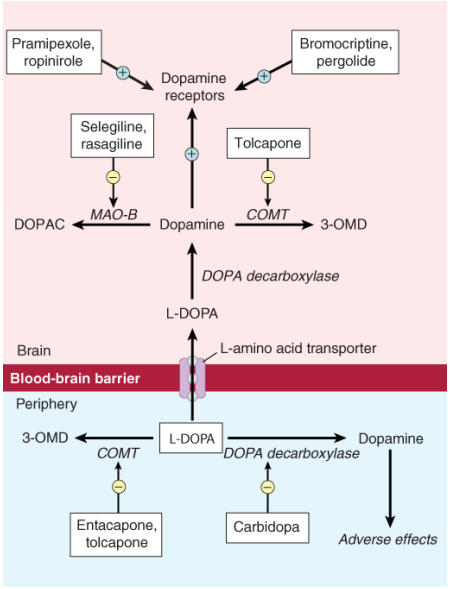
NEUROPHARMACOLOGY 2

Parkinson's disease pharmacology Parkinsonism has four cardinal features: bradykinesia (slowness and poverty of movement), muscular rigidity, resting tremor (which usually abates during voluntary movement), and an impairment of postural balance leading to disturbances of gait and falling. The pathological hallmark of PD is a loss of the pigmented, dopaminergic neurons of the substantia nigra pars compacta (SNpc) that provide dopaminergic innervation to the striatum (caudate and putamen). Ultimately leading to decreased excitation of the motor cortex and inhibition of the thalamus. Drugs in common clinical use that may cause parkinsonism include antipsychotics such as haloperidol and thorazine and antiemetics such as prochloperazine and metoclopramide. Strategies of drug treatment of parkinsonism involve increasing dopamine activity in the brain, decreasing muscarinic cholinergic activity in the brain, or both. Although several dopamine receptor subtypes are present in the substantia nigra, the benefits of most antiparkinson drugs appear to depend on activation of the D_2 receptor subtype.

Levodopa Because dopamine has low bioavailability and does not readily cross the blood-brain barrier, its precursor, L-dopa (levodopa), is used. Pharmaceutical: Levodopa is usually given with carbidopa, a drug that does not cross the blood-brain barrier but inhibits dopa decarboxylase in peripheral tissues. With this combination, the plasma half-life is prolonged, lower doses of levodopa are effective, and there are fewer peripheral side effects. Pharmacodynamics: By increasing the concentration of dopamine in the CNS many of the symptoms of PD are temporarily alleviated, although this may be at the cost of dyskinesias when the concentration is high and rapid return of PD symptoms when the concentration lowers limiting the effectiveness. Pharmacokinetics: Bioavailibility is around 75% via active transport in the small bowel, competition for binding sites means there is absorption is slowed if ingested with a meal. Levodopa enters the brain via an L-amino acid transporter (LAT) and is converted to dopamine by the enzyme aromatic L-amino acid decarboxylase (dopa decarboxylase), which is present in many body tissues, including the brain. It has a half life of 1-3 hours and requires frequent dosing. Side effects in addtion to the dyskinesias are hallucinations and confusion, and orthstatic hypotension.



Bromocriptine An ergot alkaloid. bromocriptine acts as a partial agonist at dopamine D2 receptors in the brain. The drug increases the functional activity of dopamine neurotransmitter pathways, including those involved in extrapyramidal functions. Bromocriptine has been used as an individual drug, in combinations with levodopa (and with anticholinergic drugs), and in patients who are refractory to or cannot tolerate levodopa. Common adverse effects include anorexia, nausea and vomiting, dyskinesias, and postural hypotension. Behavioural effects, which occur more commonly with bromocriptine than with newer dopamine agonists, include confusion, hallucinations, and delusions. Ergot-related effects include erythromelalgia and pulmonary infiltrates. Use of bromocriptine in patients with Parkinson's disease has declined with the introduction of non-ergot dopamine receptor agonists such as pramipexole.

Monoamine oxidase inhibitors Selegine is a selective inhibitors of monoamine oxidase type B at lower doses, the form of the enzyme that metabolizes dopamine. It demonstrates modest benefit and may be useful in early disease or in combination with levodopa. Adverse effects and interactions of monoamine oxidase inhibitors include insomnia, mood changes, dyskinesias, gastrointestinal distress, and hypotension.

Catechol-O-Methyltransferase (COMT) Inhibitors Entacapone and tolcapone are inhibitors of COMT, the enzyme in both the CNS and peripheral tissues. The drugs are used individually as adjuncts to levodopa-carbidopa, decreasing fluctuations, improving response, and prolonging "on-time." Tolcapone is taken 3 times daily, entacapone 5 times daily. A formulation combining levodopa, carbidopa, and entacapone is available, simplifying the drug regimen. Adverse effects related partly to increased levels of levodopa include dyskinesias, gastrointestinal distress, and postural hypotension. Levodopa dose reductions may be needed for the first few days of COMT inhibitor use. Other side effects include sleep disturbances and orange discoloration of the urine.

Parasympathetic agonists (cholinomimetics) are drugs that mimic acetylcholine by directly or indirectly activating the receptors with which acetylcholine interacts. Cholinergic agonists can act at nicotinic receptors, muscarinic receptors or both. They are usually classified by whether they act directly on the receptor or indirectly by inhibiting cholinesterases and therefore prolonging the action of acetylcholine. Direct acting cholinomimetics comprise a group of choline esters (including acetylcholine, methacholine) and a second group of naturally occurring alkaloids (muscarine, pilocarpine, nicotine) and the depolarising neuromuscular blockers such as suxamethonium (see neuromuscular junction page). The with the exception of the DNMBs, direct acting cholinomimetics have limited uses beyond topical application to produce miosis and for diagnostic purposes in the case of methacholine. The indirect agents however are used commonly in a critical care setting for the reversal of non depolarising neuromuscular blocking agents and in the treatment of myasthenia gravis and increasingly for the percieved CNS benefits in the treatment of dementia. The indirect cholinomimetics (anticholinesterase) include the prototype neostigmine as well as edrophonium, physostigmine, donepezil (for dementia) and the organophosphates (which are irreversible and cause poisoning). The anticholinesterase drugs are ionised water soluble agents that inhibit acteylcholinesterase at the synaptic cleft. In the paralysed patient these agents reverse the nondepolarising blockade at the nicotinic ACh receptor. Because anticholinesterase drugs activate muscarinic receptors, the co-administration of a muscarinic receptor antagonist such as atropine or gylcopyrrolate can reduce the side effects of bradycardia, bronchospasm or intestinal spasm. Neostigmine is a quaternary amine. When used in theatres it is delivered IV but is also available in oral form. It is poorly absorbed from the gut and has a low oral bioavailability. It is minimally protien bound, has a low volume of distribution and is partially metabolised in the liver. It does not cross the BBB. More than 50% is excreted in the urine unchanged (therefore caution is required in renal impairment).

Parasympathetic antagonists (anticholinergics) Anticholinergic drugs (atropine, scopolamine, glycopyrrolate) competitively inhibit the action of ACh by reversibly binding to cholinergic postganglionic receptors. They are selective for muscarinic receptors at the doses normally employed clinically. Atropine and scopolamine (hyoscine hydrobromide) are naturally occuring tertiary amines derived from the belladona plant. They are able to cross the BBB. Their anticholinergic activity is primarily due to the L enantiomer although they are presented as racemic mixtures. Low doses of atropine (2mcg/kg) act centrally and may augment vagal outflow, decreasing heart rate. At normal clinical doses (15-70mcg/kg) atropine also acts on peripheral muscarinic receptors blocking the action of the vagal nerve and increasing the heart rate and pupil size whilst decreasing secretory gland activity. A limitation to the use of atropine and scopolamine is an infrequent side effect called central anticholinergic syndrome which consists of agitation, disorientation, delerium, hallucinations and restlessness but may present as increased somnolence and is a differential for delayed wakening from anaesthesia. As a quarternary amine, glycopyrrolate does not cross the BBB and therefore does not exert CNS effects. It is however, more potent and longer acting at peripheral muscarinic receptors than atropine. It is used to decrease secretions and treat vagally mediated bradycardia, and to inhibit cardiac muscarinic side effects when anticholinesterase agents are used to reverse the effects of muscle relaxants. Ipatropium, a derivative of methylatropine is an inhaled anticholinergic that is utilised for its bronchodilating effects via blockade of M3 muscarinic receptors located on smooth muscle in the airway.

Drug	Structure	Distribution	Sedation	Mydrasis	Heart rate	GI tone	Secretions	Duration (IV)
Atropine	tertiary amine	crosses BBB	mild	slight	+++	none	none	15-30mins
Scopolamine	tertiary amine	crosses BBB	major	marked	+/-	reduced	reduced	30-60mins
Glycoprolate	quaternary amine	peripheral only	none	none	++	reduced	reduced	2-4hrs

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