

# 31

## Drugs Used in Neurodegenerative Disorders

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Neurodegenerative diseases are a group of disorders characterized by neuronal loss and generally an accumulation of insoluble intracellular or extracellular material in certain brain regions. Most neurodegenerative disorders are of unknown etiology, affect the elderly, are progressive, and damage selected neuronal populations or brain regions. There are some inherited forms of these disorders; however, most are sporadic occurrences (idiopathic) with genetic predisposition, environmental factors, and aging contributing as risk factors.

The neurodegenerative disorders include (1) Alzheimer's disease, the most common cause of dementia, in which the neural injury is primarily in the hippocampus and cortex; (2) Parkinson's disease, a disabling motor impairment disorder due to the loss of nigrostriatal dopamine neurons; (3) Huntington's disease, a motor disease characterized by excessive and ab-

normal movements resulting from the loss of a specific subset of striatal neurons; (4) amyotrophic lateral sclerosis (ALS), in which progressive weakness and muscle atrophy are due to degeneration of spinal, bulbar, and cortical neurons. This chapter focuses on Parkinson's and Alzheimer's diseases, for which pharmacological intervention can alleviate the clinical symptoms. However, *drugs used in the treatment of neurodegenerative disorders only treat symptoms and do not cure or alter the progression of the disease.*

### PARKINSON'S DISEASE

The classic publication in 1817 by James Parkinson defined the triad of distinguishing symptoms that bear his name; this movement disorder is known as Parkinson's

disease or parkinsonism. It generally affects the elderly and is estimated to afflict more than 1% of individuals over the age of 65. A small subset of patients has familial forms of parkinsonism with an autosomal dominant pattern of inheritance. Genetic mutations in three proteins have been identified thus far. These genes encode for  $\alpha$ -synuclein, a protein found in abundance in vesicles and synaptic regions, and for parkin and ubiquitin carboxy-terminal hydroxylase, both of which are involved with protein degradation.

Some forms of parkinsonism have been traced to specific entities, such as viral inflammation (e.g., the postencephalitic parkinsonism of the early 1900s), brain trauma, stroke, and poisoning by manganese, carbon monoxide, pesticide, or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Intoxication with MPTP, a byproduct of the synthesis of an illegal meperidine analogue, produces a condition closely resembling parkinsonism, but there is little evidence that this or a similar toxin exists in the environment. However, the information from research with this toxin has provided important insight into mitochondrial function and has led to the theory that impairment of mitochondrial function (whether of genetic or toxin derivation) may be a relevant risk factor in Parkinson's disease.

Although the causes of some forms of parkinsonism are known, most cases are sporadic and are of unknown origin (idiopathic Parkinson's disease). The causes are likely multifactorial, with genetic predisposition, environmental toxins, and aging contributing to the initiation and progression of the disease. There is a progressive loss of dopamine neurons with age. Relatively smooth functioning of motor control is maintained until neuronal loss is such that it causes an 80% reduction of dopamine in the striatum. At this time, clinical symptoms appear and then worsen with increasing neuronal loss.

Another form of parkinsonism is drug-induced, that is, iatrogenic parkinsonism, which often is a complication of antipsychotic therapy, especially following the use of the butyrophenone and phenothiazine drug classes (see Chapter 34). Unlike idiopathic parkinsonism, striatal content of dopamine is not reduced by administration of these drugs. In contrast, they produce a functional decrease in dopamine activity by blocking the action of dopamine on postsynaptic dopamine receptors.

### Clinical Findings

The onset of symptoms of Parkinson's disease is usually gradual. The most prominent features of parkinsonism are tremor, rigidity, and bradykinesia, although the time of onset and the relative severity of each symptom may differ in individual patients. Tremors are often unilateral in onset, present at rest, and cease during voluntary movement. Rigidity, or increased muscle tone, de-

scribed as jerky resistance that has been likened to the movement of a cogwheel (*cogwheel rigidity*), is also an indication of altered motor control. Bradykinesia, an extreme slowness of movement, is the most disabling feature because it affects all motor systems. Bradykinesia results in a typical stooped posture when the person is standing or walking and a characteristic shuffling gait marked by the absence of normal arm-swinging movements. The absence of facial expression (masklike face) results from loss of facial muscle function. Inability to swallow leads to drooling, while bradykinesia of the muscles in the larynx results in changes in voice quality. Orthostatic hypotension may also be observed and may complicate therapy. Cognitive dysfunction and dementia are also seen in a small percentage of Parkinson's disease patients, especially the elderly.

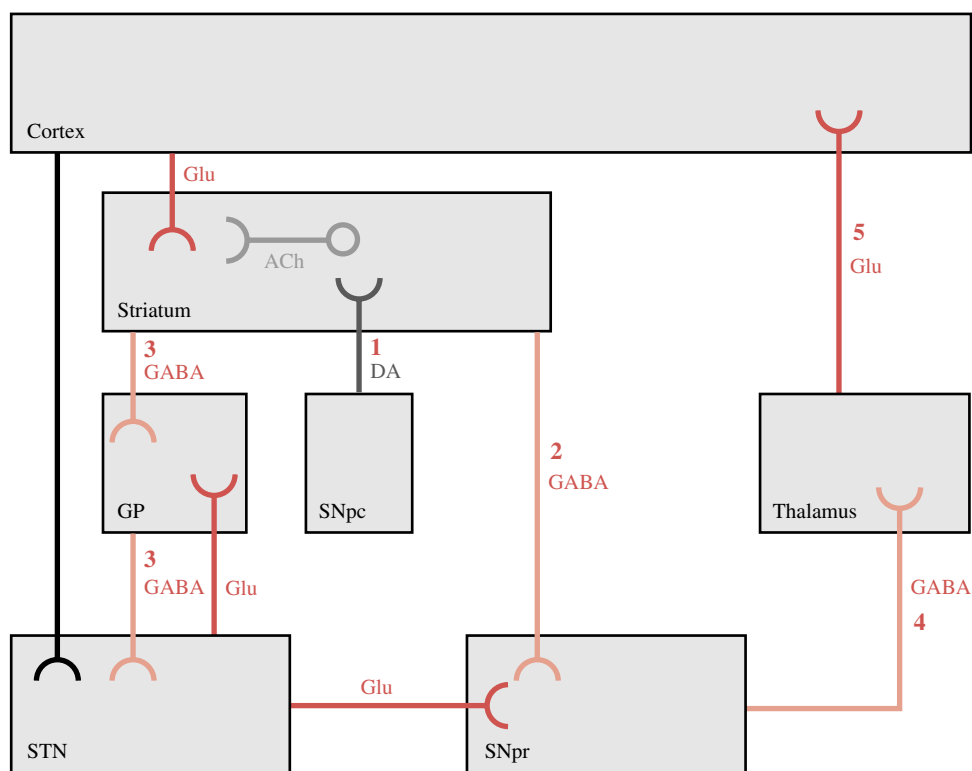
### Pathology

Parkinson's disease is one of the few neurological disorders in which knowledge of the pathology led directly to the rational development of drugs to treat the disease. *The most prominent pathological findings in Parkinson's disease are degeneration of the darkly pigmented dopamine neurons in the substantia nigra, loss of dopamine in the neostriatum, and the presence of intracellular inclusion bodies known as Lewy bodies.* Other neuronal populations are also affected in Parkinson's disease to a much lesser extent, but they may contribute to some of the other pathology seen in parkinsonism (e.g., cognitive decline, depression, and dementia).

In postmortem examination of tissue, the substantia nigra is readily identifiable because of the dark pigmentation in the neurons that is the result of the accumulation of neuromelanin, a substance whose neurochemical composition is not completely known but is thought to derive from oxidized dopamine. Lewy bodies are composed of many cytoskeleton and other proteins, including  $\alpha$ -synuclein, ubiquitin, and synaptophysin. It is not clear whether the formation of these inclusions contributes to neuronal degeneration or they are merely a byproduct of degenerating neurons.

### Basal Ganglia Anatomy

The basal ganglia can be viewed as modulators of motor function. They are composed of several brain regions, including the neostriatum and the substantia nigra (Fig. 31.1). The neostriatum receives massive excitatory input from the cortex that is mediated by neurons that use glutamate as the neurotransmitter. The dopamine neurons originate in the *substantia nigra pars compacta* and project to the neostriatum, where they synapse on the input glutamatergic terminals and on striatal projection neurons that use the neurotransmitter  $\gamma$ -aminobutyric acid (GABA).



**FIGURE 31.1**

Basal ganglia and associated circuitry. Several brain regions and numerous neurotransmitters are involved with the function and regulation of neuronal activity within the basal ganglia. In Parkinson's disease, the loss of dopamine neurons projecting from the SNpr to the neostriatum (1) leads to neuronal imbalance in this brain region and alterations in striatal outflow pathways. The direct pathway (2) the striatum to SNpr) becomes less active, whereas the indirect pathway (3) striatum to globus pallidus to STN to SNpr) increases in activity. The consequence is an enhanced activation of SNpr outflow neurons (4), which exert an overall reduction of the thalamic–cortical pathway (5). DA, dopamine; Glu, glutamate, excitatory transmitter; GABA,  $\alpha$ -amino butyric acid, inhibitory transmitter; ACh, acetylcholine, excitatory intrastriatal transmitter. GP, globus pallidus; SNpc, substantia nigra pars compacta; SNpr, substantia nigra, pars reticulata; STN, subthalamic nucleus.

Dopamine is a catecholamine (see Chapter 10 and Fig. 31.2) whose actions are mediated by dopamine receptors that are classified as  $D_1$ -like ( $D_1$ ,  $D_5$ ) or  $D_2$ -like ( $D_2$ ,  $D_3$ ,  $D_4$ ). Dopamine actions on  $D_1$  receptors exert an excitatory effect, whereas the actions of dopamine on  $D_2$  receptors inhibit neuronal activity. The loss of striatal dopamine produces an imbalance in information processing in the neostriatum that modifies transmission in other basal ganglia regions. Also important in neural transmission are the striatal interneurons that are found within the confines of the striatum, that use the excitatory neurotransmitter acetylcholine, and that modulate the activity of striatal output neurons.

### Possible Mechanisms of Neurodegeneration

The mechanisms responsible for the degeneration of dopamine neurons are not known, but hypotheses include effects such as oxidative stress and excitotoxicity.

The inability of the neurons to eliminate the oxidative load may result in a self-perpetuating cycle of oxidative damage that ultimately leads to neuronal death. One source of oxidative stress may be dopamine metabolism (Fig. 31.2). The excessive excitatory activity in the substantia nigra created by the loss of dopamine actions within the striatum could lead to excitotoxicity that is mediated by glutamate.

### Therapy of Parkinsonism

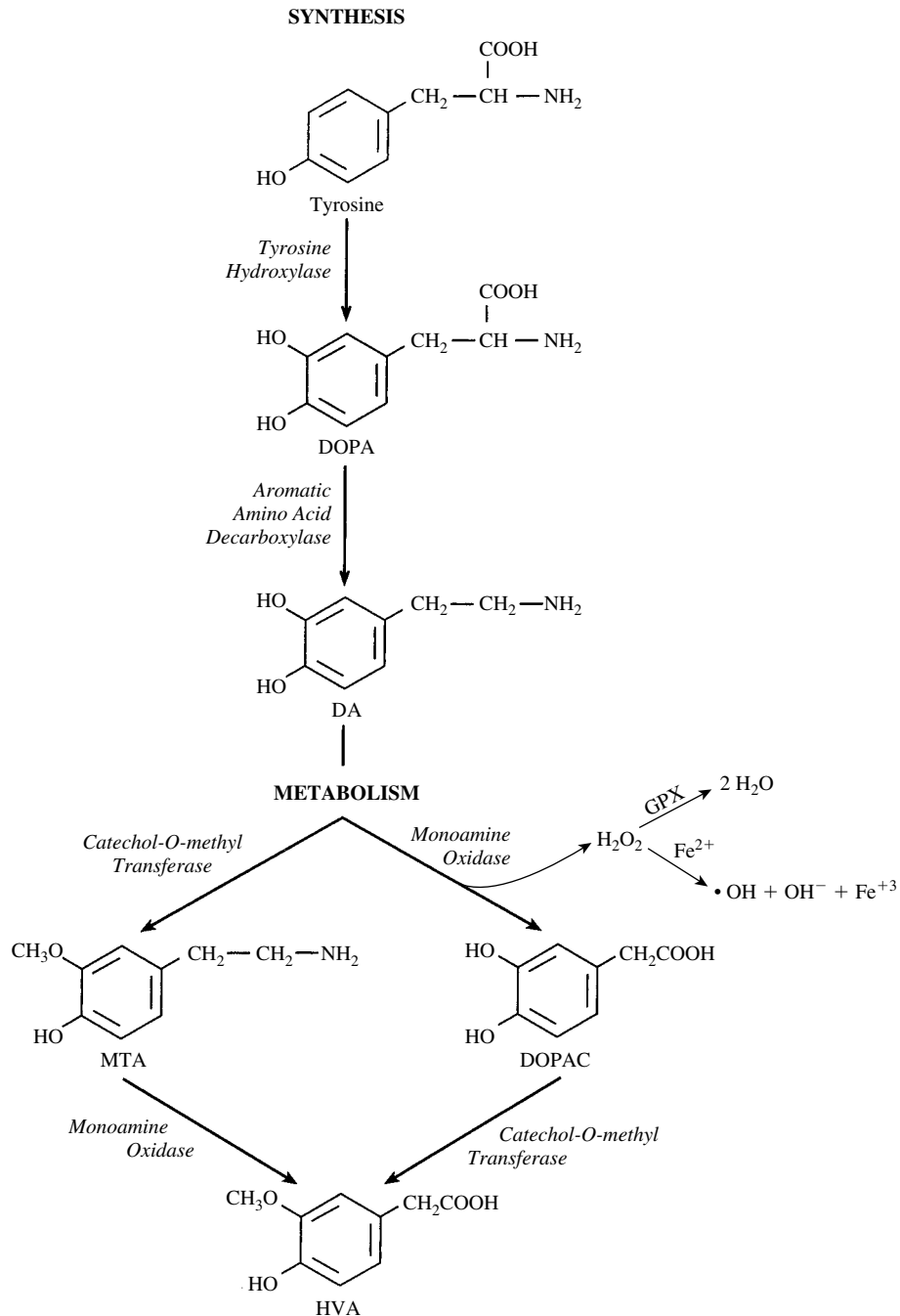
Since there is no cure for parkinsonism, the aim of pharmacological therapy is to provide symptomatic relief. This is obtained through the use of drugs that either increase dopaminergic actions or diminish neuronal outflow from the striatum. These drugs include levodopa, which increases brain dopamine levels; dopamine agonists, which directly stimulate dopamine receptors; monoamine oxidase (MAO) inhibitors, which prevent dopamine metabolism; and anticholinergic agents,

which reduce the excitatory activity within the striatum (Fig 31.3).

### Levodopa and Carbidopa

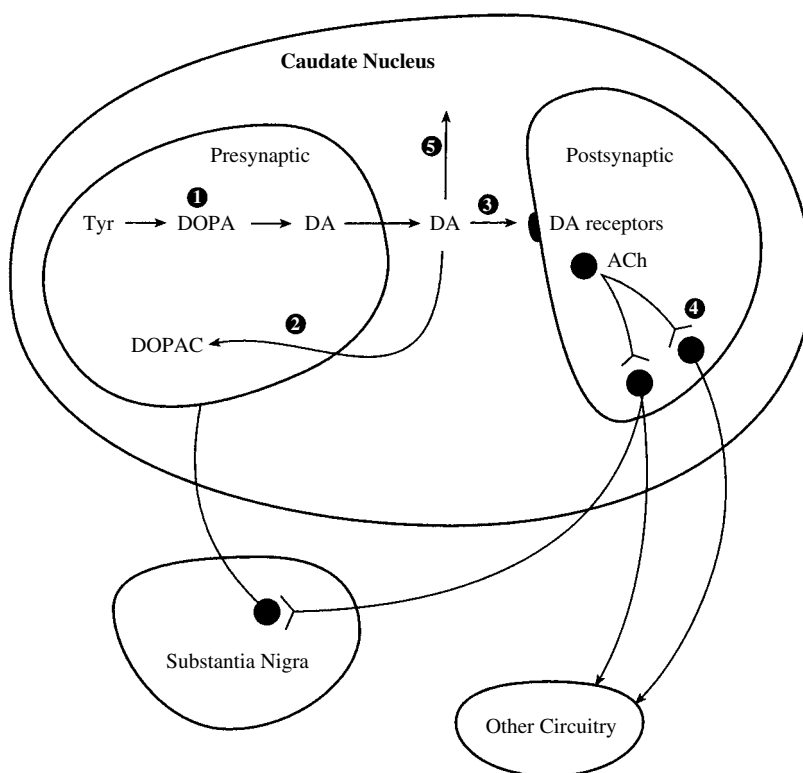
Levodopa (*L-DOPA*), the most reliable and effective drug used in the treatment of parkinsonism, can be con-

sidered a form of replacement therapy. Levodopa is the biochemical precursor of dopamine (Fig. 31.2). It is used to elevate dopamine levels in the neostriatum of parkinsonian patients. Dopamine itself does not cross the blood-brain barrier and therefore has no CNS effects. However, levodopa, as an amino acid, is transported into the brain by amino acid transport systems, where it



**FIGURE 31.2**

Pathways in the synthesis and metabolism of dopamine. The metabolism of dopamine produces hydrogen peroxide, which can be converted to water by glutathione peroxidase (GPX) or can in the presence of iron produce reactive hydroxyl radicals. DOPA, dihydroxyphenylalanine; DA, dopamine; MTA, 3-methoxytyramine; DOPAC, dihydroxyphenyl acetic acid; HVA, homovanillic acid; GPX, glutathione peroxidase;  $\text{H}_2\text{O}_2$ , hydrogen peroxide.



**FIGURE 31.3**

Pharmacological action of antiparkinsonian drugs. (1) Levodopa, as the immediate precursor of dopamine, increases dopamine production within the basal ganglia. (2) MAO-B inhibitors (selegiline) block a major pathway in dopamine metabolism and thus increase the duration of action of dopamine. (3) Dopamine receptor agonists (pramipexole, pergolide, bromocriptine) directly activate dopamine receptors on postsynaptic neurons. (4) Anticholinergic drugs block the increased excitatory activity of cholinergic interneurons on outflow pathways from the basal ganglia, which is secondary to a loss of inhibitor actions of dopamine on these cholinergic interneurons. (5) COMT inhibitors (with central actions) block an alternate pathway in the metabolism of dopamine.

is converted to dopamine by the enzyme L-aromatic amino acid decarboxylase.

If levodopa is administered alone, it is extensively metabolized by L-aromatic amino acid decarboxylase in the liver, kidney, and gastrointestinal tract. To prevent this peripheral metabolism, levodopa is coadministered with carbidopa (*Sinemet*), a peripheral decarboxylase inhibitor. *The combination of levodopa with carbidopa lowers the necessary dose of levodopa and reduces peripheral side effects associated with its administration.*

Levodopa is widely used for treatment of all types of parkinsonism except those associated with antipsychotic drug therapy. However, as parkinsonism progresses, the duration of benefit from each dose of levodopa may shorten (*wearing-off* effect). Patients can also develop sudden, unpredictable fluctuations between mobility and immobility (*on-off* effect). In a matter of minutes, a patient enjoying normal or nearly normal mobility may suddenly develop a severe degree of parkinsonism. These symptoms are likely due to the

progression of the disease and the loss of striatal dopamine nerve terminals.

Other disturbing behaviors that can be produced by levodopa therapy are the *dyskinesias*. These are excessive and abnormal choreiform movements of the limbs, hands, trunk, and tongue. These dyskinesias eventually occur in 40 to 90% of patients receiving long-term high-dosage levodopa therapy. The mechanism underlying these abnormal movements is unclear, but it may be related to fluctuating plasma levels of levodopa and the presence of hypersensitive dopamine receptors. The dyskinesias can be reduced by lowering the dosage; however, the symptoms of parkinsonism may then reappear. Most patients prefer to tolerate a certain degree of dyskinesia if their mobility can be improved by levodopa therapy.

The most common peripheral side effects are anorexia, nausea, and vomiting (likely due to dopamine's stimulation of the chemoreceptor trigger zone of the area postrema in the medulla oblongata).

Orthostatic hypotension may occur as a result of the peripheral decarboxylation of levodopa and release of dopamine into the circulation. Cardiac arrhythmias occur in some patients and are attributed to the stimulation of cardiac  $\alpha$ - and  $\beta$ -adrenoceptors by dopamine.

Centrally mediated adverse effects of levodopa therapy include vivid dreams, delusions, hallucinations, confusion, and sleep disturbances, especially in the elderly. Certain drugs can interfere with the clinical effectiveness or exacerbate the adverse reactions of levodopa therapy. For instance, nonselective MAO inhibitors (phenelzine, tranylcypromine) should not be administered with levodopa, since the combination can precipitate a life-threatening hypertensive crisis and hyperpyrexia. The additive effects of levodopa and adrenomimetic amines demonstrate that extreme care should be exercised in treating the symptoms of asthma or emphysema in patients with Parkinson's disease. Also, levodopa should not be given to patients with narrow-angle glaucoma, since it can produce severe mydriasis that would markedly aggravate the glaucoma. Patients with a history of cardiac arrhythmias or recent cardiac infarction should receive levodopa only when absolutely necessary. Also, proteins ingested with meals may produce sufficient amounts of amino acids to compete effectively with levodopa transport both in the gastrointestinal tract and in the brain. Levodopa therefore should be administered at least 30 minutes before meals.

### Dopamine Agonists

Dopamine receptor agonists are considered by many clinicians as the first approach to therapy. They have a long duration of action and are less likely to cause dyskinesias than levodopa. The rationale for the use of dopamine agonists is that they provide a means of directly stimulating dopamine receptors and do not depend on the formation of dopamine from levodopa. As monotherapy, the dopamine agonists are less effective than levodopa but are often used early in the disease to delay initiation of levodopa therapy. When used as an adjunct to levodopa in advanced stages, the dopamine receptor agonists may contribute to clinical improvement and reduce levodopa dosage needs.

The four dopamine agonists used in the United States are bromocriptine (*Parlodel*), pergolide (*Permax*), pramipexole (*Mirapex*), and ropinirole (*Requip*). Bromocriptine, an ergot derivative, is an agonist at the  $D_2$ -receptors and a partial  $D_1$ -antagonist. Pergolide, also an ergot derivative, is an agonist at both  $D_1$ - and  $D_2$ -receptor subtypes. The more recently introduced nonergot drugs, ropinirole and pramipexole, are selective agonists at  $D_2$ -receptor sites.

All four exert similar therapeutic effects and can produce the same adverse effects seen with levodopa. The differences between the ergot derivatives and the

newer agents reside primarily in their adverse effects and tolerability. Postural hypotension, nausea, somnolence, and fatigue are common adverse effects of bromocriptine and pergolide therapy and can limit the use of these drugs.

Because of these adverse effects, the drugs are generally first administered at low doses and then the dose is gradually increased over weeks or months as tolerance to the adverse effects develops. These symptoms are generally less frequent and less severe with pramipexole and ropinirole, which allows for a more rapid achievement of therapeutic response. Also, because pramipexole and ropinirole are better tolerated, they are increasingly used as monotherapy.

### Selegiline

Another drug used in the treatment of Parkinson's disease is selegiline (also known as deprenyl, or *Eldepryl*). It is an irreversible inhibitor of MAO-B, an important enzyme in the metabolism of dopamine (Fig. 33.2). Blockade of dopamine metabolism makes more dopamine available for stimulation of its receptors. Selegiline, as monotherapy, may be effective in the newly diagnosed patient with parkinsonism because its pharmacological effect enhances the actions of endogenous dopamine.

Selegiline is also used in conjunction with levodopa-carbidopa in later-stage parkinsonism to reduce levodopa dosage requirements and to minimize or delay the onset of dyskinesias and motor fluctuations that usually accompany long-term treatment with levodopa. It has also been proposed that selegiline may slow the progression of the disease by reducing the formation of toxic free radicals produced during the metabolism of dopamine (Fig.31.2). However, any neuroprotective effect of selegiline in parkinsonian patients remains to be established.

Most of the adverse reactions to selegiline are related to actions of increased levels of dopamine, as discussed earlier. At recommended doses, and unlike the nonselective MAO inhibitors used in the treatment of depression, selegiline has little effect on MAO-A and therefore generally does not cause the hypertension associated with the ingestion of tyramine-enriched foods (see Chapter 20). However, at doses higher than those usually recommended, MAO-A may be inhibited, which increases the risk of a tyramine reaction.

Selegiline should not be coadministered with tricyclic antidepressants or selective serotonin uptake inhibitors because of the possibility of a severe adverse drug reaction (e.g., hyperpyrexia, agitation, delirium, coma).

### Anticholinergic Drugs

Before the introduction of levodopa, the *belladonna alkaloids* (e.g., atropine and scopolamine) were the

primary agents used in the treatment of parkinsonism. The belladonna alkaloids have been replaced by anticholinergic agents with more selective central nervous system (CNS) effects. Trihexyphenidyl (*Artane*), benzotropine mesylate (*Cogentin*), biperiden (*Akineton*), and procyclidine (*Kemadrin*) are useful in most types of parkinsonism.

The efficacy of anticholinergic drugs in parkinsonism is likely due to the ability to block muscarinic receptors in the striatum. In the absence of the inhibitory action of dopamine, the actions of the intrastriatal cholinergic interneurons are unopposed, yielding enhanced stimulation of muscarinic receptors. Blockade of these receptors reduces striatal activity. *The muscarinic antagonists exert only modest antiparkinsonian actions and thus are most commonly used during the early stages of the disease or as an adjunct to levodopa therapy.*

Of the drugs used for treating parkinsonism, the anticholinergics are the only class that can provide benefit in the treatment of the drug-induced parkinsonism seen with antipsychotic therapy. This is because the blockade of dopamine receptors by the antipsychotics leads to increased activity of the striatal neurons. Blockade of the muscarinic receptors reduces this excitatory activity.

The adverse effects of the anticholinergic drugs are due to their antimuscarinic effects in other systems (e.g., cycloplegia, dry mouth, urinary retention, and constipation). Confusion, delirium, and hallucinations may occur at higher doses.

The antihistamine diphenhydramine (*Benadryl*), because it has anticholinergic properties, is used for mild parkinsonism and with the elderly, who may not be able to tolerate the more potent anticholinergics, levodopa, or the dopamine agonists.

### Amantadine

Amantadine was originally introduced as an antiviral compound (see Chapter 50), but it is modestly effective in treating symptoms of parkinsonism. It is useful in the early stages of parkinsonism or as an adjunct to levodopa therapy. Its mechanism of action in parkinsonism is not clear, but amantadine may affect dopamine release and reuptake. Additional sites of action may include antagonism at muscarinic and *N*-methyl-D-aspartate (NMDA) receptors. Adverse effects include nausea, dizziness, insomnia, confusion, hallucinations, ankle edema, and livedo reticularis. Amantadine and the anticholinergics may exert additive effects on mental functioning.

### Catechol-O-Methyl Transferase Inhibitors

A recently introduced class of drugs for the treatment of parkinsonism is the *catechol-O-methyl transferase (COMT) inhibitors*. COMT metabolizes catechol compounds, including dopamine and levodopa (see Chapter

9), producing the inactive compound 3-*O*-methyl DOPA. The rationale for the use of COMT inhibitors is analogous to that for carbidopa; that is, since COMT is present in the periphery as well as in the CNS, inhibition of peripheral COMT results in an increase in the plasma half-life of levodopa, thereby making more drug available for transfer to the brain. Additionally, compounds that block COMT in the CNS also prolong the brain concentration of levodopa.

The two COMT inhibitors in clinical use are tolcapone (*Tasmar*) and entacapone (*Comtan*). They are used in combination with levodopa-carbidopa. In patients with motor fluctuations, they increase the “on” time. Adverse effects are similar to those observed with levodopa-carbidopa alone. Tolcapone therapy can cause fatal hepatotoxicity and so should be used only in patients who do not respond to other therapies. Patients taking tolcapone require close monitoring of liver enzymes for signs of hepatic changes.

### Nonpharmacological Approaches to the Treatment of Parkinsonism

Additional approaches to the treatment of Parkinson’s disease include surgical procedures, brain stimulation, and transplantation of dopaminergic cells. In general, surgical procedures are reserved for patients who are refractive to levodopa or who have profound dyskinesias or fluctuations in response to levodopa. Tremor can be abolished by ablation of the ventral intermediate nucleus of the thalamus. Dyskinesias can be effectively controlled by ablation of the posteroventral portion of the globus pallidus. Brain stimulation appears to be a promising technique. High-frequency electrical stimulation of the thalamus, subthalamic nucleus, or globus pallidus can improve various symptoms of parkinsonism and reduce levodopa dosage.

A potentially promising, although very controversial, approach to the treatment of Parkinson’s disease is replacement of dopaminergic neurons. The grafting of fetal substantia nigra tissue, which contains the dopamine neurons, into the striatum of parkinsonian patients has been modestly successful. The procedure will remain experimental, however, until the many practical problems and ethical issues associated with the use of fetal tissue are resolved. The discovery of pluripotent stem cells is also being viewed as a possible way of developing dopamine neurons for transplant purposes.

## ALZHEIMER’S DISEASE

Alzheimer’s disease, the most prevalent form of dementia, afflicts approximately 10% of the population over age 65. The cardinal features of Alzheimer’s disease are progressive loss of memory and disordered cognitive function. Alterations in behavior and a decline in lan-

guage function can also be observed in the early stages of Alzheimer's disease. The impairment in cognitive abilities occurs gradually, with the loss of short-term memory generally preceding loss of long-term distant memory. In the advanced stages, the individual may not recognize spouse or children, and the levels of arousal and alertness are severely impaired. Other signs of Alzheimer's disease include reduced verbal fluency, naming deficits, and impairment of speech exemplified by failure to arrange words in proper order (dysphasia). Ultimately, with progression of the disease, motor function is impaired and the patient may fall into a vegetative state. Death is usually associated with complications of immobility (e.g., pneumonia or pulmonary embolism).

### Pathology

The pathological features of Alzheimer's disease include the presence of  $\beta$ -amyloid plaques,  $\tau$ -enriched neurofibrillary tangles, neuronal loss, and alterations in many neurotransmitter systems. Affected brain regions include the entorhinal cortex; hippocampus; amygdala; association cortices of the frontal, temporal and parietal lobes; and subcortical nuclei that project to these regions. Characteristically, the brains of Alzheimer's disease patients contain two distinct types of insoluble materials that are hallmarks of the brain lesions associated with the disorder: extracellular neuritic plaques containing  $\beta$ -amyloid ( $A\beta$ ) and intracellular  $\tau$ -enriched neurofibrillary tangles. As with Lewy bodies in Parkinson's disease, it is unclear whether the tangles and plaques are causal or byproducts of degenerative processes. However, considerable evidence suggests that alterations in  $A\beta$  processing may be necessary components of cell destruction.

One theory of the pathogenesis of Alzheimer's disease proposes that increased production or decreased secretion of the  $A\beta$  peptides leads to accumulation of these peptides. A second theory proposes that an abnormal  $\tau$ -protein causes the formation of intracellular neurofibrillary tangles.  $\tau$ -Proteins are important in the maintenance of cytoskeleton function and axonal transport of proteins. Another theory is that  $A\beta$  accumulation is a precipitating factor that is followed by the development of the  $\tau$ -enriched tangles in the dying neurons.

### Therapy of Alzheimer's Disease

The discovery of the loss of the cholinergic neurons and acetylcholine in the brain of Alzheimer's disease patients led to the use of drugs that would enhance the actions of acetylcholine in the brain. Therapeutic agents approved for the treatment of Alzheimer's disease are the *cholinesterase inhibitors*, drugs that block the breakdown of acetylcholine and increase the availability of the neurotransmitter in synapses (see Chapter 12). These drugs are palliative only and do not cure or prevent neurodegeneration.

Available drugs are tacrine (*Cognex*), donepezil (*Aricept*), rivastigmine (*Exelon*), and galanthamine (*Reminyl*). The drugs have a significant but modest effect on the cognitive status of patients, possibly because the drugs do not correct for changes that occur in other neuronal systems.

Adverse effects produced by the drugs include nausea, diarrhea, vomiting, and insomnia. These symptoms are most frequent and severe with tacrine. Hepatotoxicity is associated with tacrine therapy. Because of these significant side effects, tacrine is not widely used.

### Future Directions in the Treatment of Alzheimer's Disease

It is becoming clear that Alzheimer's disease is a multifactorial syndrome and that unraveling its causes may be difficult. However, as knowledge of the mechanisms of degeneration are elucidated, this knowledge can be applied to the development of therapies to alleviate the symptoms and hopefully to prevent the disease or inhibit its progression.

Several new directions in therapeutic approaches are being investigated. One is to lower  $A\beta$  peptide levels and thus reduce  $A\beta$  deposits through the use of molecules that prevent the proteolytic cleavage of amyloid precursor protein or through a novel immunization technique that would use antibodies to remove the  $A\beta$  peptides from the cells and brain. Other approaches being examined are targeted at blocking the more downstream effects, such as the use of antiinflammatory agents and antioxidants.

## Study QUESTIONS

- J. S. is a newly diagnosed Parkinson's disease patient who has motor difficulties. Which of the following is the most appropriate treatment for early stage parkinsonism?
  - Levodopa-carbidopa
  - Pramipexole
  - Entacapone
  - Clozapine
  - Donepezil
- M. K. is a 60-year-old woman with Parkinson's disease. Her current therapy is levodopa-carbidopa. She complains that she frequently goes from being



fairly mobile to being immobile in only a matter of a few minutes. Her neurologist decides to add tolcapone to her therapy. What blood tests should be performed before and during her treatment with tolcapone?

- (A) Red blood cell count
  - (B) White blood cell count
  - (C) Serum levels of calcium and phosphorus
  - (D) Serum levels of creatinine and uric acid
  - (E) Serum levels of transglutaminase enzymes
3. T. T. is a 75-year-old man whom you have seen off and on for 5 years. His wife accompanies him for his visit. She indicates that he is getting very forgetful and that about 2 weeks ago, he got lost on a trip to the grocery store and she had to go pick him up. You suspect that your patient is in the early stages of Alzheimer's disease. Which of the following would be most appropriate?
- (A) Tell T. T. that this is normal for his age and not to worry.
  - (B) Suggest that he begin adding a daily vitamin to his existing treatment.
  - (C) Don't tell your patient anything, but arrange for a separate appointment with his wife in which you tell her that T. T. has Alzheimer's disease.
  - (D) Tell T. T. that this may be an early sign of Alzheimer's disease and offer a prescription to a cholinesterase inhibitor approved for the treatment of Alzheimer's disease.
4. N. C. is a 67-year-old woman with Parkinson's disease. She appears in the emergency department complaining of purplish mottling of the skin on her legs. The most likely drug to be involved is
- (A) Levodopa
  - (B) Levodopa-carbidopa (Sinemet)
  - (C) Bromocriptine
  - (D) Amantadine
  - (E) Tolcapone
5. B. M. is a 45-year-old schizophrenic who finally has his antipsychotic medication adjusted properly and who is doing reasonably well at the moment. He came to your office today exhibiting many signs of parkinsonism, including tremor, rigidity, stooped posture, and shuffling gait. He indicates that even though his schizophrenia is under control, these new symptoms are very unpleasant. What do you do?
- (A) Withdraw his antipsychotic medication.
  - (B) Prescribe levodopa.
  - (C) Prescribe a muscarinic blocking agent.
  - (D) Prescribe a dopa agonist.
  - (E) Prescribe amantadine.

#### ANSWERS

1. **B.** Pramipexole is a dopamine receptor agonist. This class of drugs is often used in the early stages

of parkinsonism. Ropinirole and pergolide are other drugs in this class that could be used. Some patients also get symptomatic relief from selegiline (MAO inhibitor). Although levodopa-carbidopa would be effective, this therapy is usually delayed until other treatments become ineffective. Entacapone is a COMT inhibitor and is used only in combination with levodopa-carbidopa to inhibit the peripheral metabolism of levodopa. Clozapine is an antipsychotic drug used to treat levodopa-induced psychosis. Donepezil is an anticholinesterase inhibitor that increases acetylcholine actions in the brain. This drug may exacerbate parkinsonism.

2. **E.** The patient is feeling the on-off effects of levodopa therapy, possibly as a result of fluctuating blood and brain levels of levodopa. The rationale for adding tolcapone (a COMT inhibitor) to her therapy is to reduce the peripheral metabolism of levodopa, thus increasing its plasma half-life and its duration of action in the brain. However, tolcapone can produce hepatotoxicity. Therefore, it is important to monitor hepatic function before and during treatment. Increased levels of transglutaminase enzymes (e.g., SGOT [serum glutamic-oxaloacetic transaminase] and SGPT [serum glutamate pyruvate transaminase]) indicate compromised hepatic function. If elevations occur during treatment, tolcapone therapy must be stopped. The patient could then be treated with entacapone, a COMT inhibitor that is not associated with hepatotoxicity. Other approaches to treating the on-off symptoms may also be used. For example, the physician might consider switching the patient to a controlled-release formulation of levodopa-carbidopa, which would provide a more prolonged release of levodopa or adding a dopamine receptor agonist, which has a longer duration of action than levodopa.
3. **D.** The patient should be informed that his symptoms are consistent with early Alzheimer's disease but that he will need testing to rule out other causes of memory impairment. Subsequently he may be offered the opportunity to try one of the agents that is approved for this condition. However, you should indicate that although these agents are not curative, they are beneficial to many patients.
4. **D.** Although not widely used, amantadine may be useful in the early stages of Parkinson's disease or as an adjunct to other agents. Livedo reticularis is a characteristic purple mottling of the skin associated with amantadine.
5. **C.** A is not correct because the signs and symptoms of schizophrenia would soon reappear. The administration of levodopa will not antagonize the signs of Parkinson's disease in this patient because there is no deficit of dopa, only a blockade of dopamine receptors. Likewise the administration of either a

dopa agonist or amantadine will be ineffective. A muscarinic blocking agent will block the increased activity of striatal neurons and antagonize the parkinsonism.

#### SUPPLEMENTAL READING

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### CASE Study Early-Stage Parkinsonism

**M**. S. is a 60-year old architect who designs buildings. His drawings are very detailed and they must be drawn to a specific scale. During the past month he has developed a slight tremor in his right hand that causes some embarrassment but does not interfere with function. He has, however, noticed that his writing and drawing have gotten much smaller, causing problems with his work. His primary care physician has referred him to a neurologist for evaluation. On examination, the neurologist notes some motor rigidity in the right arm. He also observes a slight slowing in the patient's walk and a reduction in the swing of his arms as he walks. What is the diagnosis, and how should the patient be treated?

**ANSWER:** The patient is in early-stage parkinsonism, most likely idiopathic (Parkinson's disease). Clinically, the disease is very mild and the neurologist might consider not treating him at this point, but because the micrographia interferes with his work, the neurologist decides to prescribe medication. Several drugs can be used to treat early-onset parkinsonism. The most commonly used are the dopamine receptor agonists (pramipexole, ropinirole, pergolide; amantadine is also a possibility, and some people get an acceptable response to selegiline, the MAO inhibitor). Levodopa–carbidopa could also be used; however, most clinicians prefer to delay its use until absolutely needed because of the adverse effects, such as motor fluctuations and dyskinesias, that accompany long-term use of levodopa.