**THE CONCEPT OF EFFERENT INNERVATION.**

**DRUGS AFFECTING THE CHOLINERGIC SYSTEM**

When synaptic transmission depends upon acetylcholine as the primary neurotransmitter, it is labeled cholinergic. The termination of acetylcholine activity is mediated by the enzyme acetylcholinesterase. There are two subtypes of cholinergic receptors, muscarinic (M) and nicotinic (N). Agonists that mimic the effects of acetylcholine are defined as cholinomimetics. Some drugs are direct-acting agonists for the cholinergic receptors. Other drugs function as indirect-acting agonists by preventing the inactivation of acetylcholine. Antagonists that inhibit acetylcholine at muscarinic or nicotinic receptors are defined as anticholinergics. Drugs that selectively inhibit muscarinic receptors are called antimuscarinics, whereas those that selectively inhibit nicotinic receptors are antinicotinics.

**Cholinomimetic Drugs**

Direct-acting nicotinic agonists may be classified on the basis of whether ganglionic (NN) or neuromuscular (NM) stimulation predominates, but agonist selectivity is very limited. Several molecular mechanisms for receptor signaling have been identified for muscarinic receptors. In general, these receptors modulate the formation of second messengers or the activity of ion channels. In contrast, all nicotinic receptors cause the opening of a channel selective for sodium and potassium that results in cellular depolarization. This signaling mechanism occurs in the autonomic ganglia and at the neuromuscular junction.

Direct-acting cholinoceptor agonists are classified pharmacologically by the type of receptor—muscarinic or nicotinic—that is activated. Direct-acting agonists’ physiologic effects are the result of their interaction with either the muscarinic or nicotinic receptors. Indirect-acting agonists are classified as such because they inhibit the hydrolysis and inactivation of endogenous acetylcholine. This increases the concentration of acetylcholine in the synapse and augments acetylcholine binding to receptors. Indirect-acting agonists are less specific in their stimulation of muscarinic compared to nicotinic receptors.

**Direct-Acting Cholinergic Agonists**

Direct-acting agonists are divided into two groups based on chemical structure. The first group consists of choline esters, typified by acetylcholine, carbachol, and bethanechol. The second group includes naturally occurring alkaloids such as nicotine, muscarine, and pilocarpine. Further classification is based on whether muscarinic or nicotinic receptor activation dominates.

**Direct-Acting Cholinergic Agonists:**

* Acetylcholine
* Bethanechol
* Carbachol
* Cevimeline
* Methacholine
* Nkotine
* Pilocarpine

Physiologic Effects

In general, direct-acting muscarinic agonists are parasympathomimetics in that they mimic stimulation of the parasympathetic system (Table 5–3). One exception is that these agents will also stimulate muscarinic receptors located on eccrine sweat glands, which are responsible for thermoregulation and are under sympathetic, not parasympathetic, nerve control. Additionally, vasodilation is observed with clinical use of these drugs; however, this is not a parasympathetic response. The vasodilation is the result of the release of endothelium-derived relaxing factor (EDRF) from uninnervated muscarinic receptors on endothelial cells lining the vascular walls. This vasodilation may result in a decrease in blood pressure.

The physiologic response for nicotinic receptor stimulation is dependent upon whether NM or NN receptors are activated. The tissue and organ level effects of NN receptor stimulation in the ganglia depends on the organ system involved. The blood vessels are dominated by sympathetic innervation; therefore, nicotinic receptor activation of postganglionic neurons results in vasoconstriction. In contrast, the gastrointestinal (GI) system is dominated by parasympathetic control. Here stimulation of postganglionic neurons results in an increased motility and secretion. Stimulation of NM receptors at the neuromuscular junction when activated by direct-acting nicotinic agonists results in fasciculations and muscle spasms. Prolonged stimulation of NM receptors results in desensitization of the receptors and muscle paralysis. The latter event is a hazard of pesticides containing nicotine.

Muscarinic agonists find a wide clinical application. In glaucoma, these drugs decrease intraocular pressure. They also assist in micturition in the hypotonic bladder after surgery or neurologic damage. In contrast, nicotinic agonists find limited clinical application except in tobacco abstention. The use of succinylcholine to provide skeletal muscle paralysis as an adjuvant to general anesthesia is related to inhibition at the neuromuscular junction. This drug will be discussed with the nicotinic antagonists in the last section of this chapter.

Adverse Events

The adverse effects associated with stimulation of muscarinic or nicotinic receptors vary depending upon the organ system. For muscarinic agonists, these include both central nervous system (CNS) and peripheral tissue responses. The CNS effect may include generalized stimulation resulting in hallucinations or seizures. In the eye, miosis and spasm of ocular accommodation may occur. At higher doses, the peripheral responses may be generalized to excessive parasympathomimetic stimulation with bronchoconstriction and excessive mucus production, gastrointestinal distress, hyperactivity of the detrusor muscle of the bladder with increased frequency of voiding, and hypotension. Bradycardia may occur, but the hypotension usually evokes a reflex tachycardia. Finally, stimulation of muscarinic receptors on the eccrine sweat glands, which are under sympathetic control, may result in sweating.

Nicotinic agonists acting within the CNS may initiate seizures, coma, and respiratory depression. In the peripheral tissues, stimulation of the autonomic NN receptors results in either parasympathetic or sympathetic manifestations, depending upon the organ system, as previously discussed. Significant clinical manifestations may include hypertension and cardiac arrhythmias. Prolonged stimulation of the NM receptors at the neuromuscular junction and subsequent muscle paralysis leads to decreased respiratory muscle function and hypoventilation. The chronic exposure to nicotine associated with tobacco use may result in additional pathophysiologic manifestations. Nicotine has a strong addictive potential. Chronic use of nicotine has an association with cancer, increased gastrointestinal ulcers, and increased risk of vascular disease and sudden coronary death.

**Indirect-Acting Cholinergic Agonists**

Indirect-acting cholinergic agonists fall into three major classes based on chemical structure and duration of effect. These classes are alcohols (e.g., edrophonium), carbamates (e.g., neostigmine) and organophosphates (e.g., echothiophate). Both the carbamate and organophosphate classes bind to acetylcholinesterase and undergo hydrolysis. Following this enzymatic activity, the metabolite is released slowly, preventing the binding and inactivation of acetylcholine. The carbamates are released over a period of hours, whereas the organophosphates require days to weeks to be released by the acetylcholinesterase. The alcohol class (edrophonium) binds to the active site electrostatically and by hydrogen bonds. The binding is short lived — on the order of minutes. Based on the binding, all three classes may be considered pseudoirreversible antagonists of acetylcholinesterase. Finally, some drugs in this class also have some direct-acting agonist activity. For example, neostigmine both inhibits acetylcholinesterase and directly activates the postsynaptic NM receptor at the neuromuscular junction.

**Indirect-Acting Cholinergic Agonists**

*Reversible*

* Donepezil
* Edrophonium
* Galantamine
* Neostigmine
* Physostigmine
* Pyridostigmine
* Rivastigmine

*Irreversible*

* Echothiophate

Physiologic Effects

By inhibiting acetylcholinesterase, indirect-acting cholinergic agonists amplify the actions of endogenous acetylcholine at both muscarinic and nicotinic synapses. Thus, these drugs may augment sympathetic or parasympathetic functions in the peripheral tissues. The response varies based on the organ system. In the GI tract, bladder, and lungs, parasympathetic activity predominates. At the neuromuscular junction, these drugs increase the force of muscle contractions, followed by fasciculations at higher concentrations, and ending ultimately with paralysis. Finally, cholinergic activity in the CNS parallels what was previously described for the direct-acting cholinergic agonists. The one exception to this parallelism is that the indirectly acting drugs do not normally cause vasodilation because endothelial cells are not innervated, and do not release EDRF when these drugs are administered.

Clinical Use

The clinical use of indirect-acting agonists differs somewhat from the direct-acting muscarinic and nicotinic agonists. The carbamates receive wider clinical use compared to the organophosphates. The clinical use of the alcohol edrophonium is limited because of the short action of the drug (5–15 minutes). Unique to these indirect-acting agonists is their use in the treatment of myasthenia gravis and dementia. Direct-acting muscarinic or nicotinic agonists are not currently in clinical use for either of these conditions.

Adverse Events

The clinical hazards of indirect-acting agonists parallel those of the direct-acting agonists with the following exceptions. First, vasodilation is late and uncommon, and bradycardia is more common than reflex tachycardia. The CNS manifestations are common following organophosphate overdose, with convulsions followed by respiratory and cardiovascular depression. A mnemonic for remembering the spectrum of adverse effects is DUMBBELSS (diarrhea, urination, miosis, bronchoconstriction, bradycardia, excitation of skeletal muscle and the CNS, lacrimation, salivation, and sweating). As with nicotinic agonists, prolonged stimulation of the NM receptors at the neuromuscular junction results in muscle paralysis, and is a hazard of pesticides containing these indirect-acting agonists.

Toxicology of Anticholinesterase Agents

Irreversible AChE inhibitors (mostly organophosphate compounds} are commonly used as agricultural insecticides in the United States, which has led to numerous cases of accidental poisoning with these agents. In addition, they are frequently used for suicidal and homicidal purposes. Organophosphate nerve gases such as sarin are used as agents of warfare and chemical terrorism. Toxicity with these agents is manifested as nicotinic and muscarinic signs and symptoms (cholinergic crisis). Depending on the agent, the effects can be peripheral or can affect the whole body.

Reactivation of acetylcholinesterase Pralidoxime (2-PAM) can reactivate inhibited AChE. However, it is unable to penetrate into the CNS and therefore is not useful in treating the CNS effects of organophosphates. The presence of a charged group allows it to approach an anionic site on the enzyme, where it essentially displaces the phosphate group of the organophosphate and regenerates the enzyme. If given before aging of the alkylated enzyme occurs, it can reverse both muscarinic and nicotinic peripheral effects of organophosphates, but not the CNS effects. With the newer nerve agents that produce aging of the enzyme complex within seconds, pralidoxime is less effective. In addition, it cannot overcome toxicity of reversible AChE inhibitors (for example, physostigmine).

Atropine is administered to prevent muscarinic side effects of these agents. Such effects include increased bronchial and salivary secretion, bronchoconstriction, and bradycardia. Diazepam is also administered to reduce the persistent convulsion caused by these agents. General supportive measures, such as maintenance of patent airway, oxygen supply, and artificial respiration, may be necessary as well.

**Anticholinergic Drugs**

Direct-acting cholinoreceptor antagonists are classified based on their blockade of muscarinic or nicotinic receptors. Further subdivisions for the muscarinic receptors include drugs that are selective antagonists of M1 receptors located on nerve endings as well as nonselective muscarinic antagonists. All antimuscarinic drugs currently available in the United States are nonselective antagonists.

Nicotinic antagonists are subdivided based on whether the drug inhibits postsynaptic NM receptors at the neuromuscular junction or postsynaptic NN receptors at the parasympathetic and sympathetic ganglia. The former have clinical application as general anesthesia adjuvants by inducing skeletal muscle paralysis. The latter drugs have limited clinical applications and will be discussed briefly.

**Muscarinic Antagonists**

Muscarinic antagonists may be further subdivided based on their clinical application and target organ system. Drugs used for either CNS or ophthalmic applications must be sufficiently lipid soluble to cross hydrophobic barriers such as the blood-brain barrier in the CNS. A major determinant for the pharmacokinetics is the presence or absence of a permanently charged quaternary amine group on these drugs. The presence of this charged group diminishes the penetration across these hydrophobic barriers and, to some extent, the uptake by the GI system. Atropine is a plant alkaloid and a nonselective muscarinic antagonist. The drug is the prototypical nonselective muscarinic antagonist and is lipid soluble.

**Antimuscarinic Agents**

* Atropine
* Benztropine
* Cyclopentolate
* Darifenacin
* Fesoterodine
* Glycopyrrolate
* Hyoscyamine
* Ipratropium
* Oxybutynin
* Scopolamine
* Solifenacin
* Tiotropium
* Tolterodine
* Trihexyphenidyl
* Tropicamide
* Trospium

Physiologic Effects

The peripheral actions of muscarinic blockers are mostly predicted by considering the removal of parasympathetic function on various organ systems. At therapeutic doses, cardiovascular effects include an initial bradycardia, possibly as a result of the blockade of postganglionic-presynaptic muscarinic receptors. The bradycardia is followed by tachycardia and increased atrioventricular conduction rate that would be predicted from the blockade of parasympathetic activity in the heart. In the respiratory system, bronchodilation and reduced secretion occurs. Inhibition of parasympathetic activity in the GI system results in decreased motility, relaxation, and reduction in gastric secretions. In the genitourinary system there is a decrease in detrusor muscle tone and increased bladder capacity. Lacrimation, salivation, and sweating are also reduced. The reader should remember that lacrimation and salivation are under parasympathetic cholinergic activity; however, the eccrine sweat glands are under sympathetic cholinergic control. The CNS effects are less predictable. Most common are sedation, decreased motion sickness, and improved motor function in patients with Parkinson’s disease.

Clinical Use

Significant and clinically useful applications of these drugs include treatment of Parkinson’s disease and reversal of bronchospasm. Treatment of Parkinson disease include use of antimuscarinic agents with central action. Direct ocular application of these drugs inhibits accommodation in the eye and causes dilation of the pupils. This application preceded that of the modern drug atropine. Extract of belladonna, the source of atropine, was used as a cosmetic to dilate the pupil centuries ago. Scopolamine decreases motion sickness and can be applied as a passive transdermal patch. In gastroenterology antimuscarinic agents used in treatment of ulcer disease and exactly pirenzepin by block of first subtype of muscarinic receptors selectively reduce acidity and stomach secretion. This drug class also decreases hypertonicity of the bladder that results from neural damage above the micturition reflex arc, and can be used to decrease urgency and relieve stress incontinence. Oxybutynin is clinically used in this application, and may be applied as a passive transdermal patch. Rarely these drugs are also used clinically in cardiovascular or GI dysfunction, having been replaced by other drug classes with fewer adverse effects.

Adverse Effects

The traditional mnemonic for antimuscarinic toxicity may be “Dry as a bone, red as a beet, and mad as a hatter.” This description reflects both the predictable antimuscarinic effects and some unpredictable actions. The “dry as a bone” response is the result of the inhibition of sweating, salivation, and lacrimation. Patients medicated with these drugs and involved in aerobic activities may experience hyperthermia. This effect results from these drugs’ antagonism of the thermoregulatory eccrine sweat glands. Moderate tachycardia is also common, with arrhythmias a much less common but life-threatening event. Dilation of cutaneous blood vessels occurs with toxic doses, and accounts for the “red as a beet” description. Finally, in the geriatric population, these drugs may exacerbate acute angle-closure glaucoma and urinary retention, especially in men with prostate hyperplasia. In the CNS, sedation, amnesia, and delirium with hallucinations contribute to the “mad as a hatter” description.

**Nicotinic (NM) Antagonists**

Skeletal muscle contraction is evoked by postsynaptic NM receptor-mediated signaling at the motor end plate. Activation of the NM receptor results in channel opening, with subsequent influx of Na+ and efflux of K+ (motor end plate potential). This motor end plate potential, when large enough, results in adjacent muscle depolarization and propagation along the entire muscle fiber. Drugs that block the neuromuscular junction at the postsynaptic NM receptor are clinically useful in producing muscle relaxation as an adjunct to major surgery. Neuromuscular blocking drugs are hydrophilic quaternary amines related to acetylcholine. As such, these drugs must be administered parenterally, and do not cross the blood-brain barrier into the central nervous system.

Most neuromuscular blocking drugs are direct-acting NM receptor antagonists that are nondepolarizing. The prototypical drug is tubocurarine. These drugs all produce a reversible blockade of the postsynaptic NM receptor. In general, they are metabolized and eliminated by either the kidney or the liver.

One neuromuscular blocking drug, succinylcholine, is defined as a depolarizing neuromuscular blocking drug. Succinylcholine is a direct-acting agonist that binds to the postsynaptic NM receptor. The binding of succinylcholine to the NM receptor results in the opening of channels at the motor end plate and an initial depolarization—like that produced by acetylcholine—but greatly prolonged. This depolarization spreads to adjacent membranes causing contractions of surrounding muscle fibers. Visually this presents as twitching and fasciculation of the skeletal muscle. Because the muscle is unable to maintain tension without periodic depolarization and repolarization at the neuromuscular junction, the depolarized muscle undergoes relaxation and paralysis denoted “phase I blockade.” With continued exposure to the drug, the motor end plate depolarization ceases, and repolarization occurs. Even with this repolarization, the motor end plate cannot undergo depolarization because it is desensitized. The mechanism for this desensitization is uncertain; however, blockade of the channel by succinylcholine may be important to the “phase II blockade”. Succinylcholine is included with neuromuscular blocking drugs because the final physiologic effect is inhibition of the neuromuscular junction.

**Nicotinic (NM) Antagonists**

* Cisatracurium
* Mivacurlum
* Pancuronlum
* Rocuronium
* Succinylcholine
* Vecuronlum

Physiologic Effects

Both the nondepolarizing and depolarizing drugs produce flaccid muscle paralysis. The order of sensitivity of muscles to the nondepolarizing drugs proceeds from the smaller muscles (the first to undergo paralysis, and the last to recover) to larger ones, with the diaphragm being the most resistant. For succinylcholine, paralysis appears initially in the legs and arms followed by paralysis of the axial musculature.

Clinical Use

Nondepolarizing blockers are used frequently in major surgery to provide relaxation throughout the procedure. They are occasionally used in the intensive care unit to prevent respiratory complications when patients are on ventilators. The time of onset and duration of action varies with each drug. Succinylcholine is the only clinically relevant depolarizing neuromuscular blockade drug. It is used almost exclusively to provide brief relaxation during intubation (placing an endotracheal tube) when patients are being prepared for artificial ventilation.

Adverse Effects

Several of the nondepolarizing blockers can have cardiovascular effects. Hypotension as a result of generalized histamine release occurs with older agents. Cardiac dysfunction is also possible as a result of the effects of these drugs on autonomic ganglia, cardiac muscarinic receptors, or interaction with the general anesthetic. Respiratory paralysis occurs as a direct result of the inhibition of the intercostal muscles and diaphragm.

Several adverse events are unique to succinylcholine. Some inhaled anesthetics, such as isoflurane, strongly enhance and prolong the effects of this drug at the neuromuscular junction. Hyperkalemia may occur in patients with burns or spinal cord injury, peripheral nerve dysfunction, or muscular dysfunction. Emesis may occur as a result of increased intragastric pressure. Muscle pain is a common postoperative complaint, and muscle damage may occur. Finally, malignant hyperthermia is a rare autosomal dominant genetic disorder of skeletal muscle that occurs in certain individuals receiving general anesthetics with succinylcholine. The pathophysiologic mechanism appears to be an increase in intracellular free calcium from the sarcoplasmic reticulum. The syndrome has a rapid onset with tachycardia and hypertension. Severe muscle rigidity and hyperthermia are hallmark features. Hyperkalemia and eventual acidosis may also occur. Treatment is with dantrolene, a drug that inhibits intracellular calcium release, and measures that control body temperature and blood pressure.

**Nicotinic (NN) Antagonists**

Postsynaptic NN receptors are located in both parasympathetic and sympathetic ganglia. Similar to the NM receptors, NN receptors are susceptible to both nondepolarizing and depolarizing inhibition. The ganglion-blocking drugs used clinically are all nondepolarizing direct-acting competitive antagonists (hexamethonium, mecamylamine, trimethaphan); however, there is evidence that these drugs may also block the nicotinic ion channel.

**Nicotinic (NN) Antagonists**

* Hexamethonium
* Mecamylamine
* Trimethaphan

Physiologic Effect

Owing to the inhibition of sympathetic control of venous tone, these drugs cause venous pooling and orthostatic hypotension. Moderate tachycardia and decreased cardiac output due to reduced venous return and a negative inotropic effect may also occur.

Clinical Use

Owing to the fact that the adverse effects of these drugs are so severe, patients are able to tolerate these drugs for only a limited period. Additionally, some drugs demonstrate short half-lives or are orally inactive, reducing their clinical value. At present, two drugs are used clinically. Mecamylamine, a lipophilic synthetic amine that crosses into the CNS, is being studied to decrease nicotine addiction and to treat Tourette’s syndrome. Trimethaphan is clinically used during a hypertensive crisis, and to produce controlled hypotension in some surgical scenarios.

Adverse Events

As a result of the inhibition of the autonomic nervous system by the ganglion-blocking drugs, patients tolerate them for only acute situations.