Pharmacology 4th class
Drugs Affecting the central nervous system
(treatment of neurodegenerative disease)

ANTI-PARKINSON DRUGS

Amantadine SYMMETREL
Apomorphine APOKYN
Benztropine COGENTIN
Biperiden AKINETON
Bromocriptine PARLODEL, CYCLOSET
Carbidopa LODOSYN
Entacapone COMTAN
Levodopa (w/Carbidopa) SINEMET, PARCOPA
Pramipexole MIRAPEX
Procyclidine KEMADRIN
Rasagiline AZILECT
Ropinirole REQUIP
Rotigotine NOT AVAILABLE IN U.S
Selegiline (Deprenyl) ELDEPRYL, ZELAPAR
Tolcapone TASMAR
Trihexyphenidyl ARTANE

ANTI-ALZHEIMER DRUGS

Donepezil ARICEPT
Galantamine RAZADYNE
Memantine NAMENDA
Rivastigmine EXELON
Tacrine COGNEX

Overview

Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process. Drugs CNS may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitter agents may activate or block postsynaptic receptors.

Neurotransmission in the CNS

In many ways, the basic functioning of neurons in the CNS is similar to that of the autonomic nervous system described in For example, transmission of information in the CNS and in the periphery both involve the release of neurotransmitters that diffuse across the synaptic space to bind to specific receptors on the postsynaptic neuron. In both systems, the recognition of the neurotransmitter by the membrane receptor of the postsynaptic neuron triggers intracellular changes.

Synaptic Potentials

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 ions inside and cell membrane to flow down their concentration gradients. The resulting change in the ionic composition across the membrane neuron alters the postsynaptic potential, producing either depolarization or hyperpolarization of the postsynaptic membrane depending on the specific ions that move and the direction of their movement.

A. Excitatory pathways

Neurotransmitters can be classified as either excitatory or inhibitory, depending on the nature of the action they elicit. excitatory neurons causes a movement of ions that results in a depolarization of the postsynaptic membrane. These excit 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 membra causes a transient increase in the permeability of sodium (Na+) ions. 2) The influx of Na+ causes a weak depolarization or moves the postsynaptic potential toward its firing threshold.

3) If the number of stimulated excitatory neurons increases, excitatory neurotransmitter is released.

B. 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 δ-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 postsynapticpotential away from its firing threshold. This diminishes the generation of action potentials.

Neurodegenerative Diseases

Neurodegenerative diseases of the CNS include Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. These devastating illnesses are characterized by the progressive loss of selected neurons in discrete brain areas, resulting characteristic disorders of movement, cognition, or both. For example, Alzheimer's disease is characterized by the loss of cholinergic neurons in the nucleus basalis of Maynert, whereas Parkinson's disease is associated with a loss of dopaminergic neurons in the substantia nigra. The most prevalent of these disorders is Alzheimer's disease.

V. Overview of Parkinson's 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. Most cases involve people over the age of 65, among whom the incidence is about 1 in 100 individuals.

A. Etiology

The cause of Parkinson's 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. The loss of dopamine neurons in the substantia nigra is evidenced by diminished overall uptake of dopamine precursors in this region. Genetic factors do not play a dominant role in the etiology of Parkinson's disease, although they may exert some influence on an individual's susceptibility to the disease.

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. These drugs should not be used in parkinsonian patients.

B. Strategy of treatment

In addition to an abundance of inhibitory dopaminergic neurons, the neostriatum is also rich in excitatory cholinergic neurons oppose the action of dopamine . Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons. Therapy is aimed at restoring dopamine the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance. Because long-term treatment with levodopa is limited by fluctuations in therapeutic responses, strategies to maintain dopamine levels as constant as possible have been devised.

Drugs Used in Parkinson's Disease

Currently available drugs offer temporary relief from the symptoms of the disorder, but they do not arrest or reverse the neuronal degeneration caused by the disease.

(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. In patients with early disease, the number of residual dopaminergic neurons in the substantia nigra (typically about percent of normal) is adequate for conversion of levodopa to dopamine. Thus, in new patients, the therapeutic response to levodopa consistent. 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.

Mechanism of action:

Levodopa: Because parkinsonism results from insufficient dopamine in specific regions of the brain, attempts have been made to replenish the dopamine deficiency. Dopamine itself does not cross the blood-brain barrier, but its immediate precursor, 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: The effects of levodopa on the CNS can be greatly enhanced by coadministering carbidopa [kar-bi-DOE-pa], a dopa decarboxylase inhibitor that does not cross the blood-brain barrier. Carbidopa diminishes the metabolism of levodopa in the gastrointestinal tract and peripheral tissues; thus, it increases the availability of levodopa to the CNS. The addition of carbidopa lowers the dose

of levodopa needed by four- to five-fold and, consequently, decreases the severity of the side effects arising from peripherally formed dopamine.

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

Therapeutic uses: Levodopa in combination with carbidopa is a potent and efficacious drug regimen currently available to treat Parkinson's disease. In approximately two-thirds of patients with Parkinson's disease, levodopa-carbidopa treatment substantially reduces the severity of the disease for the first few years of treatment.

Absorption and metabolism:

1-The drug is absorbed rapidly from the small intestine (when empty of food).

2-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. Motor fluctuations may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and immobility.

3- Ingestion of meals, particularly if high in protein, interferes with the transport of levodopa into the CNS.

4- 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.

5-levodopa should be taken on an empty stomach, typically 45 minutes before a meal.

6-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. (Tachycardia and ventricular extra systoles result from dopaminergic action on the heart. Hypotension may also develop.

CNS effects: Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur. These CNS effects are the opposite of parkinsonian symptoms and reflect the overactivity of dopamine at receptors in the basal ganglia. Levodopa can also cause mood changes, depression, psychosis, and anxiety.

Interactions: The vitamin pyridoxine (B_6) increases the peripheral breakdown of levodopa and diminishes its effectiveness . Concomitant administration of levodopa and monoamine oxidase (MAO) inhibitors, such as phenelzine, can produce a hypertensive crisis caused by enhanced catecholamine production.

(Selegiline and Rasagiline):- Selegiline , also called deprenyl 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 . Therefore, it enhances the actions of levodopa when these drugs are administered together. Selegiline substantially reduces the required dose of levodopa. **Rasagiline** ,an irreversible and selective inhibitor of brain (MAO) Type B, has five times the potency of selegiline. Unlike selegiline.

Catechol-O-methyltransferase inhibitors

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.

Pharmacokinetics:

1- Oral absorption of both drugs occurs readily and is not influenced by food.
2- They are extensively bound to plasma albumin (>98 percent), with limited volumes of distribution.
3- Tolcapone differs from entacapone in that the former penetrates the blood-brain barrier and inhibits COMT in the CNS. However, the inhibition of COMT in the periphery appears to be the primary therapeutic action.
4- Tolcapone has a relatively long duration of action (probably due to its affinity for the enzyme) compared to entacapone, which requires more frequent dosing.
5- Both drugs are extensively metabolized and eliminated in the feces and urine. Dosage may need to be adjusted in patients with moderate or severe cirrhosis.

Adverse effects: Both drugs exhibit adverse effects that are observed in patients taking levodopa-carbidopa, including diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations, and sleep disorders. Most seriously, fulminating hepatic necrosis is associated with tolcapone use. Therefore, it should be used-along with appropriate hepatic function monitoringâ€”only in patients in whom other modalities have failed. Entacapone does not exhibit this toxicity and has largely replaced tolcapone.

Dopamine-receptor agonists

This group of anti-Parkinson compounds includes **bromocriptine,**and **pergolide** an ergot derivative, and two newer, nonergot drugs, ropinirole, pramipexole and rotigotine. These agents have durations of action longer than that of levodopa and, thus, 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's disease complicated by motor fluctuations and dyskinesias. However, these drugs are ineffective in patients who have shown no therapeutic response to levodopa. Apomorphine is also used in severe and advanced stages of the disease as an injectable dopamine agonist to supplement the oral medications commonly prescribed.

(Bromocriptine): Bromocriptine , a derivative of the vasoconstrictive alkaloid, ergotamine, is a dopamine-receptor agonist. The dose is increased gradually during a period of 2 to 3 months. Side effects severely limit the utility of the dopamine agonists . 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.

(Apomorphine, pramipexole, ropinirole, and rotigotine):- These are nonergot dopamine agonists that have been approved for the treatment of Parkinson's disease. Pramipexole and ropinirole are agonists at dopamine receptors. Apomorphine and rotigotine are newer dopamine agonists available in injectable and transdermal delivery systems, respectively.

(Amantadine)

It was accidentally discovered that the antiviral drug amantadine which is effective in the treatment of influenza ,has an antiparkinsonism action.
Amantadine has several effects on a number of neurotransmitters implicated in causing parkinsonism, including
1- increasing the release of dopamine,
2- blockading cholinergic receptors .
3- 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
dopamine release is already at a maximum, amantadine has no effect.]

Side effects 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.

Antimuscarinic agents:-

The antimuscarinic agents are much less efficacious than levodopa and play only an adjuvant role in antiparkinsonism therapy. The actions of **benztropine** ,**trihexyphenidyl** , **procyclidine , and biperiden, orphenadrine** are similar, although individual patients may respond more favorably to one drug. All of these drugs can induce mood changes and produce xerostomia (dryness of the mouth) and visual problems, as do all muscarinic blockers. They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis.

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.

Drugs Used in Alzheimer's Disease

Alzheimer's Disease has three features **1**) accumulation of senile plaques (β-amyloid accumulations), **2)** formation of numerous neurofibrillary tangles, and **3)** loss of cortical neurons-particularly cholinergic neurons. Current therapies are aimed at either improving cholinergic transmission within the CNS or preventing excitotoxic actions resulting from overstimulation of N-methyl-D-aspartic acid (NMDA)-glutamate receptors in selected brain areas.

Acetylcholinesterase inhibitors:-

Numerous studies have linked the progressive loss of cholinergic neurons and, presumably, cholinergic transmission within the cortex to the memory loss that is a hallmark symptom of Alzheimer's disease. 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's 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. At best, these compounds provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer's patients.

Common adverse effects include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps-all of which are predicted by the actions of the drugs to enhance cholinergic neurotransmission . Unlike the others, tacrine is associated with hepatotoxicity.

NMDA-receptor antagonist

Mode of action :-Stimulation of glutamate receptors in the CNS appears to be critical for the formation of certain memories; however, 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 (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. Unfortunately, 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 often neuroprotective, preventing the loss of neurons following ischemic and other injuries. **Memantine** is a dimethyl adamantane derivative. **Memantine** acts by physically blocking the NMDA receptors associated ion channel, but at therapeutic doses, only a fraction of these channels are actually blocked. This partial blockade may allow memantine to limit Ca^{2+} influx into the neuron such that toxic intracellular levels are not achieved during NMDA receptor overstimulation, while still permitting sufficient Ca^{2+} flow through unblocked channels to preserve other vital processes that depend on Ca^{2+} (or Na^+) influx through these channels. This is in contrast to psychotoxic agents such as phencyclidine, which occupy and block nearly all of these channels. In short term studies, memantine has been shown to slow the rate of memory loss in both vascular-associated and Alzheimer's dementia in patients with moderate to severe cognitive losses.