**Neurodegenerative Diseases**

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* Most drugs that affect the central nervous system (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.
* The CNS, unlike the peripheral autonomic nervous system, contains powerful networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission. In addition, the CNS communicates through the use of more than 10 different neurotransmitters. In contrast, the autonomic nervous system uses only two primary neurotransmitters, acetylcholine and norepinephrine.
* In the CNS, receptors at most synapses are coupled to ion channels. That is, binding of the neurotransmitter to the postsynaptic membrane receptors results in a rapid but transient opening of ion channels. Open channels allow specific c ions inside and outside the cell membrane to flow down their concentration gradients. The resulting change in the ionic composition across the membrane of the neuron alters the postsynaptic potential, producing either depolarization or hyper-polarization of the postsynaptic membrane, depending on the specific ions that move and the direction of their movement.

**Excitatory pathways**: Stimulation of excitatory neurons causes a movement of ions those results in a depolarization of the postsynaptic membrane. These excitatory postsynaptic potentials (EPSP) are generated by the following: 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. This ultimately causes the EPSP depolarization of the postsynaptic cell to pass a threshold, thereby generating an all-or-none action potential.

**Inhibitory pathways**: Stimulation of inhibitory neurons causes movement of ions those results in a hyper-polarization 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. This causes a transient increase in the permeability of specific ions, such as potassium (K+) and chloride (Cl–) ions. 2) The influx of Cl– and efflux of K+ cause a weak hyperpolarization, or IPSP, that moves the postsynaptic potential away from its fi ring threshold.

**Combined effects of the EPSP and IPSP**: Most neurons in the CNS receive both EPSP and IPSP input. Thus, several different types of neurotransmitters may act on the same neuron, but each binds to its own specific receptor.

**PARKINSON DISEASE**

Parkinsonism is a progressive neurological disorder of muscle Movement, characterized by tremors, muscular rigidity, bradykinesia (slowness in initiating and carrying out voluntary movements), and postural and gait abnormalities.

The cause of Parkinson disease is unknown for most patients. The disease is correlated with destruction of dopaminergic neurons in the substantia nigra with a consequent reduction of dopamine actions in the corpus striatum, parts of the brain’s basal ganglia system that are involved in motor control.

**Substantia nigra:** The substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons that terminate in the neostriatum.

**Neostriatum:** Normally, the neostriatum is connected to the substantia nigra by neurons that secrete the inhibitory transmitter GABA at their termini in the substantia nigra. In turn, cells of the substantia nigra send neurons back to the neostriatum, secreting the inhibitory transmitter dopamine at their termini. Thus, the normal modulating inhibitory influence of dopamine on cholinergic neurons in the neostriatum is significantly diminished, resulting in overproduction or a relative over activity of acetylcholine by the stimulatory neurons.

**Secondary Parkinsonism:** Parkinsonian symptoms infrequently follow viral encephalitis or multiple small vascular lesions. Drugs such as the phenothiazines and *haloperidol*, whose major pharmacologic action is blockade of dopamine receptors in the brain, may also produce parkinsonian symptoms.

**DRUGS USED IN PARKINSON DISEASE**:

1. Decreasing cholinergic activity by

 **Antimuscarinic agents**: *benztropine*, *procyclidine* and *biperiden* Adverse effects are similar to those caused by high doses of *atropine*, for example, pupillary dilation, confusion, hallucination, sinus tachycardia, urinary retention, constipation, and dry mouth.

2. Increasing dopaminergic activity via:

a. Increasing brain dopamine synthesis: **(Levodopa and carbidopa**) It restores dopaminergic neurotransmission in the corpus striatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra. Thus, in new patients, the therapeutic response to *levodopa*is consistent and the patient rarely complains that the drug effects “wear off.” Unfortunately, with time, the number of neurons decreases and fewer cells are capable of taking up exogenously administered *levodopa* and converting it to dopamine for subsequent storage and release. Consequently, motor control fluctuation develops. 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 co-administering *carbidopa* a dopa decarboxylase inhibitor that does not cross the blood-brain barrier. *Levodopa* is actively transported into the CNS and is converted to dopamine in the brain .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:** *Carbidopa,* a dopa decarboxylase inhibitor, diminishes the metabolism of *levodopa* in the gastrointestinal tract and peripheral tissues, thereby increasing the availability of *levodopa* to the CNS. The addition of *carbidopa* lowers the dose of *levodopa* needed by four- to fivefold and, consequently, decreases the severity of the side effects arising from peripherally formed dopamine, decreases the rigidity, tremors, and other symptoms

of parkinsonism. The drug is absorbed rapidly from the small intestine (when empty of food). *Levodopa* has an extremely short half-life (1 to 2 hours), which causes fluctuations in plasma concentration. This may produce fluctuations in motor response, which generally correlate with the plasma concentrations of *levodopa*, or perhaps give rise to the more troublesome “on-off” phenomenon, in which the motor fl uctuations are not related to plasma levels in a simple way. Motor fluctuations may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and immobility. Ingestion of meals, particularly if high in protein, interferes with the transport of *levodopa* into the CNS. Large, neutral amino acids (for example, leucine and isoleucine) compete with *levodopa* for absorption from the gut and for transport across the blood-brain barrier. Thus, *levodopa* should be taken on an empty stomach, typically 45minutes before a meal. Withdrawal from the drug must be gradual.

**Adverse effects:**

**Peripheral effects:** Anorexia, nausea, and vomiting occur because of stimulation of the chemoreceptor trigger zone of the medulla.

**CNS effects:** Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur.

**Interactions:** The vitamin pyridoxine (B6) increases the peripheral breakdown of *levodopa* and diminishes its effectiveness Concomitant administration of *levodopa* and monoamine oxidase inhibitors (MAOIs), such as *phenelzine*, can produce a hypertensive crisis caused by enhanced catecholamine production .Antipsychotic drugs are generally contraindicated in parkinsonian patients, because these potently block dopamine receptors and produce a parkinsonian syndrome themselves.

B.Decreasing metabolism of dopamine:

1-MAO-B inhibitors: *Selegiline* selectively inhibits MAO Type B (which metabolizes dopamine) at low to moderate doses but does not inhibit MAO Type A (which metabolizes norepinephrine and serotonin) unless given at above recommended doses, where it loses its selectivity. By, thus, decreasing the metabolism of dopamine, *selegiline* has been found to increase dopamine levels in the brain *.Selegiline* is metabolized to *methamphetamine* and *amphetamine,* whose stimulating properties may produce insomnia if the drug is administered later than midafternoon. *Rasagiline* an irreversible and selective inhibitor of brain monoamine oxidase Type B, has five times the potency of *selegiline*. Unlike *selegiline*, *rasagiline* is not metabolized to an amphetaminelike substance.

2- **Catechol-O-methyltransferase inhibitors** :( *entacapone* and *tolcapone*) normally, the methylation of *levodopa* by catechol-O-methyltransferase (COMT) to 3-O-methyldopa is a minor pathway for *levodopa* metabolism. However, when peripheral dopamine decarboxylase activity is inhibited by *carbidopa*, a significant concentration of 3-O-methyldopa is formed that competes with *levodopa* for active transport into the CNS. Inhibition of COMT by *entacapone* or *tolcapone* leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of *levodopa*, and greater concentrations of brain dopamine. Oral absorption of both drugs occurs readily and is not influenced by food. They are extensively bound to plasma albumin (>98 percent), with limited volumes of distribution.

*Tolcapone*: long duration, cross BBB and cause fulminating hepatic necrosis.

*Entacapone*: short duration, not cross BBB and not cause fulminating hepatic necrosis.

c. **Dopamine-receptor agonists**: This group of anti-Parkinson compounds includes *bromocriptine*, an ergot derivative, and newer, nonergot drugs, *ropinirole*, *pramipexole*,*and rotigotine* have been effective in patients exhibiting fluctuations in their response to *levodopa*. Initial therapy with the newer drugs is associated particularly with less risk of developing dyskinesias and motor fluctuations when compared to patients started with *levodopa* therapy. *Bromocriptine*, *pramipexole*, and *ropinirole* are all effective in patients with advanced Parkinson disease complicated by motor fluctuations and dyskinesias. However, these drugs are ineffective in patients who have shown no therapeutic response to *levodopa*.

The actions of *bromocriptine* are similar to those of *levodopa*, except that hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common, whereas dyskinesia is less prominent. Serious cardiac problems may develop, particularly in patients with a history of myocardial infarction. In patients with peripheral vascular disease, a worsening of the vasospasm occurs, and in patients with peptic ulcer, there is a worsening of the ulcer. Because *bromocriptine* is an ergot derivative, it has the potential to cause pulmonary and retroperitoneal fibrosis. Dopamine agonists may delay the need to use *levodopa* therapy in early Parkinson disease and may decrease the dose of *levodopa* in advanced Parkinson disease. Unlike the ergotamine derivatives, *pramipexole* and *ropinirole* do not exacerbate peripheral vasospasm, and they do not cause fibrosis.

D. Increase secretion and inhibit reuptake of dopamine :( **Amantadine)** *Amantadine* has several effects on a number of neurotransmitters implicated in causing Parkinsonism, including increasing the release of dopamine, blockading cholinergic receptors, and inhibiting the N-methyl-D-aspartate (NMDA) type of glutamate receptors. Current evidence supports an action at NMDA receptors as the primary action at therapeutic concentrations. The drug may cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic psychosis. Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur. *Amantadine* is less efficacious than *levodopa*, and tolerance develops more readily. However, *amantadine* has fewer side effects. The drug has little effect on tremor, but it is more effective than the anticholinergics against rigidity and bradykinesia.

Prevention

* Caffeine consumption appears protective against Parkinson's disease
* Tobacco smoke decreases life expectancy and quality of life, it may reduce the risk of PD act as MAO .
* Antioxidants, such as vitamins C and D,
* [Estrogens](http://en.wikipedia.org/wiki/Estrogen)
* Anti-inflammatory drugs.

**DRUGS USED IN ALZHEIMER DISEASE**

 Dementia of the Alzheimer type results from loss of cortical neurons, particularly cholinergic neurons or excitotoxic actions via overstimulation of NMDA-glutamate receptors in selected brain areas.

**A-Acetyl cholinesterase inhibitors**: It is postulated that inhibition of acetylcholinesterase (AChE) within the CNS will improve cholinergic transmission, at least at those neurons that are still functioning. Currently, four reversible AChE inhibitors are approved for the treatment of mild to moderate Alzheimer disease. They are *donepezil*, *galantamine*, *rivastigmine*, and *tacrine*. Except for *galantamine*, which is competitive, all are uncompetitive inhibitors of AChE and appear to have some selectivity for AChE in the CNS as compared to the periphery. *Galantamine* may also be acting as modulator of the nicotinic receptor in the CNS and, therefore, may increase cholinergic neurotransmission through a separate mechanism. *Rivastigmine* is hydrolyzed by AChE to a carbamylate metabolite and has no interactions with drugs that alter the activity of cytochrome P450-dependent enzymes. The other agents are substrates for cytochrome P450 and have a potential for such interactions. Common adverse effects include nausea, diarrhea, vomiting, and anorexia, tremors, bradycardia, and muscle cramps. *tacrine* is associated with hepatotoxicity.

B-**NMDA-receptor antagonist**: overstimulation of glutamate receptors, particularly of the NMDA type, has been shown to result in excitotoxic effects on neurons 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, particularly, Ca2+ to enter the neuron. Unfortunately, excess intracellular Ca2+ can activate a number of processes that ultimately damage neurons and lead to apoptosis. Antagonists of the NMDA-glutamate receptor are often neuroprotective, preventing the loss of neurons following ischemic and other injuries. These drugs are:

*Memantine* acts by blocking the NMDA receptor–associated ion channel, but, at therapeutic doses, only a fraction of these channels are actually blocked. This partial blockade may allow *memantine* to limit Ca2+ influx into the neuron, such that toxic intracellular levels are not achieved during NMDA-receptor overstimulation, while still permitting sufficient Ca2+ flow through unblocked channels to preserve other vital processes that depend on Ca2+ (or Na+) influx through these channels.

*memantine* has been shown to slow the rate of memory loss in both vascular-associated and Alzheimer dementia in patients with moderate to severe cognitive losses. However, there is no evidence that *memantine* prevents or slows the neurodegeneration in patients with Alzheimer disease or is more effective than the AChE inhibitors. side effects are confusion, agitation, and restlessness.

**DRUGS USED IN MULTIPLE SCLEROSIS**

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS). It is a chronic, relapsing, or progressive disease that may span 10 to 20 years. Historically, medications, such as the corticosteroids (for example, *dexamethasone* and *prednisone*), have been used to treat acute attacks of the disease. Newer medications that have been approved for the treatment of MS include:

***Mitoxantrone:*** The cytotoxic anthracycline analog, kill T cells, the major target of this agent is to modify 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 include depression; local injection or infusion reactions; hepatic enzyme increases; flulike symptoms, such as fever and myalgias and leucopenia.

***Fingolimod*** is the first oral drug that can slow the progression of disability and reduce the frequency and severity of symptoms in MS *Fingolimod* alters lymphocyte migration, resulting in sequestration of lymphocytes in lymph nodes. *Fingolimod* is effective for reducing the relapse rate in patients with MS. butincreased risk of life threatening infection.

***Dalfampridine***, a potassium channel blocker administered orally, improves walking speeds. It is indicated to decrease relapse rates.

***Glatiramer***is a synthetic polypeptide that resembles myelin protein and may act as a “decoy” to T-cell attack.

***Natalizumab*** A monoclonal antibody, is indicated for MS in patients who have failed first-line therapies.

**DRUGS USED IN AMYOTROPHIC LATERAL SCLEROSIS**

*Riluzole* blocks glutamate, sodium channels, and calcium channels. It may improve the survival time and delay the need for ventilator support in patients suffering from ALS.