GANGLION STIMULANTS AND BLOCKERS

Ganglionic Stimulating Drugs

History

Two natural alkaloids, nicotine and lobeline, exhibit peripheral actions by stimulating autonomic ganglia. Nicotine was first isolated from leaves of tobacco, Nicotiana tabacum, by Posselt and Reiman in 1828, and Orfila initiated the first pharmacological studies of the alkaloid in 1843.

Langley and Dickinson painted the superior cervical ganglion of rabbits with nicotine and demonstrated that its site of action was the ganglion rather than the preganglionic or postganglionic nerve fiber.

Lobeline, from Lobelia inflata, has many of the same actions as nicotine but is less potent.

A number of synthetic compounds also have prominent actions at ganglionic receptor sites. The actions of the "onium" compounds, of which tetramethylammonium (TMA) is the simplest prototype, were explored in considerable detail in the last half of the nineteenth century and the early twentieth century.

Nicotine

Nicotine is of considerable medical significance because of its toxicity, presence in tobacco, and propensity for conferring a dependence on its users.

Nicotine is one of the few natural liquid alkaloids. It is a colorless, volatile base ($pK_a = 8.5$) that turns brown and acquires the odor of tobacco on exposure to air.

Pharmacological Actions

The complex and often unpredictable changes that occur in the body after administration of nicotine are due not only to its actions on a variety of neuroeffector and chemosensitive sites but also to the fact that the alkaloid can stimulate and desensitize receptors.
The ultimate response of any one system represents the summation of stimulatory and inhibitory effects of nicotine. For example, the drug can increase heart rate by excitation of sympathetic or paralysis of parasympathetic cardiac ganglia, and it can slow heart rate by paralysis of sympathetic or stimulation of parasympathetic cardiac ganglia.

In addition, the effects of the drug on the chemoreceptors of the carotid and aortic bodies and on brain centers influence heart rate, as do also the cardiovascular compensatory reflexes resulting from changes in blood pressure caused by nicotine.

Finally, nicotine elicits a discharge of epinephrine from the adrenal medulla, which accelerates heart rate and raises blood pressure.

Peripheral Nervous System

The major action of nicotine consists initially of transient stimulation and subsequently of a more persistent depression of all autonomic ganglia.

Small doses of nicotine stimulate the ganglion cells directly and may facilitate impulse transmission.

When larger doses of the drug are applied, the initial stimulation is followed very quickly by a blockade of transmission. Whereas stimulation of the ganglion cells coincides with their depolarization, depression of transmission by adequate doses of nicotine occurs both during the depolarization and after it has subsided.

Nicotine also possesses a biphasic action on the adrenal medulla; small doses evoke the discharge of catecholamines, and larger doses prevent their release in response to splanchnic nerve stimulation.

The effects of nicotine on the neuromuscular junction are similar to those on ganglia. However, with the exception of avian and denervated mammalian muscle, the stimulant phase is obscured largely by the rapidly developing paralysis.

In the latter stage, nicotine also produces neuromuscular blockade by receptor desensitization.
Nicotine, like ACh, is known to stimulate a number of sensory receptors. These include mechanoreceptors that respond to stretch or pressure of the skin, mesentery, tongue, lung, and stomach; chemoreceptors of the carotid body; thermal receptors of the skin and tongue; and pain receptors. Prior administration of hexamethonium prevents stimulation of the sensory receptors by nicotine but has little, if any, effect on the activation of sensory receptors by physiological stimuli.

Central Nervous System

Nicotine markedly stimulates the CNS. Low doses produce weak analgesia; with higher doses, tremors leading to convulsions at toxic doses are evident.

The excitation of respiration is a prominent action of nicotine; although large doses act directly on the medulla oblongata, smaller doses augment respiration reflexly by excitation of the chemoreceptors of the carotid and aortic bodies.

Stimulation of the CNS with large doses is followed by depression, and death results from failure of respiration owing to both central paralysis and peripheral blockade of muscles of respiration.

Nicotine induces vomiting by both central and peripheral actions. The central component of the vomiting response is due to stimulation of the emetic chemoreceptor trigger zone in the area postrema of the medulla oblongata.

In addition, nicotine activates vagal and spinal afferent nerves that form the sensory input of the reflex pathways involved in the act of vomiting. Studies in isolated higher centers of the brain and spinal cord reveal that the primary sites of action of nicotine in the CNS are prejunctional, causing the release of other transmitters.

Accordingly, the stimulatory and pleasure-reward actions of nicotine appear to result from release of excitatory amino acids, dopamine, and other biogenic amines from various CNS centers.

Release of excitatory amino acids may account for much of nicotine’s stimulatory action.
Chronic exposure to nicotine in several systems causes a marked increase in the density or number of nicotinic receptors (Di Chiara et al., 2000; Stitzel et al., 2000). While the details of the mechanism are not yet understood, the response may be compensatory to the desensitization of receptor function by nicotine.

Absorption, Fate, and Excretion

Nicotine is readily absorbed from the respiratory tract, buccal membranes, and skin. Severe poisoning has resulted from percutaneous absorption. Being a relatively strong base, its absorption from the stomach is limited. Intestinal absorption is far more efficient. Nicotine in chewing tobacco, because it is absorbed more slowly than inhaled nicotine, has a longer duration of effect. The average cigarette contains 6 to 11 mg nicotine and delivers about 1 to 3 mg nicotine systemically to the smoker; bioavailability can increase as much as threefold with intensity of puffing and technique of the smoker (Henningfield, 1995; Benowitz, 1998).

Nicotine is available in several dosage forms to help achieve abstinence from tobacco use. Efficacy results primarily from preventing a withdrawal or abstinence syndrome. Nicotine may be administered orally as a gum (*nicotine polacrilex*, NICORETTE), transdermal patch (NICODERM, HABITROL, others), a nasal spray (NICOTROL NS), and a vapor inhaler (NICOTROL INHALER). The first two are used most widely, and the objective is to obtain a sustained plasma nicotine concentration lower than venous blood concentrations after smoking.

Arterial blood concentrations immediately following inhalation can be as much as tenfold higher than venous concentrations. The efficacy of the preceding dosage forms in producing abstinence from smoking is enhanced when linked to counseling and motivational therapy.

Approximately 80% to 90% of nicotine is altered in the body, mainly in the liver but also in the kidney and lung. Cotinine is the major metabolite, with nicotine-1'-N-oxide and 3-hydroxycotinine and conjugated metabolites found in lesser quantities. The profile of metabolites and the rate of metabolism appear to be similar in smokers and nonsmokers. The half-life of nicotine following inhalation or parenteral administration is about 2 hours. Nicotine and its metabolites are eliminated rapidly by the kidney. The rate of urinary
excretion of nicotine diminishes when the urine is alkaline. Nicotine also is
excreted in the milk of lactating women who smoke; the milk of heavy
smokers may contain 0.5 mg/L.

Acute Nicotine Poisoning

Poisoning from nicotine may occur from accidental ingestion of nicotine-
containing insecticide sprays or in children from ingestion of tobacco
products. The acutely fatal dose of nicotine for an adult is probably about
60 mg of the base. Smoking tobacco usually contains 1% to 2% nicotine.
Apparently, the gastric absorption of nicotine from tobacco taken by mouth
is delayed because of slowed gastric emptying, so vomiting caused by the
central effect of the initially absorbed fraction may remove much of the
tobacco remaining in the GI tract.

The onset of symptoms of acute, severe nicotine poisoning is rapid; they
include nausea, salivation, abdominal pain, vomiting, diarrhea, cold sweat,
headache, dizziness, disturbed hearing and vision, mental confusion, and
marked weakness. Faintness and prostration ensue; the blood pressure falls;
breathing is difficult; the pulse is weak, rapid, and irregular; and collapse
may be followed by terminal convulsions. Death may result within a few
minutes from respiratory failure.

Therapy

Vomiting may be induced, or gastric lavage should be performed. Alkaline
solutions should be avoided. A slurry of activated charcoal is then passed
through the tube and left in the stomach. Respiratory assistance and
treatment of shock may be necessary.

Other Ganglionic Stimulants

Stimulation of ganglia by tetramethylammonium (TMA) or 1,1-dimethyl-4-
phenylpiperazinium iodide (DMPP) differs from that produced by nicotine in
that the initial stimulation is not followed by a dominant blocking action.
DMPP is about three times more potent and slightly more ganglion-selective
than nicotine. Although parasympathomimetic drugs stimulate ganglia, their
effects usually are obscured by stimulation of other neuroeffector sites.
McN-A-343 represents an exception to this; in certain tissues its primary action appears to occur at muscarinic M₁ receptors in ganglia.

Ganglionic Blocking Drugs

The chemical diversity of compounds that block autonomic ganglia without causing prior stimulation is well established.

History and Structure-activity Relationship

Although Marshall first described the "nicotine-paralyzing" action of tetraethylammonium (TEA) on ganglia in 1913, TEA was largely overlooked until Acheson and Moe published their definitive analyses of the effects of the ion on the cardiovascular system and autonomic ganglia.

The bis-quaternary ammonium salts were developed and studied independently by Barlow and Ing and Paton and Zaimis.

The prototypical ganglionic blocking drug in this series, hexamethonium (C6), has a bridge of six methylene groups between the two quaternary nitrogen atoms. It has minimal neuromuscular and muscarinic blocking activities.

Triethylsulfoniums, like the quaternary and bis-quaternary ammonium ions, possess ganglionic blocking actions.

This knowledge led to the development of sulfonium ganglionic blocking agents such as trimethaphan. Mecamylamine, a secondary amine, was introduced into therapy for hypertension in the mid-1950s.

Pharmacological Properties

Nearly all the physiological alterations observed after the administration of ganglionic blocking agents can be anticipated with reasonable accuracy by knowing which division of the autonomic nervous system exercises dominant control of various organs.

For example, blockade of sympathetic ganglia interrupts adrenergic control of arterioles and results in vasodilation, improved peripheral blood flow in some vascular beds, and a fall in blood pressure.
Generalized ganglionic blockade also may result in atony of the bladder and gastrointestinal tract, cycloplegia, xerostomia, diminished perspiration, and by abolishing circulatory reflex pathways, postural hypotension.

These changes represent the generally undesirable features of ganglionic blockade, which severely limit the therapeutic efficacy of ganglionic blocking agents.

Cardiovascular System

Existing sympathetic tone is critical in determining the degree to which blood pressure is lowered by ganglionic blockade; thus blood pressure may be decreased only minimally in recumbent normotensive subjects but may fall markedly in sitting or standing subjects. Postural hypotension was a major limitation in ambulatory patients receiving ganglionic blocking drugs.

Absorption, Fate, and Excretion

The absorption of quaternary ammonium and sulfonium compounds from the enteric tract is incomplete and unpredictable. This is due both to the limited ability of these ionized substances to penetrate cell membranes and to the depression of propulsive movements of the small intestine and gastric emptying. Although the absorption of mecamylamine is less erratic, a danger exists of reduced bowel activity leading to frank paralytic ileus.

After absorption, the quaternary ammonium- and sulfonium-blocking agents are confined primarily to the extracellular space and are excreted mostly unchanged by the kidney. Mecamylamine concentrates in the liver and kidney and is excreted slowly in an unchanged form.

Untoward Responses and Severe Reactions

Among the milder untoward responses observed are visual disturbances, dry mouth, conjunctival suffusion, urinary hesitancy, decreased potency, subjective chilliness, moderate constipation, occasional diarrhea, abdominal discomfort, anorexia, heartburn, nausea, eructation, and bitter taste and the signs and symptoms of syncope caused by postural hypotension. More severe reactions include marked hypotension, constipation, syncope, paralytic ileus, urinary retention, and cycloplegia.
Therapeutic Uses

Of the ganglionic blocking agents that have appeared on the therapeutic scene, only mecamylamine (INVERSINE) is currently available in the United States. Ganglionic blocking agents have been supplanted by superior agents for the treatment of chronic hypertension. Alternative agents also are available for management of acute hypertensive crises.

The therapeutic use of the ganglionic blocking agents in the production of controlled hypotension [e.g., reduction in blood pressure during surgery to minimize hemorrhage in the operative field, to reduce blood loss in various orthopedic procedures, and to facilitate surgery on blood vessels] has been supplanted largely by nitroprusside or depressor sedatives.