
  - Alzheimer's disease (AD)
  - 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

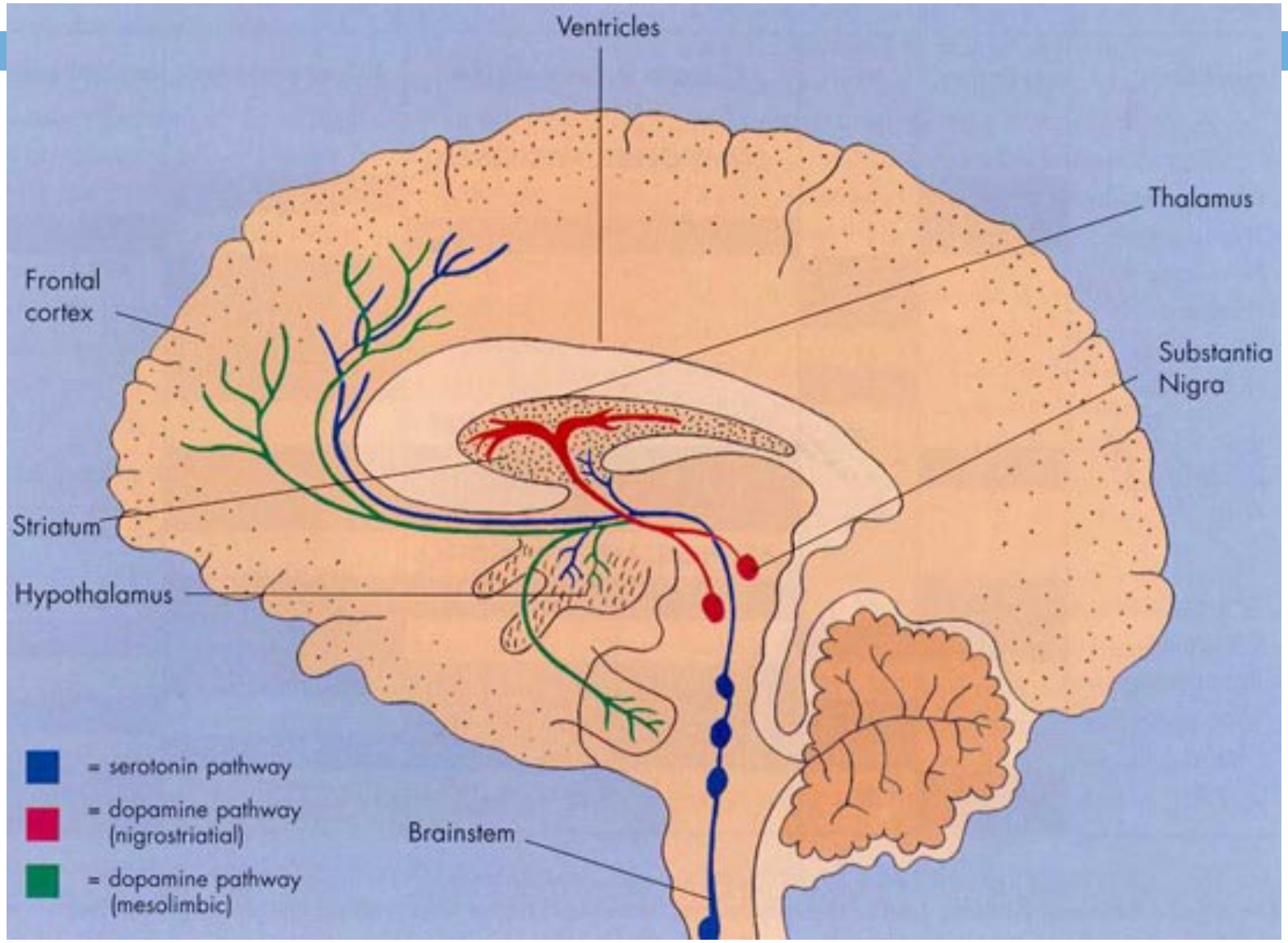
- Etiology (cause) is unkown
- Destruction of dopaminergic neurons in the substantia nigra reducing dopamine actions in corpus striatum, motor control areas of the brain
- The dopamine influence on cholinergic neurons in the neostriatum is reduced, resulting in overactivity of acetylcholine causing loss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

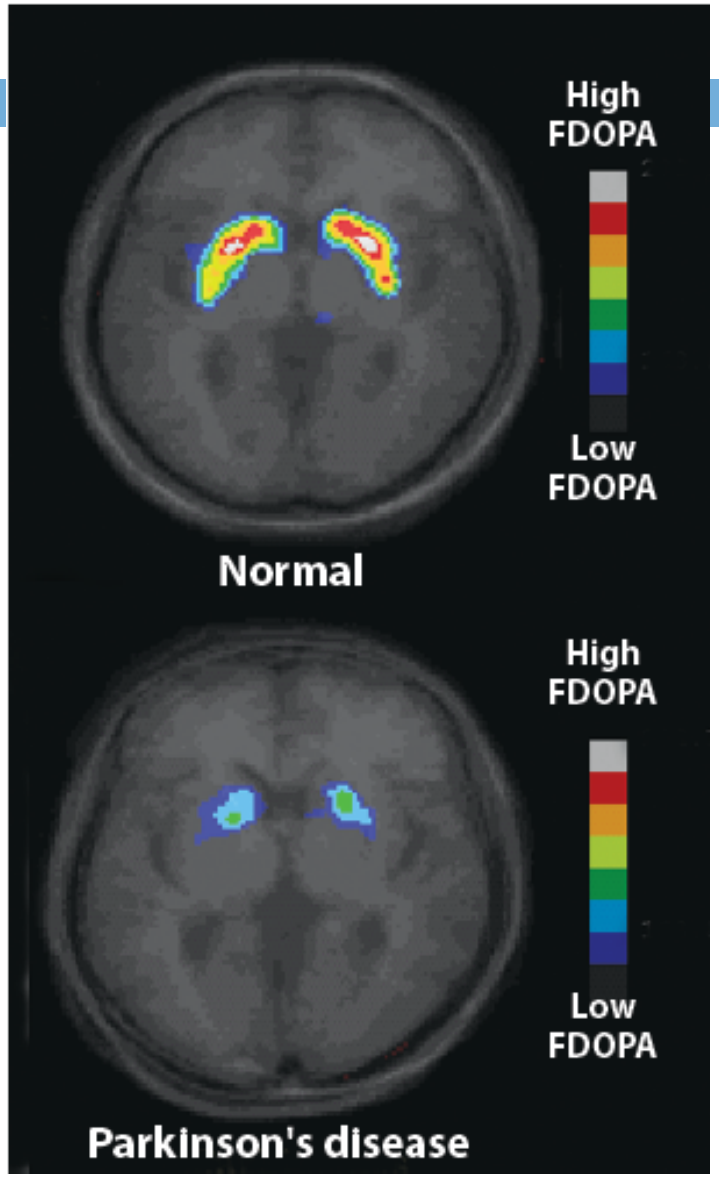
Neurotransmitters

- 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


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



Positron-emission tomographic scan of the brain showing the difference in fluorodopa (FDOPA) levels between normal and Parkinson's brain

Parkinson's disease

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

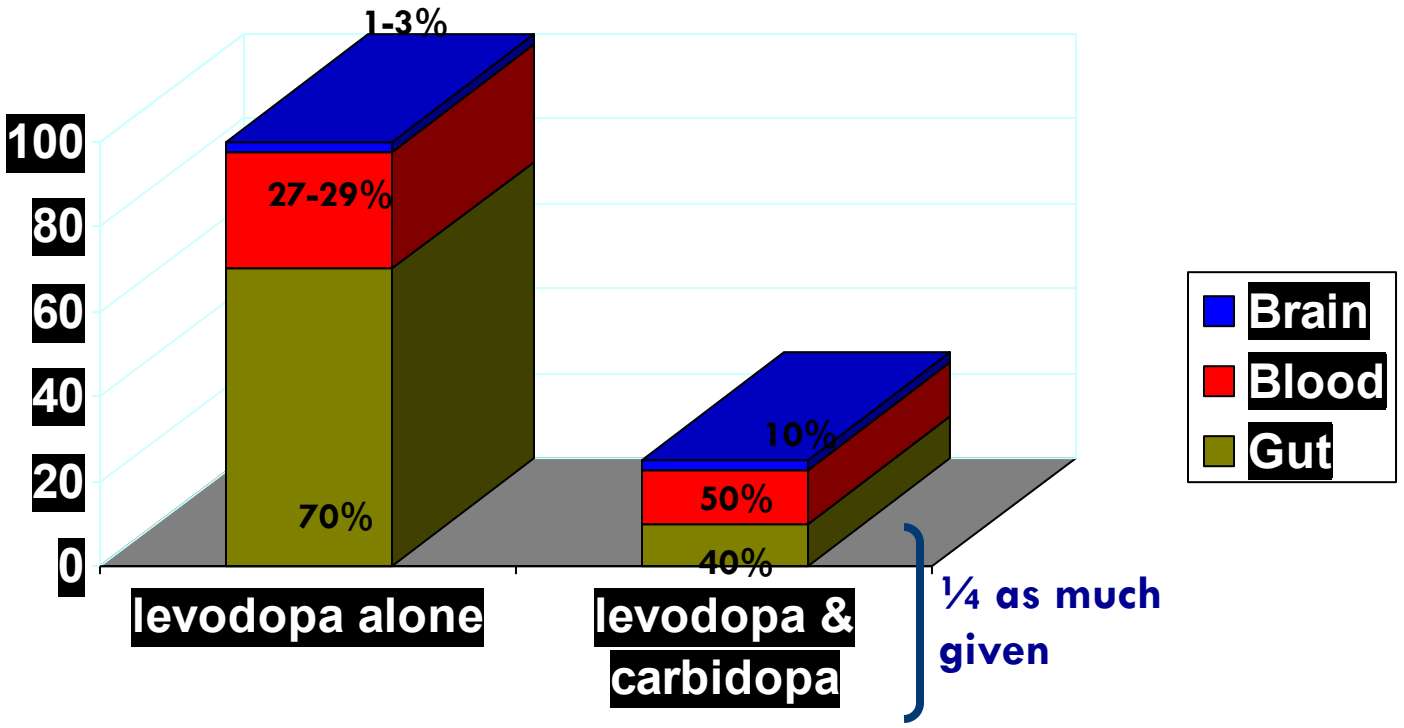
Parkinson's disease

- Drugs used in Parkinson's disease
  - Levodopa and carbidopa
  - Selegiline and rasagline (MAO_B inhibitors)
  - Catechol-O-methyltransferease (COMT) inhibitors
  - Dopamine receptor agonists
  - Amantadine
  - Antimuscaranic agents

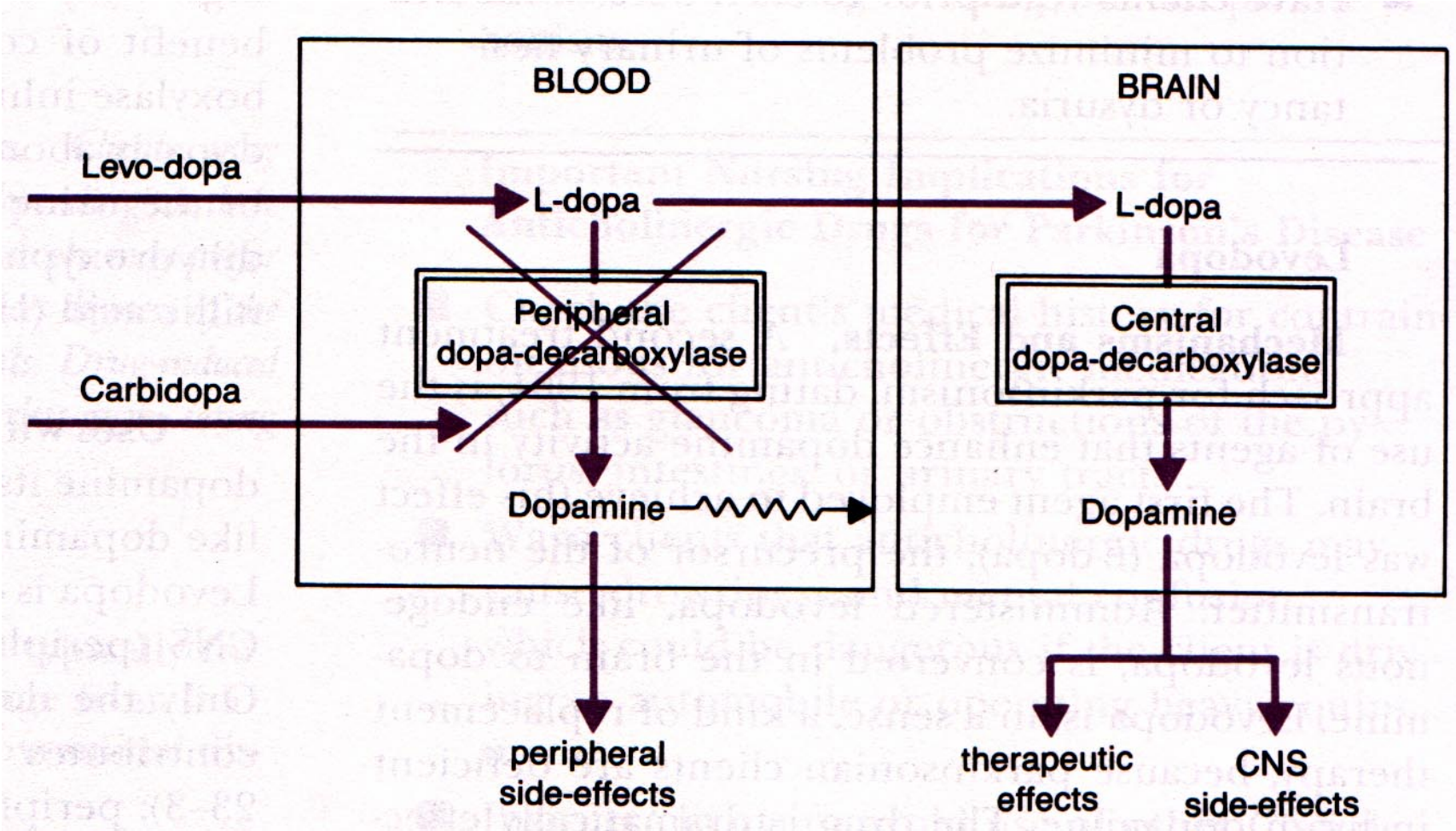
Levodopa and carbidopa

- Mechanism of action:
  - Restore dopaminergic neurotransmission in the brain
  - Levodopa is a dopamine precursor
  - Carbidopa inhibits the enzyme dopamine decarboxylase but does not cross the BBB
- Actions: reduce rigidity, tremors and other symptoms of Parkinson's disease
- More effective in early stages
- Adverse effects
  - Anorexia, Nausea
  - Tachycardia
  - CNS effects: hallucination, psychosis, anxiety

Levodopa and Carbidopa



Pharmacokinetic Potentiation



Selegiline and rasagiline

- Monoamine oxidase B (MAO_B) inhibitors
- MAO_B metabolize dopamine
- Mechanism of action: decrease dopamine metabolism and so increase dopamine levels in the brain
- Can be co-administered with levodopa and carbidopa

COMT inhibitors

- Catechol-O-methyltransferase is an enzyme that metabolizes dopamine
- Entacapone and tolcapone are examples on COMT inhibitor used for Parkinson's
- Can be given in combination with levodopa and carbidpa
- Adverse effects
  - Anorexia
  - Hallucination

Dopamine receptor agonists

- Bromocriptine
- Effective in advanced Parkinson's patients
- Adverse effects
  - Nausea
  - Hallucination, confusion

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
- Mechanism of action: block cholinergic transmission to restore the balance between acetylcholine and dopamine
- 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

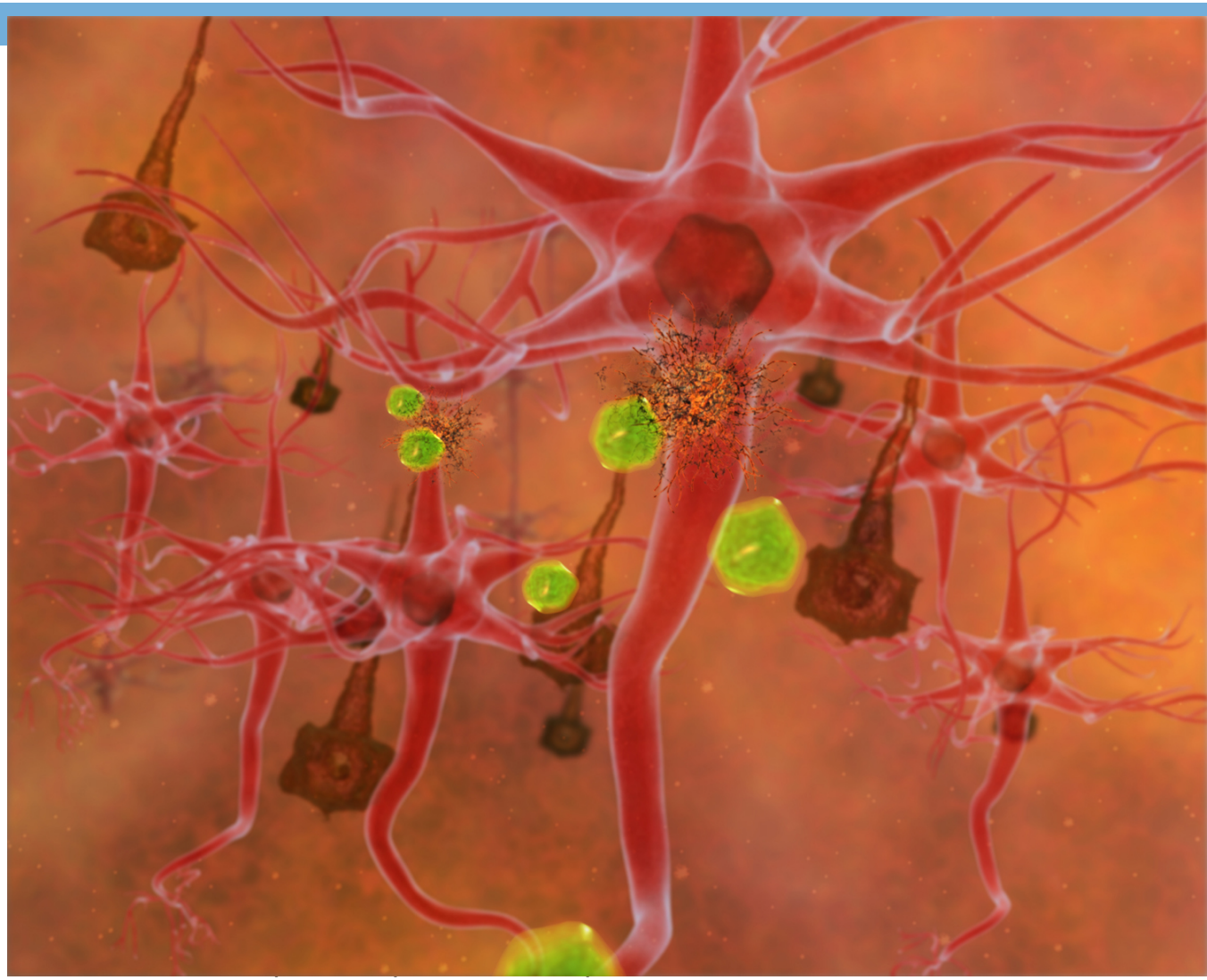
- Progressive neurodegenerative disorder characterized by progressive loss of brain function
  - Memory loss, confusion, dementia

- Characterized by:
  - Accumulation of plaque and tangle deposits in the brain
  - Loss of cortical neurons, particularly cholinergic neurons

Pathological features

Plaques

Tangles



http://www.tpt.org/NPD/forgetting/press/brain_image.jpg

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
- Mechanism of action: inhibit the enzyme acetylcholinesterase and thus improve cholinergic transmission in the brain
- Adverse effects
  - Nausea, vomiting
  - Bradycardia, tremor
  - Tacrine is hepatotoxic

NMDA receptor antagonists

- Memantine
- Mechanism of action: act as neuroprotective, prevent the neuron loss by blocking NMDA glutamate receptor and preventing its overstimulation and excitotoxic effects on neurons

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

Multiple sclerosis

- Drugs used for multiple sclerosis
  - Corticosteroids example: prednisone and dexamethasone
  - Interferon β1a and interferon β1b: immune system modulators of interferons and T-helper cell response that contribute to inflammatory processes causing demyelination of axons
  - Mitoxantrone: cytotoxic drug that kills T cells

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