Pharmacology of the Autonomic Nervous System

Lecture Outline

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- B. Nonclassical Neurotransmitters
- C. Synthesis and Metabolism of Acetylcholine
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Learning Objectives: Autonomic and Neuromuscular Pharmacology

1) An understanding of the clinical physiology of the autonomic nervous system
   a) Key structures in central cardiovascular control
   b) Neurotransmitters involved in major central and peripheral neuronal pathways
   c) Synthesis and metabolism of norepinephrine (NE) and acetylcholine (Ach)

2) An understanding of α and β adrenoreceptors, their subtypes and the clinical spectrum of their general and selective stimulation and blockade
   a) Key uses and side effects of major drugs in each category
   b) Clinical circumstances where these agents may be beneficial

3) An understanding of muscarinic agonists and antagonists, and cholinesterase inhibitors

4) An understanding of agents that stimulate or relax skeletal muscle, including the cholinergic neuromuscular agonists and antagonists as well as the neuromuscular agents acting at noncholinergic sites.

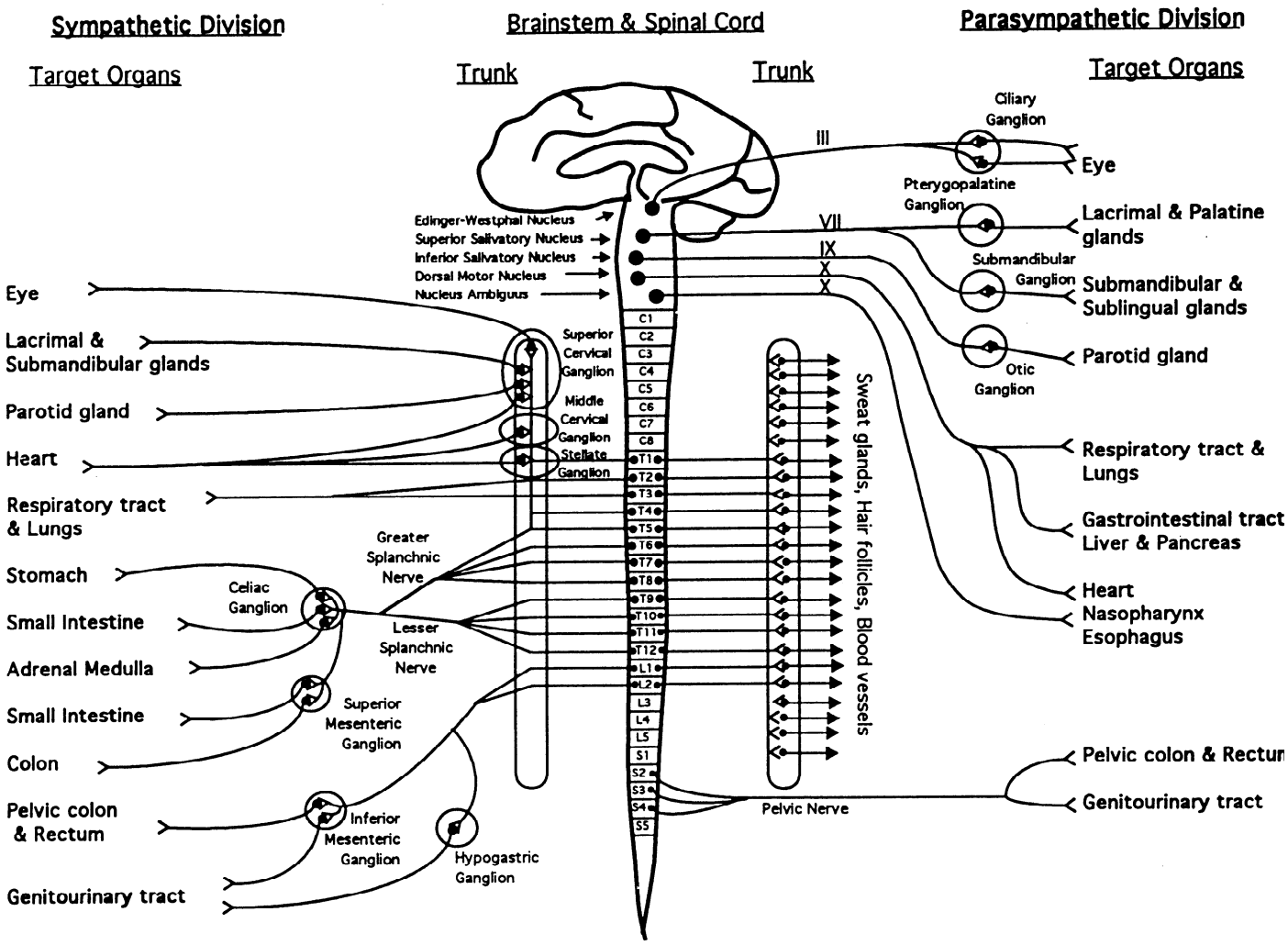

Figure 1: Schematic diagram of the sympathetic and parasympathetic divisions of the peripheral autonomic nervous system. The paravertebral chain of the sympathetic division is illustrated on both sides of the spinal outflow in order to demonstrate the full range of target structures innervated. Although the innervation pattern is diagrammatically illustrated to be direct connects between preganglionic outflow and postganglionic neurons, there is overlap of innervation such that more than one spinal segment provides innervation to neurons within the ganglia.

I. Introduction

The CNS receives diverse internal and external stimuli. These are integrated and expressed subconsciously through the **autonomic nervous system** to modulate the involuntary functions of the body. This overlies a strong **circadian rhythm** of autonomic function. The **somatic** nerves that innervate voluntary skeletal muscle are not part of the autonomic system, but will be discussed in the final lecture.

The autonomic nervous system consists of two large divisions (Figure 1):

- **sympathetic** (thoracolumbar) outflow, and
- **parasympathetic** (craniosacral) outflow.

The two divisions are defined by their anatomic origin rather than by their physiological characteristics.

II. Anatomy

A. Central

The circadian rhythm of autonomic function originates in the **suprachiasmatic nucleus (SCN)** in the hypothalamus, and is entrained by light falling on melanopsin-containing retinal ganglion cell dendrites (not rods or cones) in the eye and transmitted to the SCN by the retinohypothalamic tract. The integration of autonomic outflow to the cardiovascular system lies in the medulla. Stretch-sensitive mechanoreceptors in the blood vessels of the thorax and neck relay information about blood pressure and blood volume through the **glossopharyngeal** (from carotid arteries) and **vagus** (from aorta) nerves to the **nucleus tract solitarii (NTS)** in the posterior medulla.

Excitatory neurons from the NTS innervate the dorsal motor nucleus of the vagus, where parasympathetic outflow is regulated. Inhibitory neurons, using **gamma-aminobutyric acid (GABA)** as neurotransmitter, innervate areas in the ventrolateral medulla from which sympathetic outflow is regulated. The most important such site is the **rostral ventrolateral medulla (RVLM).**

Destruction of the NTS or its afferent input in experimental animals (Figure 2) or by tumors, radiation or infarction in patients can lead to the syndrome of ***baroreflex failure.*** *A family in Nashville with a genetic defect leading to tumors in the carotid body and other paragangliomas has taught us most of what we know about baroreflex failure. There is an acute period of dramatic hypertension during which stroke or pulmonary edema may occur. This is followed by a syndrome of wide swings in blood pressure, from hypotensive to hypertensive levels, with pressure determined by anxiety (pressor), sedation (depressor), noise (pressor), and sunlight (pressor).*

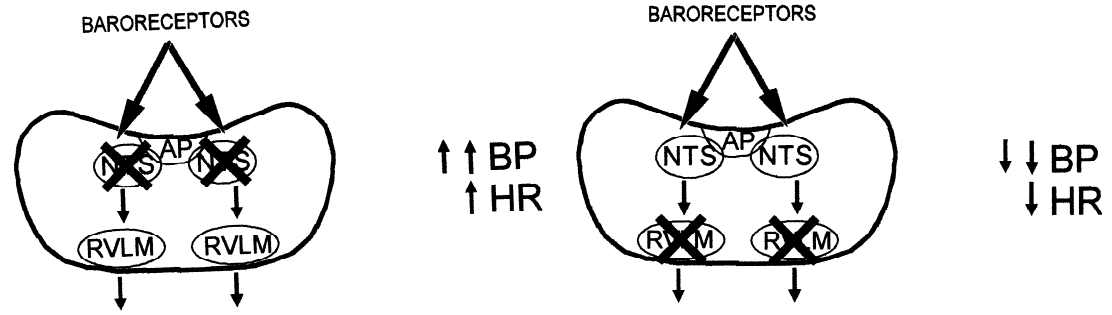

Figure 2: Contrast between clinical effects of NTS (afferent) destructive lesions on left and RVLM (efferent) destructive lesions on the right. The contast is due to an inhibitory neuron that communicates from the NTS to the RLM.

Efferent parasympathetic outflow to the cardiovascular system goes through the vagus nerve. Efferent sympathetic outflow from the **RVLM** travels in the **bulbospinal tract** to the **intermediolateral column** of the spinal cord.

Glossopharyngeal neuralgia *(glossopharyngeal syncope) is a disorder occurring in patients whose 9th cranial nerve becomes damaged (usually by neck tumor). Paroxysms of severe throat pain associated with hypotension and bradycardia occur. Attacks are due to massive spontaneous afferent discharges of the*

glossopharyngeal nerve, providing excessive input into the NTS, and eliciting parasympathetic activation and sympathetic withdrawal. Although a pacemaker may be helpful in preventing bradycardia, the hypotension is sometimes so severe that surgical section of the glossopharyngeal nerve is required.

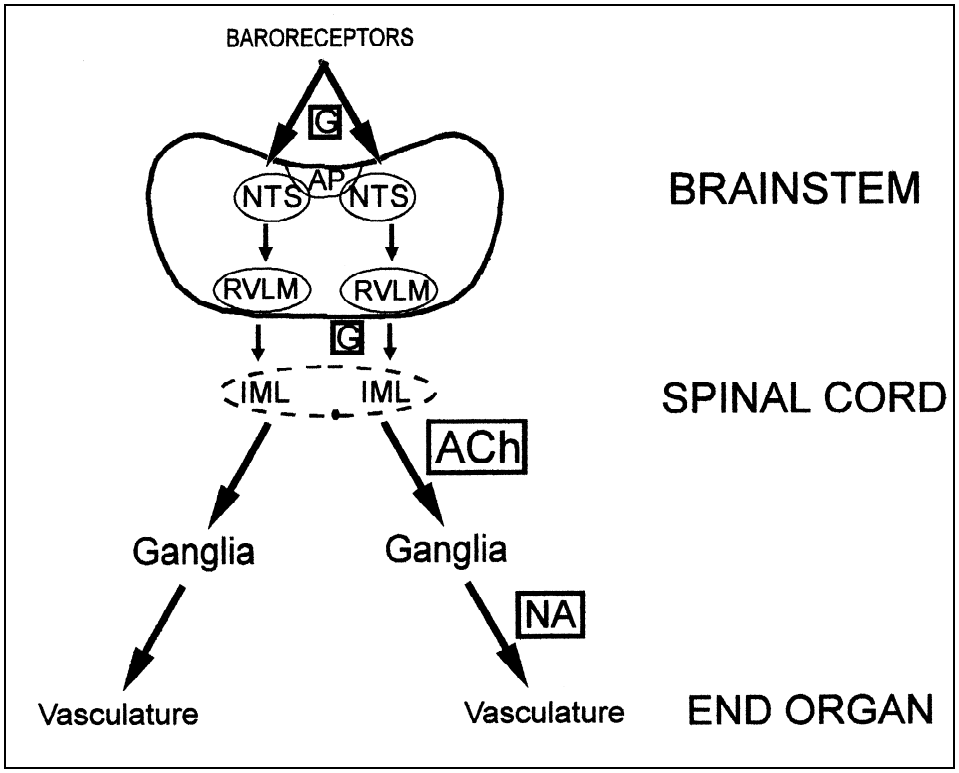

Figure 3: Efferent sympathetic outflow
Legend: AP, area postrema; NTS, nucleus tractus solitarii; RVLM, rostral ventrolateral medulla (C1 area); intermediolateral column of the spinal cord; glutamate-releasing neuron; GABA, γ-aminobutyric acid releasing neuron; ACh, acetylcholine-releasing neuron; NA, norepinephrine-releasing neuron

The vasomotor neurons of the bulbospinal activate preganglionic cells sympathetic nerves.

III. Biochemistry

A. Neurotransmitters

The primary neurochemical mediator of both sympathetic and parasympathetic preganglionic neurons is **acetylcholine (ACh).** The primary mediator of sympathetic postganglionic fibers is usually **norepinephrine** (NE), but at least some sympathetic postganglionic fibers to sweat glands are cholinergic (**acetylcholine**). The mediator of parasympathetic postganglionic fibers is **acetylcholine**. **Epinephrine** is found in the adrenal medulla, the central nervous system and the para-aortic bodies (organs of Zuckerkandl). **Dopamine** is a neurochemical mediator in the central nervous system and probably also in some neurons in the superior cervical ganglion and the kidney. Norepinephrine, epinephrine and dopamine are sometimes collectively referred to as **catecholamines.** Outside the United States, norepinephrine is often called noradrenaline, and epinephrine, adrenaline. These endogenous compounds plus drugs that resemble them functionally and structurally are also called **sympathomimetic amines**.

B. Nonclassical Neurotransmitters

Although it was initially assumed that each neuron would have one and only one neurotransmitter, it is now clear that multiple neurotransmitters commonly exist within one neuron, and they may be differentially released. It is not fully understood why such **cotransmission** occurs, but autonomic nerve stimulation may consist of several phases with distinctive time courses, each of which is mediated by a different cotransmitter. Furthermore, cotransmitters usually interact at various levels, ranging from modulation of neurotransmitter release to the regulation of calcium concentrations of the effector cells.

Thus, cotransmission may be a fundamental mechanism employed by autonomic neurons to achieve efficient and precise control of their target tissues over a range of functional demands.

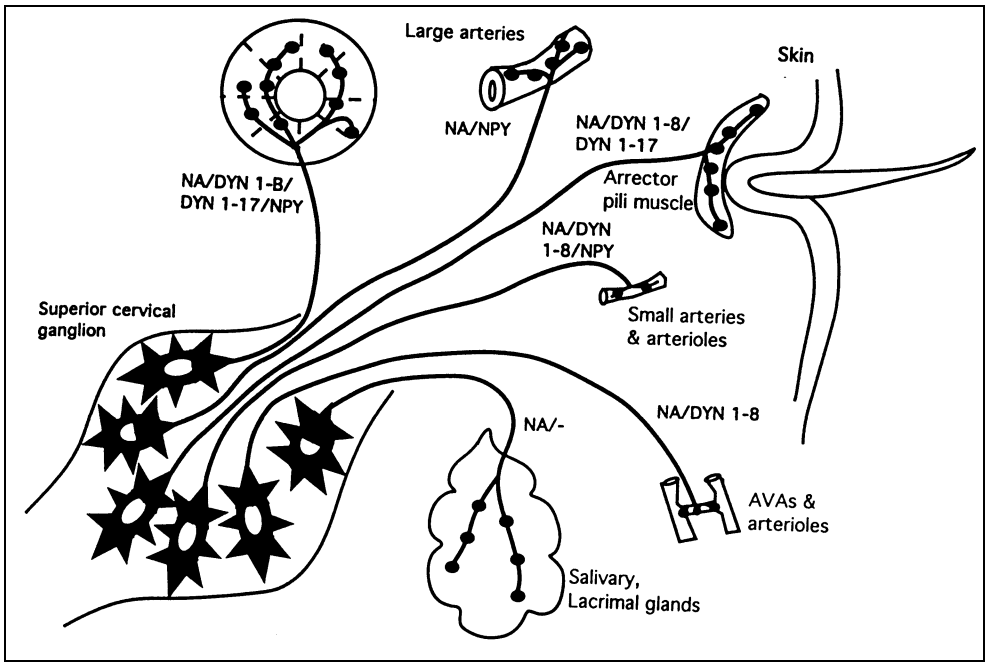

Figure 4: Complexity of neurotransmission.

The complexity of cotransmission is well-illustrated in selected sympathetic neurons. It can be seen that in various neurons, norepinephrine (NE), neuropeptide Y (NPY), dynorphin 1-8 (DYN 1-8), and dynorphin 1-17 (DYN 1-17), are all involved, presumably in addition to ATP (not shown in the figure) which is a cotransmitter in almost all sympathetic neurons.

The neurotransmitter role of **ATP** deserves special consideration. ATP is localized, and released from, sympathetic, parasympathetic, enteric, and even sensory neurons. ATP acts at prejunctional or postjunctional sites, either directly as ATP on **purinergic receptors**, or after metabolism to **adenosine** on **adenosine receptors**.

Purinergic receptors *are categorized into P_1 (sensitive to* ***adenosine****) and P_2 (sensitive to* ***ATP****), but many people subcategorize P_1 receptors as adenosine receptors (A_1, A_2, and A_3). These adenosine receptors will be detailed by other lecturers in this course.*

C. Synthesis and Metabolism of Acetylcholine

Acetylcholine (ACh) is synthesized by **choline acetyltransferase,** a soluble cytoplasmic enzyme that catalyzes the transfer of an acetyl group from acetylcoenzyme A to choline. The activity of choline acetyltransferase is much greater than the maximal rate at which ACh synthesis occurs. Choline acetyltransferase inhibitors have little effect to alter the level of this bound ACh. ACh is stored in a bound form in vesicles. Choline must be pumped into the cholinergic neuron, and the action of the choline transporter is the rate-limiting step in ACh synthesis.

Upon the arrival of an action potential in the cholinergic neuron terminal, voltage-sensitive calcium channels open and ACh stores are released by exocytosis to trigger a postsynaptic physiological response. The release of acetylcholine can be blocked by **botulinum toxin,** the etiologic agent in botulism. Fortunately, botulinum toxin has been used to treat dystonias and spastic disorders, and has turned out to be uniquely effective. Although it requires local injection, it is often effective for weeks or months.

Much of the ACh released into the synapse is transiently associated with ACh receptors.

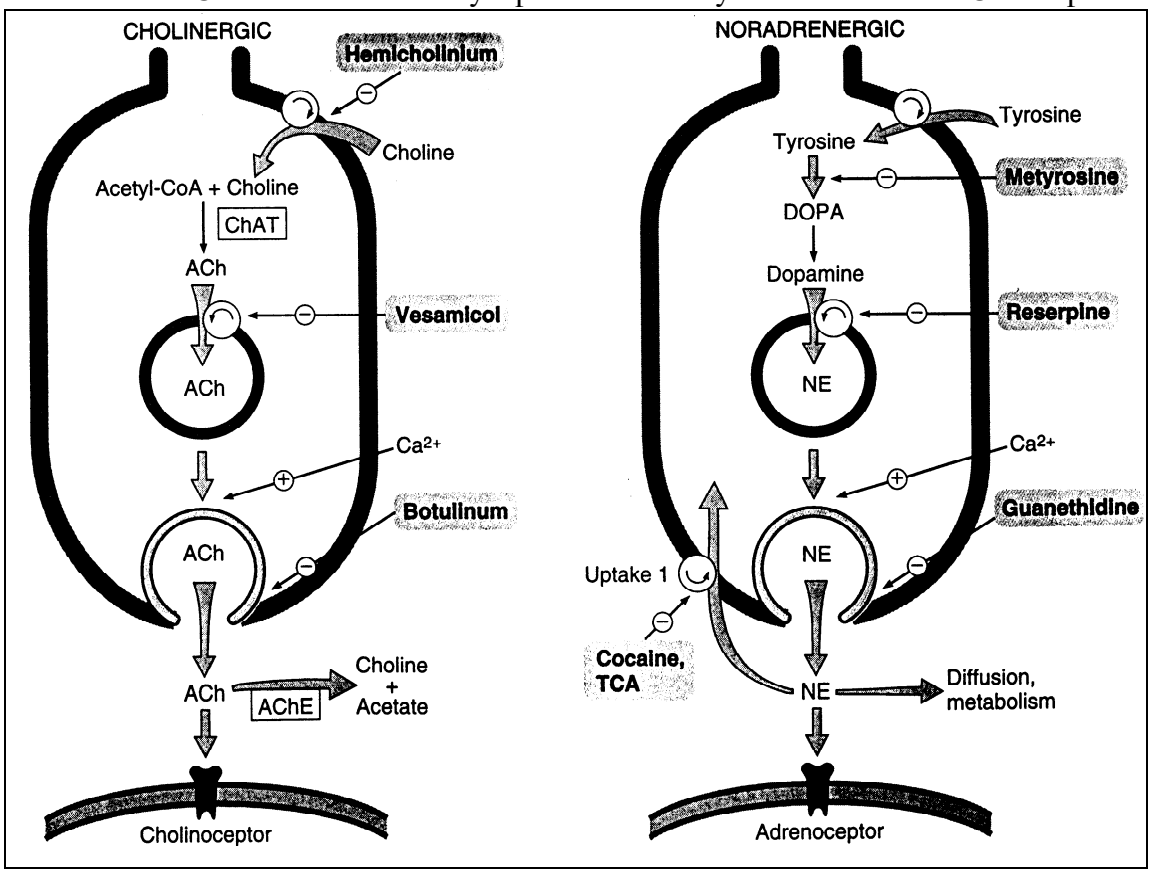

Figure 5: Characteristics of transmitter synthesis, storage, release, and termination of action at cholinergic and noradrenergic nerve terminals are shown from the top downward. Circles with rotating arrows represent transporters; ChAT, choline acetyltransferase; ACh, acetylcholine; AChE, acetylcholinesterase; NE, norepinephrine.

This action is terminated by the rapid hydrolysis of ACh into choline and acetic acid, a reaction catalyzed by the enzyme **acetylcholinesterase**. The transient, discrete, localized action of ACh is due in part to the great velocity of this hydrolysis. The choline liberated locally by acetylcholinesterase can be reutilized by presynaptic reuptake (by the high-affinity system described above) and resynthesis into ACh.

In addition to **acetylcholinesterase** (true cholinesterase) which is found near cholinergic neurons and in red blood cells (but not in plasma), there is also a non-specific cholinesterase (pseudocholinesterase or butyrylcholinesterase) which is present in plasma and in some organs but not in the red blood cell or the cholinergic neuron.

The genetic abnormalities in **pseudocholinesterase** can result in a marked deficiency. One in 30,000 people are homozygotes for the most common functionally abnormal variant, dibucaine-resistant pseudocholinesterase (3.8% of people are therefore heterozygotes for this gene). Cholinergic nerve activity in such people is normal but some drugs such as succinylcholine (used during anesthesia) which are normally broken down by pseudocholinesterase, are very poorly metabolized by this variant enzyme. Such patients may have prolonged muscle paralysis from succinylcholine.

D. Synthesis and Metabolism of Catecholamines

Tyrosine in the bloodstream is taken up into nerves and converted into catecholamine. The five main enzymes whose functions are critical to the formation of catecholamines are discussed below (Figure 6).

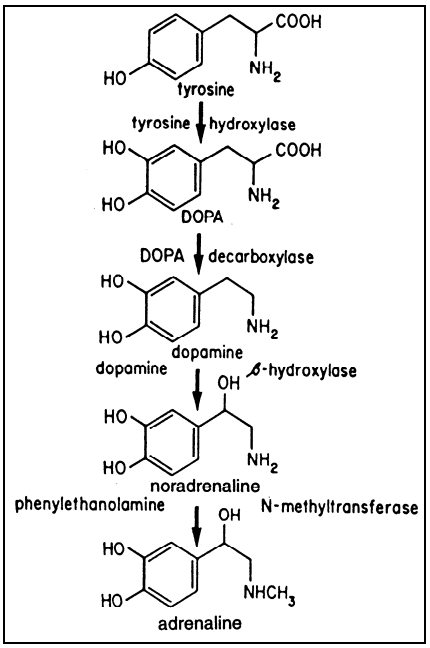

Figure 6: Metabolic pathway of catecholamine synthesis.

Tyrosine hydroxylase (tyrosine to dopa) is the *rate-limiting step* in NE synthesis and is located in the cytoplasm. Catecholamines act as feedback inhibitors of this enzyme. During increased sympathetic stimulation, dopa production is increased in two ways: a) more enzyme is synthesized, and b) the physical properties of the enzyme are altered (allosteric activation) so that affinity for tyrosine is increased and affinity for end products like NE is reduced. A clinically useful inhibitor of this enzyme is **metyrosine** (α-methyl-p-tyrosine).

Dopa decarboxylase (dopa to dopamine) is found in the cytoplasm of many nonneural as well as neural tissues and had been called "**aromatic-L-amino acid decarboxylase**" because of its broad substrate specificity. Peripheral (non-neuronal) dopa decarboxylase can be inhibited by **carbidopa** when one is trying to prevent formation of peripheral dopamine during dopa therapy of Parkinsonism. This limits dopamine production to the central nervous system during dopa therapy, thus limiting peripheral side effects.

<u>Dopamine-ß-hydroxylase</u> (dopamine to norepinephrine) is a copper-containing enzyme located primarily within the membrane of amine storage granules.

Some individuals have been found to have dopamine-ß-hydroxylase deficiency. They present with lifelong orthostatic hypotension, and ptosis of the eyelids. Their sympathetic neurons contain large quantities of dopamine, but little or no norepinephrine. They can be treated with the drug dihydroxyphenylserine (DOPS), which is decarboxylated directly into norepinephrine by dopa decarboxylase, thus restoring the appropriate neurotransmitter.

Phenylethanolamine-N-methyltransferase (norepinephrine to epinephrine) is restricted to the adrenal medulla, the brain and the organ of Zuckerkandl, with only trace amounts in other locations. It is strongly inhibited by physiological concentrations of epinephrine providing feedback regulation of enzyme synthesis. Glucocorticoid increases enzyme activity.

Much neuronal NE is located in neuronal vesicles. They store NE and protect it from breakdown by monoamine oxidase (MAO) in the surrounding cytoplasm. These vesicles are subsequently transported to the neuron terminal region for release.

Release occurs when acetylcholine liberated from preganglionic neurons induces depolarization of postganglionic sympathetic neurons by acting on a nicotinic receptor (see below). The influx of calcium stimulates migration of vesicles to the cell membrane for excretion, by membrane fusion and exocytosis.

Local synaptic concentrations of catecholamines modulate their own release by interacting with **presynaptic α_2-receptors** to **reduce release** of additional norepinephrine and presynaptic β_2-receptors to **increase release** of norepinephrine (more about this below).

The reason for this bidirectional control is not known with certainty, but may function to **stabilize synaptic neurotransmitter levels.** In addition, other substances may increase (**angiotensin**, and **acetylcholine** via a nicotinic receptor) and decrease (**dopamine, histamine, serotonin, adenosine, PGD_2, PGE_2** and **acetylcholine** via a muscarinic receptor) norepinephrine release in selected tissues.

Released catecholamines may a) be retaken up into the neuron (**norepinephrine transporter or uptake I**), b) be taken up by the extraneuronal tissue (**uptake II**), or c) be washed into the extracellular fluid and ultimately into the circulation. Termination of action of released catecholamine varies with organ site. Thus, heavily innervated tissues like the heart with narrow synaptic clefts tend to rely heavily on the norepinephrine transporter (90% uptake of released NE), while tissues such as the aorta with wide synaptic clefts and less dense innervation tend to rely on it less. The catecholamines may be metabolized by one of two enzymes.

Monoamine oxidase occurs in two forms (A and B). Monoamine oxidase is located in the outer membrane of mitochondria as well as extraneuronally. It converts catecholamines to their corresponding aldehydes. Inhibitors include pargyline, tranylcypromine, and selegiline (Deprenyl®) that will be covered in part 2 of the course with COMT inhibitors below.

Catechol-o-methyltransferase (COMT) converts NE into normetanephrine and epinephrine into metanephrine. It is found especially in liver and kidney.

Uptake into the neuron terminal by the NE transporter is very efficient. Fully half of an intravenous infusion of NE is taken up and stored in neurons, primarily in heart, spleen, and blood vessels, The structure of the NE transporter and elucidation of its regulation was achieved by Vanderbilt's Dr. Randy D. Blakely. The uptake mechanism is an energy requiring, saturable membrane transport system, that can be blocked tricyclic antidepressants, amphetamine and cocaine (more from Dr. Sanders-Bush, next section).

In healthy persons at rest, plasma NE is about 250 pg/ml and plasma A is 25 pg/ml. Normally, plasma norepinephrine level is doubled by standing, but it is several fold elevated by running, and in myocardial infarction (MI), delirium tremens (DT's), and pheochromocytoma (pheo).

E. **Summary of Intervention Mechanisms**

1. Cholinergic neurotransmission can be modified at several sites, including**:**

a)	Precursor transport blockade	hemicholinium
b)	Choline acetyltransferase inhibition	no clinical example
c)	Promote transmitter release	choline, black widow spider venom (latrotoxin)
d)	Prevent transmitter release	**botulinum toxin**
e)	Storage	vesamicol prevents ACh storage
f)	**Cholinesterase inhibition**	**physostigmine, neostigmine**
g)	**Receptors**	agonists and antagonists

2. There are also many sites at which pharmacological alteration of sympathetic noradrenergic function can take place (Figure 4). They are reviewed below**:**

a)	Precursor transport blockade	no clinical example
b)	Tyrosine hydroxylase inhibition	**metyrosine**, used to treat pheochromocytoma
c)	**Dopa decarboxylase inhibition**	**carbidopa**
d)	Dopamine-ß-hydroxylase inhibition	disulfiram
e)	Monoamine oxidase inhibition	pargyline, tranylcypromine, selegiline
f)	Storage	reserpine prevents NE storage
g)	Release	guanethidine, guanadrel cause initial release of NE leading to depletion of catecholamine; bretylium blocks NE release
h)	Receptors	α-and β-agonists and antagonists
i)	Norepinephrine transporter (Uptake I) blockade	cocaine, tricyclic antidepressants
j)	Catechol-o-methyltransferase inhibition	entacapone
k)	Uptake II	glucocorticoids

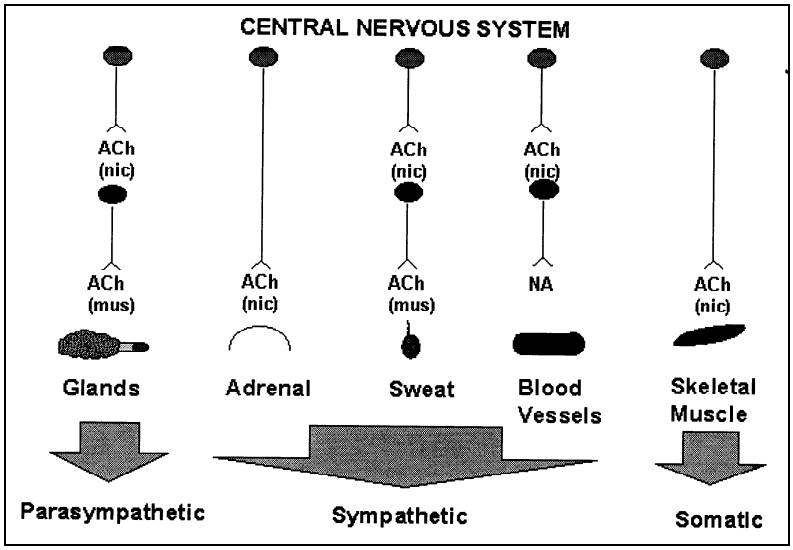

Figure 7: Simplified summary of parasympathetic, sympathetic somatic innervation.

IV. Norepinephrine, Epinephrine, and Dopamine

A. Adrenoreceptors

It is convenient to distinguish several receptor types in explaining the effects of catecholamines. Many more receptor-types can be subtly distinguished by their affinity for different agonists and antagonists and, in even more cases, by their structures. For practical purposes, however, it is probably sufficient to use a classification scheme such as the following:

1. α_1 (three subtypes): α_{1A}, α_{1B}, α_{1C}
2. α_2 (three subtypes): α_{2A}, α_{2B}, α_{2C}
3. β_2
4. β_2
5. β_3
6. D_1, D_2, D_3, D_4, D_5

Most people reserve the term "adrenoreceptor" for α_1, α_2, β_1, β_2, and β_3-receptors. The D receptors are dopamine receptors and are highly relevant to behavior and to Parkinson's disease and will be treated only briefly in my lectures.

- The expressions "adrenoreceptor", "adrenoceptor" and "adrenergic receptor" are synonymous.

The actions of α and β adrenoreceptors are mediated by diverse intracellular mechanisms. Activation of β-adrenoreceptors by neurotransmitter, hormone or drug leads to synthesis of cAMP by ***adenylyl cyclase*** *at the cytoplasmic facet of the plasma membrane. The hormone-receptor ("liganded receptor") interacts with a stimulatory guanine nucleotide-binding regulatory protein (G_s), which then activates the adenylyl cyclase.*

A related regulatory protein (G_i) also binds to GTP in the presence of hormone stimulation of the α_2 adrenoreceptor (or muscarinic M_2 receptor). The interaction of G_i leads to inhibition of adenylyl cyclase. The G_i regulatory protein sometimes also interacts with ion channels to activate (K^+ channels) or inhibit (voltage-gated Ca^{++}

channels) them. The intracellular receptor for cyclic AMP is cyclic AMP-dependent protein kinase (protein kinase A). When activated by cyclic AMP, the kinase phosphorylates a variety of cellular proteins and regulates their activities.

The stimulation of α_1 adrenoreceptors causes activation of a membrane-bound ***phospholipase C (PLC)****. Phospholipase C hydrolyzes a membrane phospholipid, phosphatidylinositol-4,5-biphosphate (PIP_2), resulting in the formation of diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP_3). IP_3 causes the release of Ca^{2+} from intracellular stores, which then initiates a variety of cellular responses. Some of these responses result from activation of Ca^{2+}/calmodulin-dependent enzymes (phosphorylase kinase, myosin light-chain kinase). DAG stimulates the activity of a Ca^{2+}-sensitive enzyme, protein kinase C, which phosphorylates a distinct set of substrates; some of these are also substrates for protein kinase A (glycogen synthase).*

Many of the most useful agents in clinical medicine act at the level of catecholamine receptors. Such agents may be agonists or antagonists. The agonists may be subdivided into directly and indirectly-acting agents. The indirectly-acting agents (**tyramine)** elicit their effect primarily by uptake into the postganglionic sympathetic neuron where they displace norepinephrine from cytoplasmic sites and into the synaptic cleft. Thus, it is norepinephrine that mediates their effect. Because they affect sympathetic neurons throughout the body and because **tachyphylaxis** occurs they are seldom used clinically, but will be reviewed briefly later.

Although catecholamine receptors tend to be most heavily concentrated in the vicinity of neuron terminals, some are located at more distant sites. In fact some can be found on circulating blood cells. The nearer a receptor site is to a neuron terminal, the more likely it is to depend on neuronally released catecholamine (usually norepinephrine) for stimulation. The farther a receptor site is from a neuron terminal, the more likely it is that circulating epinephrine and norepinephrine stimulate it.

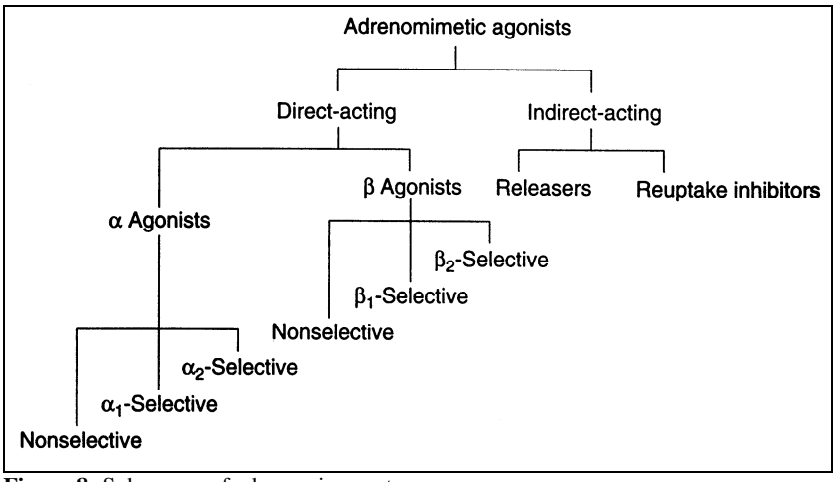

Figure 8: Subgroups of adrenergic agents

Table 1: Autonomic and Adrenoreceptor Effects of Norepinephrine

Organ	Receptor	Response
***Medulla Oblongata**	α_2	**Reduced sympathetic outflow**
***Pupil**	α_1	**Mydriasis (radial muscle contraction)**
***Heart**	β_1	**Acceleration, contractility increase**
***Arterioles**	α_1,α_2	**Constriction**
***Arterioles**	β_2	**Dilation**
***Veins**	α_1,α_2	**Constriction**
Salivary Glands	α_1,α_2	**Viscous secretion**
Pilomotor Muscles	α_1	**Contraction (horripilation, "chill bumps")**
***Bronchial Muscle**	β_2	**Relaxation**
Gastrointestinal Muscle	$\alpha_1,\alpha_2,\beta_2$	**Relaxation**
****Uterus***	β_2	**Relaxation**
****Bladder Sphincter***	α_1	**Contraction**
Spleen Capsule	α_1	**Contraction**
Pancreas	α_2	**Reduced insulin**
Pancreas	β_2	**Increased insulin**
Liver	α_1,β_2	**Hyperglycemia**
Adipose Tissue	β_1,β_3	**Lipolysis**
Adipose Tissue	α_2	**Reduced lipolysis**
Adipose Tissue	β_3	**Heat production**
***Kidney**	β_1	**Renin release**
Kidney	α_2	**Sodium conservation, reduced renin**
***Platelet**	α_2	**Aggregation**
White Blood Cells	β_2	**Demargination**

***clinically important effect**

Most agonists and antagonists at catecholamine receptors interact with more than one receptor type. For example, epinephrine (adrenaline) will stimulate α_1, α_2, β_1, β_2 and β_3-receptors if given in sufficiently high dosages. Epinephrine has relatively more activity at β_2-adrenoreceptors than does norepinephrine. Norepinephrine is especially potent at α_1 and at β_3-adrenoreceptors.

It is advisable to learn the effects of "pure" agonists and antagonists on the various adrenoreceptor types and then learn the adrenoreceptor type specificity of individual drugs. Considerable intellectual effort is required to assimilate adrenoreceptor pharmacology, which constitutes a major category of drug use in man.

Since 2000, there has been much new information implicating the autonomic nervous system in the control of both bone and adipose tissue. Sympathetic activation seems to reduce bone mass, whereas reduced sympathetic models have increased bone mass. Sympathetic activation of fat tissues leads to breakdown (lipolysis) whereas parasympathetic activation leads to build up of fat in the abdominal adipose tissue.

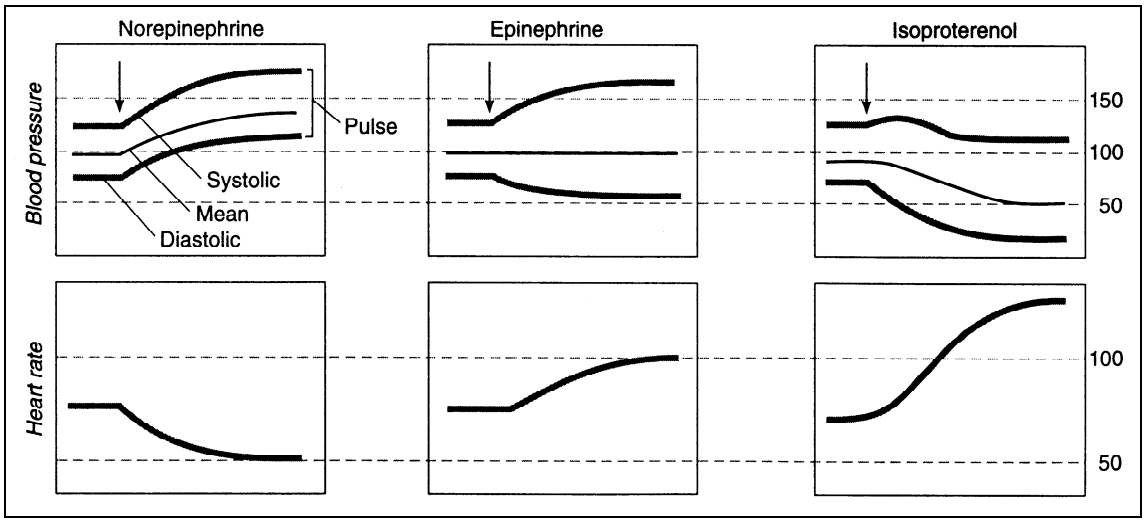

Figure 9: Typical effects of principal catecholamines on blood pressure and heart rate. Note that the pulse pressure ("Pulse") is only slightly increased by norepinephrine but is markedly increased by epinephrine and isoproterenol. The reduction in heart rate caused by norepinephrine is the result of baroreceptor reflex activation of vagal outflow to the heart. The blood pressure effects of epinephrine are typically dose-dependent: small doses exhibit more beta effect (isoproterenol-like; large doses exhibit more alpha effect (norepinephrine-like).

B. Alpha$_1$-Agonists:

The most important effects of α_1-agonists (**phenylephrine,** ***methoxamine*****, norepinephrine**) are apparent from inspection of Table 1. The dilator muscle of the pupil is constricted giving **mydriasis** (dilated pupil). Some of the smooth muscle tissue in the eyelids is constricted leading to a widened palpebral fissure. Most arterioles are constricted and peripheral vascular resistance is increased, raising blood pressure. Veins (capacitance vessels) are also constricted leading to a central redistribution of blood into the thorax. Stimulation of pilomotor nerves causes hair to "stand on end" (horripilation or **piloerection**). The associated stimulation of myoepithelial tissue in the vicinity of the **apocrine** glands (axilla, crural areas) causes gland emptying although the glands themselves are not stimulated. (The **eccrine** sweat glands are stimulated by sympathetic postganglionic fibers that are cholinergic and hence do not fit into either α or β classification, but rather respond to acetylcholine and are blocked by atropine.) Bladder sphincters are contracted by α_1-stimulation. The spleen capsule is contracted. There is CNS stimulation with agents which cross the blood-brain barrier (norepinephrine, dopamine, and epinephrine do not). Some agonists at α_1-adrenoreceptors increase myocardial contractility (but not heart rate) in some circumstances, but β_1 stimulation of contractility is more important clinically.

Phenylephrine (Neosynephrine®) and methoxamine are far more potent in stimulating α_1-receptors than in stimulating other receptor types. For practical purposes, they can be considered pure α_1-agonists. In clinical practice they are used systemically to treat hypotensive states. Locally they cause mydriasis. They are useful in treating nasal congestion. **Phenylephrine** is occasionally used to restore paroxysmal atrial tachycardia to normal sinus rhythm (via baroreceptor-mediated enhancement of vagal tone).

Norepinephrine is very close to phenylephrine in its effects and has enjoyed wider clinical use in the treatment of shock. Norepinephrine differs from phenylephrine primarily in having a greater capacity to stimulate β_1-adrenoreceptors as well as α_1-adrenoreceptors. **Epinephrine** is used clinically primarily to support blood pressure, especially during anaphylaxis. **Dopamine**, the immediate metabolic precursor of norepinephrine, has wide use in the drug treatment of shock. At high but not at low dosages, it stimulates α_1-adrenoreceptors. (More in Dr. Blackwell's lecture).

These agents are sometimes used with local anesthetics; by causing vasoconstriction at the site of the injection, they delay the absorption of the local anesthetic and prolong anesthesia.

C. **Alpha$_1$-Antagonists**

Blockade of the α_1-receptor negates the responses discussed above. In subjects on no other medications, α_1-blockers (prazosin, phentolamine, tolazoline, phenoxybenzamine) reduce blood pressure, especially in the upright posture. Some agents (prazosin) selectively block the α_1- receptor. Others (phenoxybenzamine, tolazoline, phentolamine) block the α_2-receptor as well.

Phentolamine is a competitive, short-acting α-antagonist. It is used to determine whether a given level of hypertension is catecholamine-mediated. This is sometimes helpful in diagnosing **pheochromocytoma** at the bedside. In addition to its α blocking properties phentolamine antagonizes some effects of serotonin. Its major side effect is cardiac stimulation (arrhythmias and angina pectoris). Abdominal cramping, ulcer exacerbation and diarrhea occur with chronic use.

Phenoxybenzamine is a noncompetitive, long-acting α-antagonist. Unlike phentolamine it can be reliably given orally with its clinical effect developing over hours and lasting several days. Like phentolamine, it frequently causes postural hypotension. Its main clinical use is in the medical management of pheochromocytoma.

Prazosin differs from phentolamine, tolazoline and phenoxybenzamine in that it selective blocks α_1-receptors without blocking the α_2-receptors that mediate feedback inhibition of norepinephrine synthesis/release. Thus there is less spillover stimulation of α-receptors with prazosin than in the case of the other two agents. Prazosin is used in hypertension and in congestive heart failure. The major problem in its use has been "prazosin syncope," fainting that occasionally occurs on standing 2-4 hours after the first oral dose, and a tendency toward reduced efficacy with chronic use. Terazosin and doxazosin are similar to prazosin and have been used to relieve the symptoms of benign prostatic hypertrophy. (More about the α-adrenergic blockers from Dr. Oates later.)

D. **Alpha$_2$-Agonists**

The most important effects of α_2-agonists (**clonidine,** guanabenz**,** guanfacine, and α-methylnorepinephrine) are only partially apparent from Table 1. In many tissues **presynaptic α_2- stimulation mediates feedback-inhibition of norepinephrine release**. When there is sufficient norepinephrine in the synaptic cleft to effect a response, it would be uneconomical of the neuron to continue to release still more transmitter.

Certain postsynaptic α_2 receptors in the vicinity of the NTS and the RVLM are important determinants of sympathetic outflow. There is currently great interest in understanding these receptors better since they have differences from most other α_2 adrenoreceptors. Some of them functionally resemble "imidazoline receptors"; no one knows for sure the identity of the endogenous agonist for imidazoline receptors in the brain. **Clonidine** stimulation of brainstem α_2-receptors and binding to imidazoline receptors significantly reduces sympathetic outflow to the cardiovascular system: hypotension and bradycardia result. This effect accounts for much of the usefulness of clonidine in treating hypertension.

Methyldopa, used as an antihypertensive agent, appears to be effective because its metabolite, **α-methylnorepinephrine**, stimulates these receptors. High doses of α_2-agonists may stimulate peripheral postsynaptic vascular α_2-receptors mediating vasoconstriction and thus actually raise blood pressure. Thus, we sometimes speak of clonidine as having a "therapeutic window."

Causalgia *is a pain syndrome that develops in the joints especially after nerve injuries. Other names include Sudeck's atrophy, Sudeck's dystrophy, algodystrophy, shoulder-hand syndrome, and reflex sympathetic dystrophy. The major features are (1) pain; (2) dystrophy in involved skin, tissue, muscle, and bone; and (3) abnormal sweating and blood flow regulation in the affected area. Sometimes there is also hypertrichosis and ridging of nails. Weeks or months after myocardial infarction, this syndrome may develop in the left arm and hand ("shoulder-hand syndrome" or "Dressler's syndrome") and mimic the pain of angina pectoris.*

After years of skepticism, most investigators now acknowledge the key role of the sympathetic nervous system in mediating causalgia. Destruction of the relevant sympathetic nerves often completely eliminates the pain. There is recent experimental evidence that blockade of α_2-adrenoreceptors may also be helpful. The precise mechanism of autonomic mediation of causalgia remains unknown.

E. **Alpha$_2$-Antagonists**

While phentolamine and phenoxybenzamine block α_2-receptors, their major clinical action is to block α_1-receptors. The only widely available, relatively specific α_2-antagonist is **yohimbine**. By blocking α_2-adrenoreceptors in the medulla, it **increases** sympathetic outflow. By blocking presynaptic α_2-adrenoreceptors in the periphery, it enhances norepinephrine release. Yohimbine has long been reputed to be an aphrodisiac, for which purpose the plant from which it is derived it has been sold throughout the world. Studies during the last several years seem to confirm that α_2-agonists reduce and α_2-antagonists increase copulatory behavior in rats.

F. **Beta Agonists**

Isoproterenol stimulates both β_1- and β_2-receptors. The heart contracts with greater force (increased contractility) and heart rate is increased. Cardiac output rises. There is an increased likelihood of premature heartbeats and other arrhythmias. Many arterioles are dilated, with consequent reduced resistance. Mean blood pressure is at least transiently lowered. The gravid uterus is relaxed. Bronchioles are relaxed (useful in

asthmatics) and metabolic effects on the liver and adipose tissue lead to hyperglycemia and lipolysis. Some CNS stimulation occurs.

While it is advantageous to stimulate β_2-receptors in the bronchial tree of asthmatic patients or the uterus of a woman in premature labor, the attendant β_1-cardiac stimulation is an unwanted effect. This has led to efforts to achieve selective β_2 stimulation. A variety of putative β_2-agonists have been developed, but their selectivity is partial. (More later in the course when asthma therapy is discussed).

On the other hand, in certain patients, the cardiac stimulation of β-agonists is desirable (pulmonary edema, coronary bypass post-op) and a relatively selective β_1-agonist like **dobutamine** is indicated. Moderate doses of dobutamine increase myocardial contractility without significantly altering blood pressure. The relatively small effect of dobutamine on blood pressure is due to counterbalancing effects of β_1 stimulation and β_2 stimulation on arteriolar and venous tone.

A β_3 adrenoreceptor has recently been identified that is sensitive to norepinephrine and not easily blocked by the usual β-antagonists. It mediates heat production and energy expenditure in adipose tissue.

G. **Beta Antagonists (see Dr. Awad's lecture on this topic for greater detail)**

Propranolol is a competitive inhibitor of sympathomimetic amines at both the β_1- and β_2- receptor. It counteracts the effect of isoprenaline in the vasculature, heart and liver. In persons on no medication, propranolol reduces heart rate, contractility and blood pressure. Atrioventricular conduction is slowed. There is increased bronchiolar tone; therefore, the drug is avoided in asthmatics and in patients with chronic obstructive pulmonary disease. The reduced myocardial function may worsen heart failure in patients with borderline cardiac status but low doses of beta-blockers are sometimes helpful in limiting excessive sympathetic stimulation in severe heart failure. In addition to its β-blocking properties, propranolol possesses "quinidine-like" antiarrhythmic properties and is a local anesthetic.

Propranolol is widely used to reduce heart work in patients with angina pectoris and to treat ventricular arrhythmias. It is also an effective antihypertensive agent, probably by reducing renin production. It produces subjective improvement in thyrotoxicosis and certain anxiety states and may reduce the incidence of migraine headaches. There is increasing evidence that long-term treatment of post-myocardial infarction patients with beta blockers (timolol, metoprolol, propranolol) reduces mortality, perhaps because these drugs prevent fatal arrhythmias. Side effects of propranolol include worsened heart failure, reduced AV conduction, worsened obstructive lung disease, vivid nightmares, fatigue, and cold extremities.

Metoprolol is a relatively selective blocker of the β_1-receptor and may give cardiac effects with minimal worsening of asthma. **Atenolol** is also relatively selective for the β_1-receptor, does not cross the blood-brain barrier well, and can be given once daily in managing hypertension. Timolol eye drops are used in glaucoma patients to reduce intraocular pressure. Pindolol is primarily a beta-antagonist but has some agonist activity (intrinsic sympathomimetic effect).

H. Dopamine Agonists and Antagonists

There are distinct dopaminergic receptors in several peripheral tissues, notably in the renal vasculature. Agonists at the receptor include fenoldopam, apomorphine, **bromocriptine**, and other agents used in treating Parkinson's disease (More later in course when Parkinson's Disease therapy discussed).

Fenoldopam is a dopaminergic agonist with nine-fold specificity for the D_1 receptor. D_1 receptors mediate vasodilatation in the coronary, cerebrovascular, renal, and mesenteric vascular beds, whereas D_2 receptors also cause emesis and inhibition of prolactin Fenoldopam's ultimate role in therapy remains uncertain, but it may be helpful in hypertension, heart failure, myocardial ischemia, and as a diuretic.

Recently, an abnormality in an exon of the D_4 receptor has been reported to correlate with innovation and risk-taking behavior. If confirmed, this may open a new era of understanding human behavior.

Other dopaminergic antagonists include metoclopramide, haloperidol, domperidone, and a variety of phenothiazine derivatives that will be discussed during the lectures on psychotropic drugs and gastrointestinal motility.

I. Indirectly Acting Phenylethylamines

Tyramine enters noradrenergic neurons via the norepinephrine transporter and displaces NE from the "labile pool" (non-stored NE) and into the synaptic cleft onto postsynaptic receptors. This drug is present in cheddar cheese, certain wines, marmite, country ham, and broadbeans (fava beans).

Although norepinephrine is usually rapidly metabolized by **monoamine oxidase**, patients on inhibitors of this enzyme (e.g., pargyline) may have profound hypertension from over-indulgence in tyramine-containing foods.

Ephedrine is the active ingredient in the herbal product Ephedra (Ma Huang). It is both a directly and indirectly acting agent. The drug has been used to promote weight loss, in therapy of asthma (over-the-counter, OTC) and as a nasal decongestant. Because it increases skeletal muscle tone (slightly), it has been used as adjunctive therapy in myasthenia gravis. CNS effects (anxiety, insomnia, mental stimulation) may be prominent, and it has been used to treat narcolepsy. Amphetamine is a congener of ephedrine with even more potent CNS effects. These and similar agents have been used to induce weight loss (OTC). Ephedra's widespread availability over the counter caused it to be used to achieve weight loss and to enhance physical performance of athletes. In hot weather and with the thermic stimulus of exercise, Ephedra's own hyperthermic effect has caused illness and death. After several years of hesitation, the FDA initiated actions to remove this agent from sale in the United States in December 2003.

> ***Horner's syndrome*** *occurs when sympathetic nerves to the eye are interrupted. Three consecutive neurons are involved in conveying sympathetic outflow from the medulla to the eye, and a lesion of any one of them leads to Horner's syndrome. The syndrome includes miosis, ipsilateral anhidrosis, and ipsilateral ptosis. The diagnosis is made by documenting that an* α_1*-adrenoreceptor agonist (phenylephrine) will dilate the patient's constricted pupil. Hydroxyamphetamine, a tyramine-like agent, will also dilate the pupil if the neuron innervating the iris is*

intact (that is, if the lesion is more central). If the most peripheral nerve is the damaged one, hydroxyamphetamine will not work. This differentiation is important since the etiologies of more central lesions are very different than those of more peripheral lesions.

There are a large number of sympathomimetics in nasal decongestants, nose drops, and inhalers. **Phenylpropanolamine** achieved great popularity as an over-the-counter weight loss aid ("Dexatrim®"), for which it is probably ineffective. Some of these agents act directly and others indirectly. Their vasoconstrictive properties are responsible for increasing tone in boggy mucosal surfaces; this "shrinks" mucosal membranes. The FDA removed phenylpropranolamine from the market in 2000 due to an increased risk of hemorrhagic stroke. **Pseudoephedrine (Sudafed®)**, which closely resembles phenylpropanolamine, is increasingly used to replace it, but it could be that all pressor drugs will prove to have the same increased risk of hemorrhagic stroke if carefully studied for this rare complication.

V. Acetylcholine

A. Acetylcholine Receptors

Acetylcholine (ACh) is the **postganglionic** neurotransmitter in the parasympathetic nervous system. It is also the **preganglionic** neurotransmitter for ***both*** the sympathetic and parasympathetic nervous system. It is also important at non-autonomic sites. For example, **ACh** is the neurotransmitter by which motor nerves stimulate **skeletal muscle**, and also the neurotransmitter at many sites in the **brain and spinal cord**.

As might be expected for an ancient and ubiquitous neurotransmitter, a variety of **ACh (cholinergic) receptor** types have emerged. The most important classification depends on their responsiveness to the agonist drugs, **muscarine** and **nicotine**, and this distinction is so crucial that the terms **muscarinic receptor (M)** and **nicotinic receptor (N)** are used rather then cholinergic receptor.

Muscarinic receptors are located...

- in tissues innervated by **postganglionic parasympathetic neurons**
- in ***presynaptic*** **noradrenergic and cholinergic** nerve terminals
- in non-innervated sites in **vascular endothelium**
- in the **central nervous system.**

Nicotinic receptors are located...

- in **sympathetic** and **parasympathetic ganglia**
- in the **adrenal medulla**
- in the neuromuscular junction of the **skeletal muscle**
- in the **central nervous system.**

There are at least 5 subtypes of **muscarinic receptors,** referred to as M_1, M_2, M_3, M_4, and M_5. They mediate their effects through G proteins coupled to phospholipase C ($M_{1,3,5}$), or to potassium channels ($M_{2,4}$). Because we currently have few truly *subtype*-specific muscarinic agonists and antagonists of clinical utility, there will not be detailed discussion of them this year.

There are at least two subtypes of **nicotinic receptors,** referred to as $\mathbf{N_M}$ and $\mathbf{N_N}$**.** This distinction is clinically important. The $\mathbf{N_M}$ **nicotinic receptor** mediates skeletal **<u>m</u>uscle** stimulation, while the $\mathbf{N_N}$ **nicotinic receptor** mediates stimulation of the ganglia of the autonomic **<u>n</u>ervous** system, for which reason agonists and antagonists at the latter site are sometimes called **ganglionic agonists** and **ganglionic blockers.**

> *Nicotinic receptors are ligand-gated ion channels whose activation results in a rapid increase in cellular permeability to sodium and calcium. They are pentameric arrays of one to four distinct but homologous subunits, surrounding an internal channel. The* α *subunit, which has binding sites for ACh, is present in at least two copies. Agonist molecules induce a conformational change that opens the channel. Antagonist molecules may bind to these sites but do not elicit the conformational change.*

B. Muscarinic Agonists

Acetylcholine itself is rarely used clinically because of its rapid hydrolysis following oral ingestion and rapid metabolism following intravenous administration. Fortunately, a number of congeners with resistance to hydrolysis (**methacholine**, carbachol, and **bethanechol)** have become available, and **bethanechol** has the additional favorable property of an overwhelmingly high muscarinic (vs nicotinic) specificity. There are also several other naturally occurring **muscarinic agonists** such as muscarine, arecholine, and **pilocarpine.**

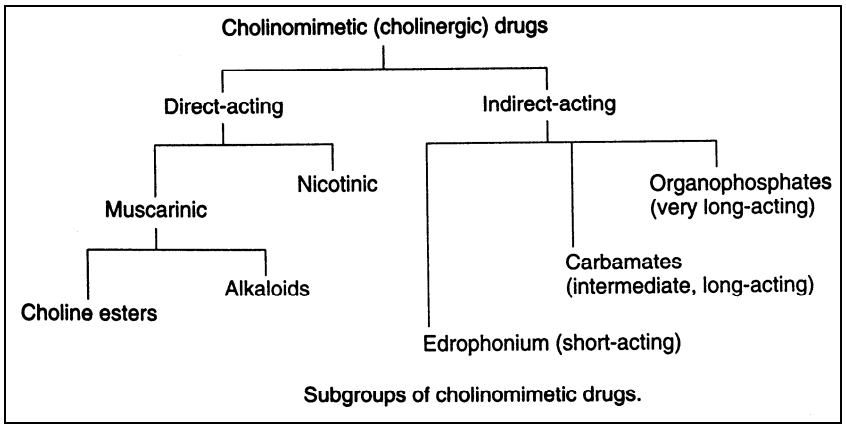

Figure 10: Subgroups of cholinomimetic drugs.

The pharmacological effects of **acetylcholine** and other **muscarinic** agonists can be seen by inspection of Table 2, where clinically important effects are designated by asterisks. All these effects are parasympathetically mediated except **sweat gland** function, which is the unique **sympathetic cholinergic category,** much beloved by examination writers; these nerves are sympathetic because of their thoracolumbar origin and cholinergic because they release acetylcholine.

Table 2: Muscarinic Autonomic Effects of Acetylcholine (*clinically important)

***Iris sphincter muscle**	**Contraction (miosis)**
***Ciliary muscle**	**Contraction (near vision)**
***SA node**	**Bradycardia**
Atrium	**Reduced contractility**
***AV node**	**Reduced conduction velocity**
Arteriole	**Dilation (via nitric oxide)**
***Bronchial muscle**	**Contraction**
***Gastrointestinal motility**	**Increased**
***Gastrointestinal secretion**	**Increased**
Gallbladder	**Contraction**
***Bladder (detrusor)**	**Contraction**
***Bladder (trigone, sphincter)**	**Relaxation**
Penis	**Erection (but not ejaculation)**
Sweat glands	**Secretion**
Salivary glands	**Secretion**
Lacrimal glands	**Secretion**
Nasopharyngeal glands	**Secretion**

Bethanechol (Urecholine®) is used (rarely) to treat gastroparesis, because it stimulates gastrointestinal motility and secretion. It is also useful in patients with autonomic failure, in whom modest improvement in **gastric emptying** and constipation may occur, but at a cost of some cramping abdominal discomfort. If gastric absorption is impaired, subcutaneous administration is sometimes employed. Especially with intravenous administration, hypotension and bradycardia may occur. Bethanechol is also widely used to treat **urinary retention** if physical obstruction (e.g., prostate enlargement) is **not** the cause. This agent also occasionally is used to stimulate salivary gland secretion in patients with xerostomia**,** which entails the dry mouth, nasal passages, and throat occurring in Sjögren's syndrome, and in some cases of traumatic or radiation injury**.** In rare cases, high doses of bethanechol have seemed to cause myocardial ischemia in patients with a predisposition to coronary artery spasm, so chest pain in a patient on bethanechol should be taken seriously.

Pilocarpine is more commonly used than bethanechol to induce salivation, and also for various purposes in ophthalmology. It is especially widely used to treat **open-angle glaucoma**, for which a topical (ocular) preparation is available. Intraocular pressure is lowered within a few minutes following ocular instillation of pilocarpine. It causes contraction of the iris sphincter, which results in **miosis** (small pupils) and contraction of the ciliary muscle, which results in near (as opposed to distant) focus of vision. Pilocarpine possesses the expected side effect profile, including increased sweating, asthma worsening, nausea, hypotension, bradycardia (slow heart rate), and occasionally hiccups.

Methacholine is often used to provoke bronchoconstriction during diagnostic testing of pulmonary function. Elicitation of significant bronchoconstriction with inhaled **methacholine challenge** sometimes leads to the diagnosis of reactive airways disease (asthma) in patients with little baseline abnormality in pulmonary function.

C. Muscarinic Antagonists

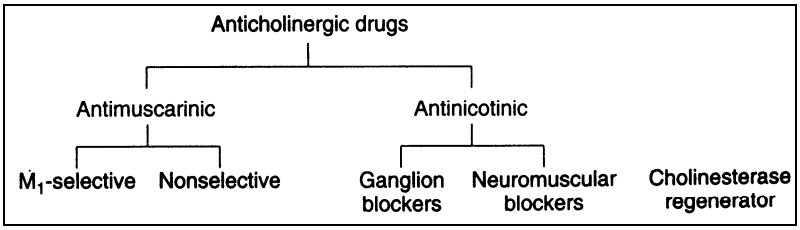

Figure 11: Subtypes of anticholinergic agents.

The classical **muscarinic antagonists** are derived from plants. The **deadly nightshade** (*Atropa belladonna*), a relative of the tomato and potato, contains **atropine. Jimson weed** (*Datura stramonium*) is even more widespread in Tennessee than the deadly nightshade. The tiny dark seeds from the Jimson weed pod are sometimes ingested for their hallucinogenic effect, a central side effect of atropine-like substances. Henbane (*Hyoscyamus niger*) contains primarily scopolamine and *hyoscine*.

Some plants of these families grow well in poor, rocky soil whereas tomatoes grow poorly in these locations. The grafting of tomato plant stalks onto the root systems of these plants yields an unusually productive "tomato" that bears well even in dry

weather. Abundant large red tomatoes result. Unfortunately, if the grafting is not done properly, belladonna alkaloids may enter the tomato fruit. Tachycardia and hallucinations (as well as more life-threatening problems) may ensue when such tomatoes are eaten.

Side effects of muscarinic antagonists include **constipation**, **xerostomia** (dry mouth), **hypohidrosis** (decreased sweating), **mydriasis** (dilated pupils), **urinary retention**, precipitation of **glaucoma**, **decreased lacrimation**, **tachycardia**, and **decreased respiratory secretions**.

Clinically, **atropine** is used for raising heart rate during situations where vagal activity is pronounced (for example, **vasovagal syncope**). It is also used for dilating the pupils. Its most widespread current use is in preanesthetic preparation of patients; in this situation, atropine reduces respiratory tract secretions and thus facilitates intubation. It probably also has some efficacy as a bronchodilator. Inhaled ipratropium is marketed for maintenance therapy in chronic obstructive pulmonary disease (COPD). It has a long half-life.

Pirenzepine shows selectivity for the M_1 muscarinic receptor. Because of the importance of this receptor in mediating gastric acid release, M_1 antagonists such as pirenzepine help patients with ulcer disease or gastric acid hypersecretion. However, antihistamines and proton pump inhibitors are more useful and more widely used for control of gastric acidity.

D. Nicotinic Agonists

Nicotine is the most commonly encountered nicotinic agonist. It is found in the leaves of the tobacco plant (*Nicotiana tabacum*) in concentrations of 0.3 to 0.7%. It is responsible for the addicting properties of tobacco. Nicotine's actions are complex. At low dosages it stimulates ganglionic nicotinic receptors thus enhancing both sympathetic and parasympathetic neurotransmission. These are the effects nicotine has been classically considered to have. In practice there is stimulation of nicotinic receptors in many other sites especially as nicotine dosages increase. Nicotine possesses some antagonist effect at nicotinic receptors at high dosages.

Smoking one cigarette or intravenous administration of 1 mg nicotine will usually raise blood pressure about 10 mm Hg and increase heart rate 15 beats per minute. Peripheral vascular resistance increases, as do cardiac output and heart work. Vasopressin and epinephrine are released. Higher doses stimulate the heart eliciting the **Bezold-Jarisch reflex** (bradycardia, hypotension, nausea), and may eventually result in weakness, tremors, and convulsions. A dosage of 60 mg is lethal; there are two lethal doses in one cigar (if it were absorbed rather than smoked).

Chronic smoking has effects unrelated to nicotine (or related to nicotine in a still poorly understood way). HDL cholesterol is reduced, LDL cholesterol is increased, and plasma fibrinogen is elevated. There is excessive free radical production. All these changes could promote atherosclerosis. Smokers have increased metabolic rate that keeps them relatively lean; on discontinuation of smoking the reduction in metabolism usually causes a weight gain. On average the babies of smoking mothers weigh 0.5 pound less than those of non-smoking mothers. Smokers have an increased risk of cancer (129,000 extra deaths per year), coronary heart disease (170,000 extra deaths per

year), and chronic obstructive pulmonary disease (62,000 extra deaths per year). The persistence of widespread tobacco use into the 21st century is an incongruity that future historians will probably find tragic and inexplicable.

Addiction to nicotine makes it very difficult for regular cigarette users to stop smoking. Since the overwhelming majority of the bad effects of smoking are due to factors other than nicotine itself, nicotine products such as patches (for transdermal nicotine administration), chewing gum, and nasal sprays have been developed to try to administer nicotine without the involvement of tobacco use. In general, this approach has worked well. Only time will tell to what extent the patches and nasal spray will themselves cause addiction, but experience so far is encouraging. The principal side effects noted have included alterations in taste or smell and increased heart rate.

E. Nicotinic Antagonists (Ganglionic Blockers)

The actions of drugs on autonomic ganglia are complex. The primary receptors at ganglia are cholinergic receptors of the **nicotinic (N_N)** type. The effects observed clinically with **ganglionic blocking agents** are due to blockade of these receptors. Nearly all effects are predictable from the knowledge that ganglionic blockers reduce transmission in **all** autonomic ganglia, both sympathetic and parasympathetic. In some sites, sympathetic activation seems to predominate over parasympathetic, while in other sites, the opposite is true. Ganglionic blockade thus "uncovers" the predominant system. This class of drugs is now rarely used.

Table 3: Mediators and Effects of Ganglionic Blockade on Organ Systems

Tissue	Predominant System	Ganglionic Blockade Effect
Arterioles	Sympathetic	Vasodilation
Veins	Sympathetic	Vasodilation
Heart	Parasympathetic	Tachycardia
Iris	Parasympathetic	Mydriasis
Ciliary muscle	Parasympathetic	Cycloplegia
Gastrointestinal tract	Parasympathetic	Hypomotility
Urinary bladder	Parasympathetic	Urinary retention
Salivary glands	Parasympathetic	Xerostomia
Sweat glands	Sympathetic cholinergic	Anhidrosis

F. Cholinesterase Inhibitors

The **muscarinic and nicotinic agonists** mimic acetylcholine effect by stimulating the relevant receptors themselves. Another way of accomplishing the same thing is to reduce the destruction of **ACh** following its release. This is achieved by **cholinesterase inhibitors,** which are also called the **anticholinesterases.** They mimic the effect of combined muscarinic and nicotinic agonists. Cholinergic neurotransmission is especially important in insects, and it was discovered many years ago that anticholinesterases could be effective **insecticides**, by “overwhelming the cholinergic circuits” (see War Gases below)

By inhibiting acetylcholinesterase and pseudocholinesterase, these drugs allow ACh to build up at its receptors. Thus they result in enhancement of both muscarinic and nicotinic agonist effect.

"Reversible" cholinesterase inhibitors are generally short-acting. They include **physostigmine** that enters the CNS and **neostigmine** and edrophonium that do not:

Physostigmine enters the CNS and can cause restlessness, apprehension, and hypertension in addition to the effects more typical of muscarinic and nicotinic agonists.

Neostigmine is a **quaternary amine** (tends to be charged) and **enters the CNS poorly**; its effects are therefore almost exclusively those of muscarinic and nicotinic stimulation. It is used to stimulate motor activity of the small intestine and colon, as in certain types of nonobstructive paralytic ileus. It is useful in treating atony of the detrusor muscle of the urinary bladder, in **myasthenia gravis**, and sometimes in **glaucoma**. Like other cholinesterase inhibitors, neostigmine requires an **intact postganglionic innervation** for full development of its actions.

Edrophonium (Tensilon®) is a quaternary amine widely used as a clinical test for myasthenia gravis. If this disorder is present, edrophonium will markedly increase strength. It often causes some cramping, but this only lasts a few minutes. *Ambenonium* and *pyridostigmine* are sometimes also used to treat myasthenia.

Many phosphorothionates, including **parathion** and **malathion** undergo enzymatic oxidation that can greatly enhance anticholinesterase activity. The reaction involves the substitution of oxygen for sulphur. Thus, parathion is oxidized to the more potent and more water-soluble paraoxon. Differences in the hydrolytic and oxidative metabolism in different organisms accounts for the remarkable selectivity of malathion. In mammals, the hydrolytic process in the presence of carboxyesterase leads to inactivation. This normally occurs quite rapidly, whereas oxidation leading to activation is slow. In insects, the opposite is usually the case, and those agents are very potent insecticides.

Some patients encounter muscarinic side effects due to the inhibition of peripheral cholinesterase by physostigmine. The most common of these side effects are nausea, pallor, sweating and bradycardia. Concomitant use of **anticholinergic drugs** which are quaternary amines (e.g., glycopyrrolate or methscopolamine) and which therefore do not cross the blood-brain barrier are recommended to prevent the peripheral side effects of physostigmine.

Several centrally acting drugs produce an acute toxic psychosis characterized by confusion and the peripheral signs of cholinergic blockade. These drugs include several plant toxins, antidepressants, H_1 receptor antagonists with central effects, and several antiparkinsonian drugs and antipsychotic drugs. Overdoses of many other drugs can also lead to this anticholinergic syndrome.

Cholinesterase inhibitors that cross the blood-brain barrier are suitable to reverse the central anticholinergic syndrome. **Physostigmine** is the drug of choice. Although physostigmine effectively wakes up such patients briefly, it is not certain that its use results in a long-term better prognosis. Some patients with Alzheimer's disease have memory improvement transiently after anti-cholinergic drugs. Tacrine (Cognex®), was found to elicit hepatotoxicity, but definitely benefited **Alzheimer's disease**, if only to a limited extent. Two newer agents donepezil (Aricept®) and rivastigmine (Exelon®) have little hepatotoxicity and have replaced tacrine.

On the accompanying tables, the effects of intoxication and the therapeutic approach to treatment are outlined. The drug **pralidoxime** deserves special comment. This drug counteracts cholinesterase inhibitor intoxication by reactivating the cholinesterase enzyme. *Pralidoxime combines with the anionic site on the enzyme by electrostatic attraction to the quaternary N atom, which orients the nucleophilic oxime group to react with the electrophilic P atom; the oxime-phosphonate is split off, leaving the regenerated enzyme.*

G. War Gases

Long-acting or "irreversible" cholinesterase inhibitors (**organophosphates**) are especially used as insecticides. Cholinesterase inhibitors enhance cholinergic transmission at **all** cholinergic sites, both nicotinic and muscarinic. This makes them useful as poisons. Sarin which is a war nerve gas is a binary agent composed of two components that are not toxic until mixed. Nerve gases such as the cholinesterase inhibitor, sarin, have been the chemical weapons of choice for over 50 years. Sarin was first produced in 1938. It is a colorless, odorless gas with a lethal dose of just 0.5 mg for an adult human. Sarin is an easily dispersed agent that acts extremely quickly when absorbed through the skin or inhaled. Although recently superseded by more deadly and more persistent compounds such as VX, sarin remains a highly dangerous and effective part of mankind's destructive arsenal. Death usually occurs by asphyxiation. The final stage of sarin synthesis usually takes place while the missile or other delivery vessel is in flight because it is safer to store the component reagents than the more dangerous sarin itself.

Table 4 :Clinical Manifestations of Cholinesterase Inhibitor Intoxication

Muscarinic
- Miosis
- Blurred vision (spasm of accommodation)
- Lacrimation
- Sweating
- Excessive respiratory secretions
- Dyspnea (bronchoconstriction)
- Bradycardia
- Hypotension
- Salivation
- Nausea
- Cramping (gastrointestinal spasm)
- Diarrhea
- Urgency (urinary incontinence)

Nicotinic
- Fasciculations (early)
- Weakness (late)
- Adrenomedullary (sympathetic) discharge (early and transient)

Central Nervous System
- Anxiety
- Insomnia
- Nightmares
- Confusion
- Hypertension (rare)
- Tremors

- Convulsions
- Respiratory depression
- Circulatory collapse

Table 5: Therapy of Cholinesterase Inhibitor Intoxication

Mild Poisoning
- Atropine sulfate, 1-2 mg intravenously, as necessary
- Termination of exposure
- Pralidoxime, 1 g infused slowly, or 1-3 orally (if no GI symptoms)
- Supportive care

Severe Poisoning
- Artificial respiration
- Atropine sulfate, 2-4 mg intravenously at 5 minute intervals until abatement of symptoms occurs or signs of atropinization (tachycardia, dilated pupil, drug skin) appear
- Pralidoxime, 1 g infused slowly
- Termination of exposure
- If convulsion, diazepam 5-10 mg intravenously
- Supportive care
- Hospitalization for 2-3 days

VI. Skeletal Muscle Relaxants

Skeletal muscle relaxants fall into two broad categories. The **neuromuscular blocking drugs** are used to produce muscle paralysis and act at the neuromuscular endplate. The **spasmolytic drugs** have much milder actions and act at sites other than the muscle endplate.

The pharmacology of the neuromuscular blocking drugs is historically very complex, and several lectures in this course were once devoted to it. This no longer seems to be necessary in order to gain the knowledge required to use these agents appropriately. Much of the complexity of these drugs relates to the varying characteristics of the blockade they induced (**depolarizing** versus **nondepolarizing**), which seems simpler now that we understand it better.

Since **skeletal muscle** contraction is elicited by **nicotinic** (N_m) cholinergic mechanisms, it has similarities to nicotinic neurotransmission at the **autonomic ganglia**. Interestingly, two different kinds of functional blockade may occur at the neuromuscular endplate. One type mechanistically resembles muscarinic blockade, α-adrenoreceptor blockade and β-blockade described above, and is called "**nondepolarizing blockade**." A second type is very different. The **depolarizing type of blockade** is elicited by an agonist effect whereby there is stimulation of the nicotinic endplate receptor to depolarize the neuromuscular endplate. This initial depolarization is accompanied by transient twitching of the skeletal muscle. However, with continued agonist effect, the skeletal muscle tone cannot be maintained, and, therefore, this continuous depolarization results in **a functional muscle paralysis**. Thus, the effects of a depolarizing neuromuscular blocking agent move from a continuous depolarization (phase I) to a gradual repolarization with resistance to depolarization (phase II)

Nondepolarizing neuromuscular blocking drugs. **Tubocurarine** is a prototype for this class of drugs. It has a comparatively long (60 minutes) half-life, but this can be increased in patients with impaired renal function. Blockade by agents such as tubocurarine, pancuronium, and doxacurium **can be reversed by increasing the**

amount of acetylcholine in the synaptic cleft, for example, by the administration of a cholinesterase inhibitor.

Depolarizing neuromuscular blocking drugs. Succinylcholine is a prototype for this class of drug. It has a shorter half-life (5-10 minutes) and must be given by continuous infusion if prolonged paralysis is required. In practice, succinylcholine is often used to initiate paralysis and paralysis is then continued with a non-depolarizing agent. An important aspect of succinylcholine is its hydrolysis by pseudocholinesterase. In patients with **pseudocholinesterase deficiency**, succinylcholine half-life is greatly prolonged, and such patients may regain control of their skeletal muscles slowly after a surgical procedure. This is the most serious complication of pseudocholinesterase deficiency. While reversal of blockade is relatively easily accomplished with non-depolarizing blockers, the paralysis by depolarizing blockers during phase I is facilitated by cholinesterase inhibitors while the block achieved during phase II is reversed by cholinesterase inhibitors.

Side Effects. It is obvious that patients with myasthenia gravis would be dangerously sensitive to the effects of neuromuscular blockers, as are patients with certain forms of carcinomatous neuropathy. There is a typical pattern of relaxation of muscles after the administration of an agent such as tubocurarine: extraocular muscles are affected first, then the muscles of the hands and feet, head and neck, abdomen and limbs, and finally the muscles of ventilation. For this reason, in deep paralysis, **patients must be maintained on a respirator**. With the administration of neuromuscular blockers, there is often **histamine release** and this can reduce blood pressure, increase respiratory secretions, and sometimes produce a degree of bronchospasm. Some agents can also stimulate or block **sympathetic and parasympathetic effects** on various tissues. In practice, some neuromuscular blockers have resulted in very high blood pressures and heart rates in occasional individuals and very low blood pressures and heart rates in others, primarily because of their disparate effects on autonomic ganglia and muscarinic receptors.

Drug Interactions. A number of drugs may potentiate the effects of neuromuscular blockers. These include a number of antibiotics (aminoglycosides gentamicin, kanamycin, and streptomycin) and inhaled anesthetics such as isoflurane.

Spasmolytic Drugs. Neuromuscular blocking agents produce general relaxation of all skeletal muscles. They are not useful for specific muscle relaxation. Furthermore, they have to be administered parenterally. Therefore, there is a great need for specific muscle relaxants, which can be used in spastic states associated with trauma, inflammation or psychogenic disorder. They are of two types, (a) those that act directly on muscle and (b) those that act indirectly by depressing nerves.

- **Dantrolene** is the only muscle relaxant which reduces muscle tension through a direct effect at a site proximal to the contractile mechanism. It does not affect neuromuscular transmission. Dantrolene **reduces the release of activator calcium** from the sarcoplasmic reticulum. Its effect is dose-dependent and is of long duration. **Dantrolene** is widely used to treat the muscle contractures associated with **malignant hyperthermia**. It may be effective in relieving spasticity due to cerebrovascular damage, spinal cord lesions, multiple sclerosis or cerebral palsy. It is not useful in the treatment of fibrositis, bursitis, arthritis or acute muscle spasm of

local origin. Dantrolene is potentially hepatotoxic, especially in women over 35 year of age who have taken the drug for 60 days or longer. The lowest effective dose should be prescribed and thereby should be discontinued if clear benefits are not observed.

- Baclofen is a generally effective muscle relaxant that acts as a partial GABA agonist, probably in the spinal cord.

Finally, there are a number of antianxiety agents that also have a significant ability to reduce nerve stimulation of the muscles (diazepam, chlordiazepoxide, carisoprodol, meprobamate). (More later in course)

Glycine, like GABA, is an important CNS inhibitory amino acid neurotransmitter. Its effects are antagonized by strychnine, which may cause hypersensitivity to stimuli and eventually convulsions. Strychnine was used to stimulate respiration before ventilators became widely available

> *Several dozen small churches in Appalachia and the Appalachian diaspora have developed a tradition of drinking strychnine (and handling rattlesnakes) during certain religious services. A number of deaths have resulted from such overdose, including some not far from Nashville. Several states have passed laws to prevent this practice, but these laws have been challenged by legal scholars concerned about civil and religious liberty. On the other hand, some congregants seem to have ingested strychnine during the services against their better judgment, in response to a perceived social pressure.*

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