Nervous system

Two major subdivisions:	
1. Central nervous system	(CNS; the brain and spinal cord)
2. Peripheral nervous system	(PNS; neuronal tissues outside the CNS).

Anatomically divided into the:

1. Autonomic
2. Somatic

Autonomic nerves can also influence cancer development and progression.

ANATOMY OF THE AUTONOMIC NERVOUS SYSTEM

Two major portions:

1. Sympathetic (thoracolumbar) division
2. Parasympathetic (traditionally “craniosacral").

---- ----

a. The **sympathetic preganglionic fibers** leave CNS through the *thoracic, lumbar, and sacral spinal nerves.*

b. The **parasympathetic preganglionic fibers** leave the CNS through the *cranial nerves (3rd, 7th, 9th, and 10th).*

for Sympathetic

PARAVERTEBRAL	PREVERTEBRAL
Most thoracic and lumbar sympathetic preganglionic fibers are SHORT and terminate in ganglia located in here.	Most of the remaining sympathetic preganglionic fibers are somewhat LONGER and terminate
*Short	*Longer

For PARASYMPATHETIC:
-Preganglionic parasympathetic fibers terminate in parasympathetic ganglia located outside the organs innervated:

1.Ciliary
2. Pterygopalatine
3. Submandibular
4. Otic ganglia.

ANS vs SNS

Autonomic nervous system (ANS)	**Somatic nervous system (SNS)**
It is concerned with control and integration of visceral functions necessary for life such as cardiac output, blood flow distribution, and digestion.	Motor portion of the somatic subdivision is largely concerned with movement, respiration, and posture.
Largely independent (autonomous) in that its activities are not under direct conscious control.	Both have important afferent (sensory) inputs that provide information regarding the internal and external environments and modify motor output through reflex arcs of varying complexity.

Vagus nerve, also influences immune function and some CNS functions such as seizure discharge.

Major difference CNS vs ANS

Presence of a **GANGLION** in *ANS*

Differentiating divisions of ANS

a. **Sympathetic Nervous System**	b. **Parasympathetic Nervous System**	c. **Enteric Nervous System**
-Prepares body for intense "-FIGHT OR FLIGHT" response.	-Relaxes body and inhibits or slows many high energy functions	-Large and highly organized collection of neurons located in walls of GI system.
FIGHT OR FLIGHT (F/F	*REST OR DIGEST*	*THIRD DIVISION OF ANS*
-	-	Control motor activity of colon

ENS includes:
1. MYENTERIC PLEXUS or the *Plexus of Auerbach*
2. SUBMUCOUS PLEXUS or the *Plexus of Meissner*

ENS neuronal networks

1. **Myenteric plexus** (the plexus of Auerbach)
2. **Submucous plexus** (the plexus of Meissner).

Neurotransmitters

	Location	NT
Preganglionic		Ach
Postganglionic	**a. Parasympathetic**	Ach
	b. Sympathetic	NE & few locations Ach

Receptors

	Type	
Parasympathetic	N	Excitatory
	M	Excitatory or Inhibitory
Sympathetic	Alpha	Excitatory
	Beta	Excitatory or Inhibitory

Figure 6–1

Parasympathetic	Cardiac and smooth muscle, gland cells, nerve terminals	Ach/M
Sympathetic	Sweat glands	Ach, M
Sympathetic	Cardiac and smooth muscle, gland cells, nerve terminals	NE, α, β
Sympathetic	Renal vascular smooth muscle	NE, D/α, D1
Somatic	Skeletal muscle	Ach, N

TABLE 6–1

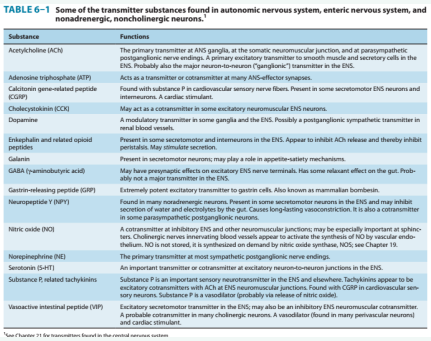

TABLE 6–1 Some of the transmitter substances found in autonomic nervous system, enteric nervous system, and nonadrenergic, noncholinergic neurons.[1]

Substance	Functions
Acetylcholine (ACh)	The primary transmitter at ANS ganglia, at the somatic neuromuscular junction, and at parasympathetic postganglionic nerve endings. A primary excitatory transmitter to smooth muscle and secretory cells in the ENS. Probably also the major neuron-to-neuron ("ganglionic") transmitter in the ENS.
Adenosine triphosphate (ATP)	Acts as a transmitter or cotransmitter at many ANS-effector synapses.
Calcitonin gene-related peptide (CGRP)	Found with substance P in cardiovascular sensory nerve fibers. Present in some secretomotor ENS neurons and interneurons. A cardiac stimulant.
Cholecystokinin (CCK)	May act as a cotransmitter in some excitatory neuromuscular ENS neurons.
Dopamine	A modulatory transmitter in some ganglia and the ENS. Possibly a postganglionic sympathetic transmitter in renal blood vessels.
Enkephalin and related opioid peptides	Present in some secretomotor and interneurons in the ENS. Appear to inhibit ACh release and thereby inhibit peristalsis. May stimulate secretion.
Galanin	Present in secretomotor neurons; may play a role in appetite–satiety mechanisms.
GABA (γ-aminobutyric acid)	May have presynaptic effects on excitatory ENS nerve terminals. Has some relaxant effect on the gut. Probably not a major transmitter in the ENS.
Gastrin-releasing peptide (GRP)	Extremely potent excitatory transmitter to gastrin cells. Also known as mammalian bombesin.
Neuropeptide Y (NPY)	Found in many noradrenergic neurons. Present in some secretomotor neurons in the ENS and may inhibit secretion of water and electrolytes by the gut. Causes long-lasting vasoconstriction. It is also a cotransmitter in some parasympathetic postganglionic neurons.
Nitric oxide (NO)	A cotransmitter at inhibitory ENS and other neuromuscular junctions; may be especially important at sphincters. Cholinergic nerves innervating blood vessels appear to activate the synthesis of NO by vascular endothelium. NO is not stored, it is synthesized on demand by nitric oxide synthase, NOS; see Chapter 19.
Norepinephrine (NE)	The primary transmitter at most sympathetic postganglionic nerve endings.
Serotonin (5-HT)	An important transmitter or cotransmitter at excitatory neuron-to-neuron junctions in the ENS.
Substance P, related tachykinins	Substance P is an important sensory neurotransmitter in the ENS and elsewhere. Tachykinins appear to be excitatory cotransmitters with ACh at ENS neuromuscular junctions. Found with CGRP in cardiovascular sensory neurons. Substance P is a vasodilator (probably via release of nitric oxide).
Vasoactive intestinal peptide (VIP)	Excitatory secretomotor transmitter in the ENS; may also be an inhibitory ENS neuromuscular cotransmitter. A probable cotransmitter in many cholinergic neurons. A vasodilator (found in many perivascular neurons) and cardiac stimulant.

[1]See Chapter 21 for transmitters found in the central nervous system.

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TABLE 6–1 (cont)	
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CHOLINERGIC TRANSMISSION	
STEP 1: Synthesized by Choline Acetyltransferase (ChAT)	-Acetyl-CoA synthesized in *mitochondria*
	Choline transported into the neuron
	Blocked by **hemicholinium** *(blocks uptake of choline)*
----	----

CHOLINERGIC TRANSMISSION (cont)

STEP 2: Ach transported into SMALL CLEAR VESICLES	Transporter can be blocked by **vesamicol** *(prevents storage or depletes transmitter storage)*
----	----
STEP 3: Release of transmitter is Calcium-d-ependent	-triggered by action potentials
	-ACh release blocked by **botulinum toxin**
----	----
STEP 4: ACh binds to receptors	(cholinoceptors)
----	----
STEP 5: Catabolized by acetylcholinesterase (AChE)	-breaks *ACh* into **choline and acetate**
	terminate action of transmitter
	half-life of ACh is very short
	AChE in other tissues (eg. **RBC**)
	Butyrylcholinesterase (pseudo-)
----	----

ChAT and AChE used during synthesis and degradation of ACh.

5 KEY FEATURES OF NEUROTRANSMITTER FUNCTION

1. **Synthesis**
2. **Storage**
3. **Release**
4. **Termination Of Action Of The Transmitter**
5. **Receptor Effects**

Acetylcholine Synthesis

1. **ACh** made from choline + acetyl CoA
2. In synaptic cleft, ACh is rapidly broken down by enzyme **Acetyl-cholinesterase**
3. **Choline** is transported back into axon terminal and used to make more ACh.

STEPS in ADRENERGIC TRANSMISSION

STEP 1	Synthesis of catecholamines **(Dopamine, NE)**
STEP 2	Uptake into storage vesicle
STEP 3	Release of NT
STEP 4	Binding to receptor
STEP 5/6	Degradation of **NE**

Termination of NORADRENERGIC TRANSMISSION

1. **Simple diffusion away from receptor site** (with eventual metabolism in plasma or liver
2. **Reuptake into the nerve terminals by NET** or into perisynaptic glia or other cells

BIOSYNTHESIS OF CATECHOLAMINES

1. **Tyrosine** convert to **DOPA** by **Tyrosine hydroxylase**	can be inhibited by *metyrosine* (a tyrosine analog)
2. **DOPA** convert to **Dopamine** by **Dopa decarboxylase**	-
3. **Dopamine** convert to **NE** by **Dopamine-β-hydroxylase**	In most sympathetic postgangl-ionic neurons, NE is the **final product**)
4. **NE** convert to **Epinephrine** by **Phenylethanolamine-N-methyltra-nsferase**	*Methylated form*
~	

Additional

a. **Tyrosine** metabolized by *L-Amino acid decarboxylase* to form **TYRAMINE** (the product of metabolism of tyrosine).

b. **Tyramine** metabolized by *Dopamine-β-hydroxylase* to **Octopamine**

c. **Octopamine** metabolized by *hydroxylase (from the liver)* to form **NE**

WAYS OF STOPPING NEUROTRANSMITTER

1. **DIFFUSION**	-
2. **DEGRADATION**	metabolic enzyme process (eg. AChE metabolize ACh)
3. **REUPTAKE**	into the noradrenergic neuron/ adrenergic neuron

NT CHEMISTRY OF THE ANS

CHOLINERGIC FIBERS	NORADRENERGIC (ADRENERGIC) FIBERS
releasing Ach (Acetylcholine)	release Norepinephrine (NE)/ Noradrenaline

AUTONOMIC RECEPTOR (NT, R)

PARASYMPATHETIC	SYMPATHETIC
NT: **ACh** *(Cholinoceptors)*	NT: **NE** *(Adrenoceptors)*
R=**N/M**	R= **α,β, D**
Nicotinic receptors= **NN/NM**	α= **1/2**
Muscarinic receptors= **M1 to M5**	β= **1-3**
	D= **(D1-D5)**

AUTONOMIC RECEPTOR

Alkaloids *Muscarine* and *Nicotine*

The **sensory fibers in the nonadrenergic, noncholinergic systems** are probably better termed *"sensory-efferent"* or *"sensorylocal effector"* fibers because, **when activated by a sensory input*, they are capable of** releasing transmitter peptides from the sensory ending itself**, from local axon branches, and from collaterals that terminate in the autonomic ganglia.

These peptides are **potent agonists** in many *autonomic effector tissues.*

METABOLISM OF CATECHOLAMINES by COMT & MAO

Catecholamines	COMT/MAO	Product 1	COMT/MAO	Product 2
EPINEPHRINE	=MAO	Dihydroxy-mandelic acid	COMT	3-Methoxy-4-hydroxymandelic acid (VMA)
	=COMT	Metanephrine	MAO	3-Methoxy-4-hydroxymandelic acid (VMA)

METABOLISM OF CATECHOLAMINES by COMT & MAO (cont)

NE	=MAO	Dihydroxy-mandelic acid	COMT	3-Methoxy-4--hydroxymandelic acid (VMA)
	=COMT	Normetanephrine	MAO	3-Methoxy-4--hydroxymandelic acid (VMA)
DOPAMINE	=MAO	Dihydroxy-phenylacetic acid	COMT	Homovanillic acid
	=COMT	3-Methoxytyramine	MAO	Homovanillic acid

Read

Read Katzung CH. 6 (P.99) **TABLE 6-2 Major autonomic receptor types**

FUNCTIONAL ORGANIZATION OF AUTONOMIC ACTIVITY

A. Integration of Cardiovascular Function

Mean arterial pressure	the primary controlled variable in cardiovascular function
	-changes in any variable contributing to mean arterial pressure (eg, a drug-induced increase in peripheral vascular resistance) evoke powerful homeostatic secondary responses
Homeostatic response	may be sufficient to reduce the change in mean arterial pressure and to reverse the drug's effects on heart rate.

Example: **Slow infusion of NE**

Increased baroreceptor activity causes the *decreased central sympathetic outflow* and *increased vagal outflow.*

Net effect of ordinary pressor doses of norepinephrine in a normal subject is to produce a **marked increase** in *peripheral vascular resistance.*
An increase in mean arterial pressure, and often, a *slowing of heart rate.*

NEGATIVE FEEDBACK RESPONSE is present.

B. Presynaptic Regulation

Autoreceptors	*Presynaptic receptors* that respond to the primary transmitter substance released by the nerve ending
	usually inhibitory, but in addition to the excitatory β receptors on noradrenergic fibers, many cholinergic fibers, especially somatic motor fibers, have excitatory nicotinic autoreceptors.
Heteroreceptors	*respond to many other substances*
	activated by substances released from other nerve terminals that synapse with the nerve ending.

Principle of **negative feedback control** is also found at the presynaptic level of autonomic function.

-have been shown to exist at **most nerve endings**

C. Postsynaptic Regulation

Can be considered from two perspectives:	1. **Modulation by previous activity at the primary receptor**
	2. **Modulation by other simultaneous events.**
--	
FIRST MECHANISM	**Up-regulation and down-regulation** are known to *occur in response to decreased or increased activation*, respectively, **of the receptors.**
	Extreme form of up-regulation *occurs after denervation of some tissues, resulting in* *denervation supersensitivity of the tissue** to activators of that receptor type.

C. Postsynaptic Regulation (cont)

	ex: **Nicotinic receptors are normally restricted to the end plate regions underlying somatic motor nerve terminals.**
	ex: **Prolonged administration of large doses of reserpine,** a norepinephrine depleter, can cause increased sensitivity of the smooth muscle and cardiac muscle effector cells
SECOND MECHANISM	**Involves modulation of the primary transmitter-receptor event** by events evoked by the same or other transmitters acting on different postsynaptic receptors.
	ex: **Ganglionic transmission**

Postganglionic cells are activated (depolarized) due to *binding of an appropriate ligand to a neuronal nicotinic (NN) acetylcholine receptor.*

Resulting:
a. Fast excitatory postsynaptic potential (EPSP) evokes a propagated action potential if *threshold is reached.*

Continued

-	-

b. Often followed by a small and slowly developing **but longer-lasting hyperpolarizing afterpotential—a** slow inhibitory postsynaptic potential (IPSP).**

1. **Hyperpolarization involves opening of potassium channels by M2 cholinoceptors.**

2. **Small, slow excitatory postsynaptic potential caused by closure of potassium channels linked to M1 cholinoceptors.**

3. **Late, very slow EPSP may be evoked by peptides released from other fibers.**