AUTONOMIC NERVOUS SYSTEM I & II

Date: August 22, 2011 – 9:30 &10:30 AM
Suggested Reading Assignment: Mason (2011), *Medical Neurobiology*, Chapter 27.

KEY CONCEPTS & LEARNING OBJECTIVES

1. The autonomic nervous system is composed of the sympathetic and parasympathetic systems. Some also categorize the enteric system as part of the autonomic nervous system. All the systems are characterized by their ability to produce involuntary efferent motor responses. Know the distinguishing characteristics of the sympathetic and parasympathetic systems in regard to the following parameters:

    - *the main neurotransmitter released from pre and post-ganglionic neurons and the types of post-synaptic potentials that can be generated by each*

    - *the characteristics of the autonomic neuro-effector junction and how this influences the response to activation of the autonomic system*

2. The sympathetic system, better known as the fight or flight system, stimulates responses that help the body cope with perturbations in the environment or in the body itself. Pre-ganglionic fibers originate from the cervical, thoracic and upper lumber spinal segments and course through very different pathways to find their target ganglion. There is also considerable anatomical variability. For instance some adjoining ganglia are fused in some individuals, but remain separate in others. The sympathetic pre-ganglionic fibers can synapse in either of two different types of ganglia that are differentiated by their location and their general target. The paravertebral ganglia run parallel to the spinal segments on both sides of the spinal cord and innervate targets in the skin and muscle as well as the head and neck. The prevertebral (or aortic) ganglia are located on the anterior side of the aorta and innervate the visceral organs. For the following ganglia, know the origin (spinal segments) of the pre-ganglionic fibers that innervate them, the major target organs they innervate and the response of the target organ when the specific ganglion is stimulated.

    Superior cervical ganglion
    Middle cervical ganglion
    Stellate ganglion
    Celiac ganglion
    Superior mesenteric ganglion
    Inferior mesenteric ganglion

3. Likewise, for the following organs and target tissue, know the sympathetic ganglia that innervate them and the approximate spinal cord levels that contribute to their sympathetic-mediated response.

    Tarsal muscle
    Iris muscle
    Salivary gland
    Lungs
    Heart
    Stomach and Small Intestines
    Spleen
    Liver and pancreas
    Adrenal medulla
    Colon
    Head and neck sweat glands and blood vessels
    Gland and blood vessels of the upper extremity and chest
    Sweat glands and blood vessels of the lower chest and abdomen
    Sweat glands and blood vessels of the lower extremities

With this knowledge you should be able to predict how a lesion that encompasses a particular spinal segment could contribute to specific deficits in the autonomic control of organ function

4. The sympathetic pre-ganglionic fibers emerge from the ventral roots of spinal segments C8-L2. To reach anatomical targets located higher (e.g., the eye) or lower (e.g., the leg) the fibers must pass into the upper or lower most ganglia associated with their spinal segment and ascend or descend through the chain ganglia to synapse with their target. The chain ganglia extend superior to C8 and inferior to L2. Therefore, pre-ganglionic cells originating in the spinal cord that target ganglia with projections to the head, for instance, pass through C8-T1 or T2 and ascend to more rostral ganglia, i.e., the middle or superior cervical ganglia. Know the <u>distinguishing characteristics</u> of the route of pre and post-ganglionic sympathetic innervation of the following targets:

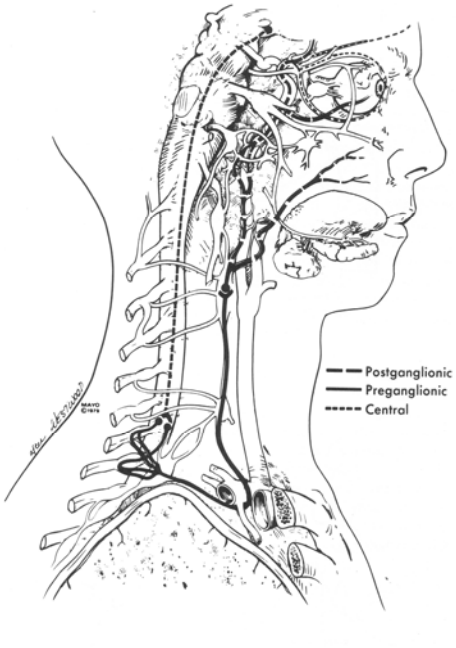
    Skin and muscle
    Thoracic viscera
    Abdominal viscera and genitalia
    Adrenal medulla
    Lower extremities
    Head and neck
        Upper parts of arm and shoulder
        Lower neck
        Upper neck, head and eye

5. Parasympathetic pre-ganglionic fibers originate from nuclei in the brain stem and sacral segments of the spinal column. For the following parasympathetic cell bodies that give rise to pre-ganglionic sympathetic fibers, know the ganglia they innervate, the effector

organ innervated by their associated ganglia and the effector response of the organ elicited by ganglion stimulation.

Edinger-Westphal nucleus
Lacrimal nucleus
Superior salivatory nucleus
Inferior salivatory nucleus
Dorsal motor nucleus
Nucleus ambiguous
Intermedial spinal gray of S2-S4

6. The head and neck region receives innervation through the stellate, middle and superior cervical ganglia as pictured below.



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a. Identify the stellate, middle and superior cervical ganglia in the picture to the left.

b. Recognize the pathways and projection targets of the pre and post-ganglionic neurons pictured (neurons in black).

7. The origin of pre-ganglionic parasympathetic neurons and their respective targets are shown in the cartoon below.

Drawn by Dr. Robert Wurster

Recognize the nuclei depicted in the drawing and their approximate location as well as their target projections within the parasympathetic system. Predict how lesions in the parasympathetic nuclei will affect the function of the following target organs

Heart
Genitalia
Bladder
Eye

8. Sympathetic reflex activation can be initiated by sensory stimuli that reach spinal or supraspinal regions. If the sympathetic reflex is initiated by a local spinal circuit, the response tends to be limited to the ipsilateral side of the stimulus and may affect limited neighboring spinal segments. Sympathetic reflex activation by sensory afferents that reach supraspinal pathways is typically larger and more diffuse than that elicited by local spinal circuits. Understand how autonomic reflexes are involved in the following clinical findings:

    a. *hypertensive crisis from bladder distension in individuals with a chronic relatively high and compelte thoracic spinal cord lesion.*
    b. *sweating of the skin*
    c. *syncope during standing in patients with chronic peripheral neuropathy of the autonomic nerves*

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General Properties of the autonomic nervous system:

- Involuntary efferent motor system.
- Provides efferent innervation to smooth muscle, cardiac muscle, gland cells, fat cells and immune cells
- Autonomic nerves also contain afferent nerve fibers, e.g. vagus nerve contains 90% afferents

Divisions of the autonomic nervous system:

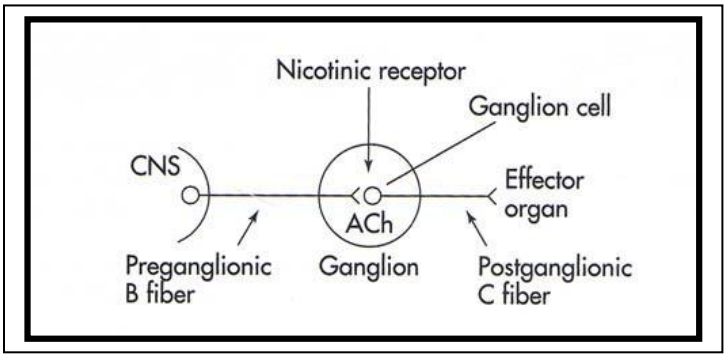
Sympathetic (thoracolumber). Also known as "fight or flight" system regulates responses to environmental stimuli that require action, regulates homeostasis of blood pressure.

Parasympathetic (craniosacral). "Rest and digest". Predominates in healthy individuals at rest.

Enteric. Regulates GI activity including peristalsis and appropriate secretions, innervated by sympathetic and parasympathetic systems but can work independently.

Basic Unit of sympathetic and parasympathetic system

Pre-ganglionic fiber- originates in CNS but travels out to the periphery to innervate target (ganglion), **releases acetylcholine**, thinly myelinated axons called B fibers have an intermediate speed of conduction (3-14 m/sec).



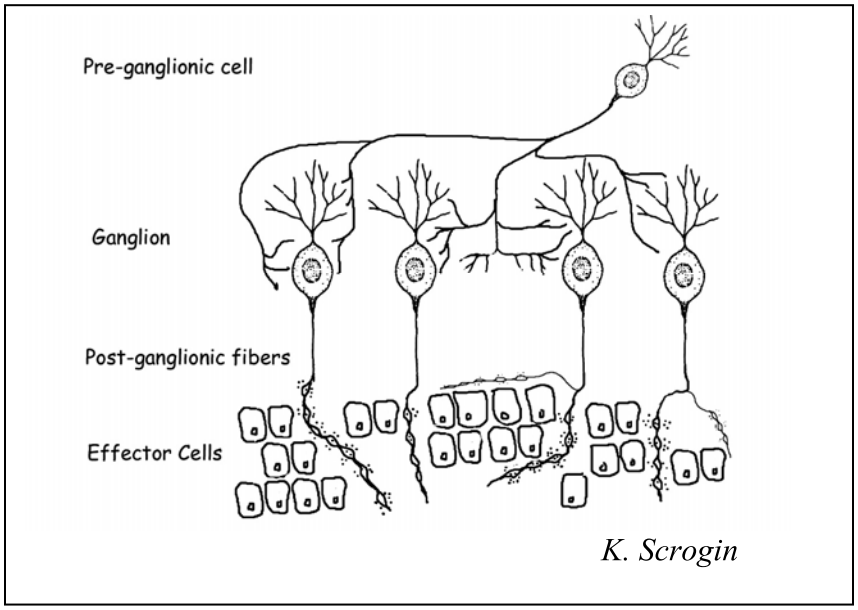
Ganglion - collection of post-ganglionic cell bodies that **receive input from pre-ganglionic fibers** and other input from outside the sympathetic system, expresses multiple receptor subtypes that are sensitive to various

neurotransmitters released by pre-ganglionic cells (e.g., acetylcholine). Main receptor that conveys sympathetic information is nicotinic (Nn) receptor.

Post-ganglionic fibers- project to effector targets. **Sympathetic cells release primarily norepinephrine (NE)**, the **exception is eccrine sweat glands that release acetylcholine** as their major neurotransmitter. **Parasympathetic neurons release primarily acetylcholine.** Post-ganglionic axons are unmyelinated C fibers with a relatively slow speed of conduction (<2 m/sec).

Synapses-

Ganglionic cells express multiple receptor subtypes, the nicotinic receptor mediates the majority of excitatory neurotransmission between pre and post-ganglionic cells. The ratio of post-ganglionic to pre-ganglionic cells varies greatly from 2:1 up to 100:1. This great **divergence** leads to a wide spread diffuse response.

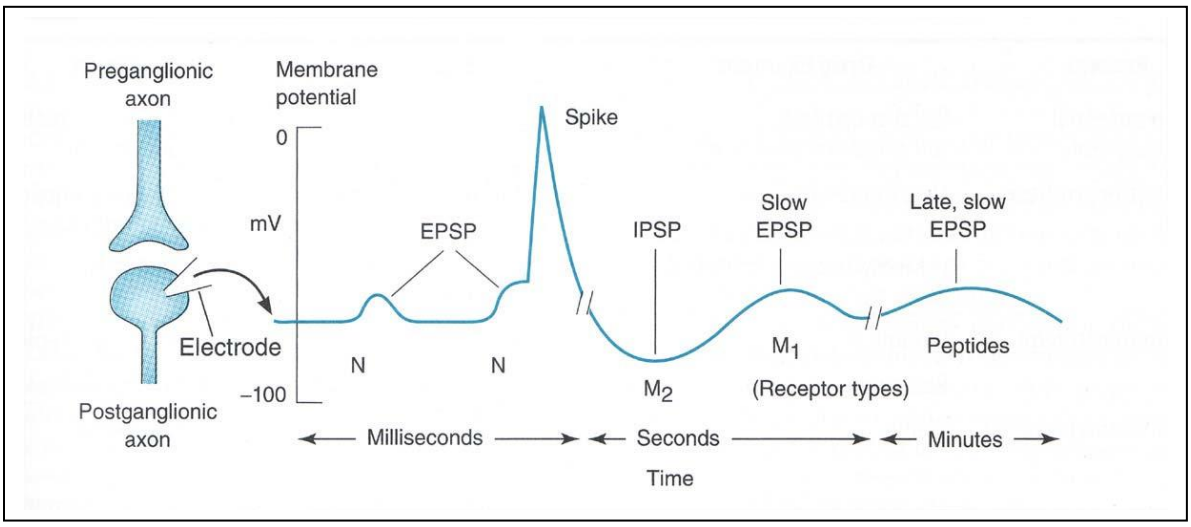


Ganglion cells receive input from many different pre-ganglionic fibers (**convergence**).

Autonomic ganglia mediate some **reflexes without the CNS** (e.g.,intestino-intestinal reflex), i.e., they receive input from ascending sensory fibers that influence their activity. For example stretch of the intestine stimulates ascending afferents that send collaterals to synapse on sympathetic ganglia innervating the gut. Stretch causes excitation of the sympathetic ganglia that then leads to inhibition of intestinal activity.

Numerous receptors govern post-synaptic potentials e.g., muscarinic receptors that mediate multiple post-synaptic potentials. Ganglion cells may require **spatial and temporal summation** to generate an action potential.

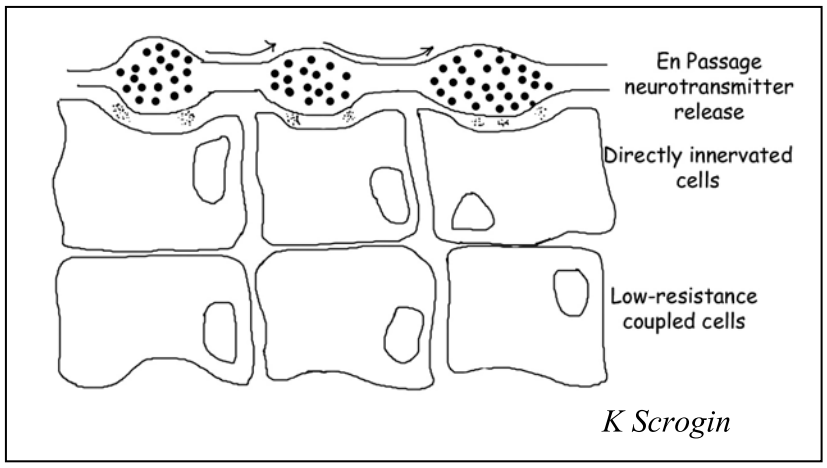
Post-Synaptic potentials



When activated, various receptors expressed by ganglion cells mediate changes in post-synaptic membrane potential in response to changes in ion conductance. **Ligand-gated ion channels such as the nicotinic receptor produce very fast changes in membrane potential** that, when summed with other changes in post-synaptic membrane potential from other sources, can generate an action potential. Prior activation by G-protein coupled muscarinic receptors can influence responses to nicotinic receptor activation through their ability to produce inhibitory post-synaptic potentials (IPSPs) and excitatory post-synaptic potentials (EPSPs). Peptides produce slow EPSPs, which can also influence the ability of subsequent post-synaptic events to generate an action potential. The prevailing membrane potential can influence whether activation of a nicotinic receptor will lead to generation of an action potential.

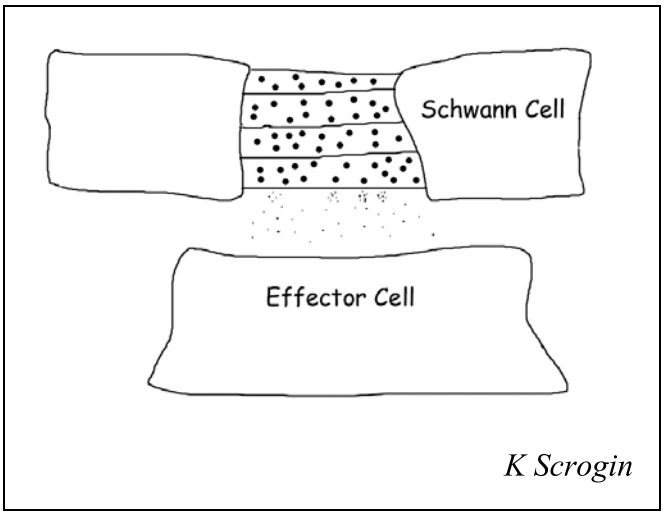
Neuroeffector Junction

The neuroeffector junction of the autonomic system is quite different from the neuromuscular junction of skeletal muscle. The junction has **no post-junctional specialization** and neurotransmitter released from the synapse must pass by diffusion sometimes long-distances to reach an effector cell.

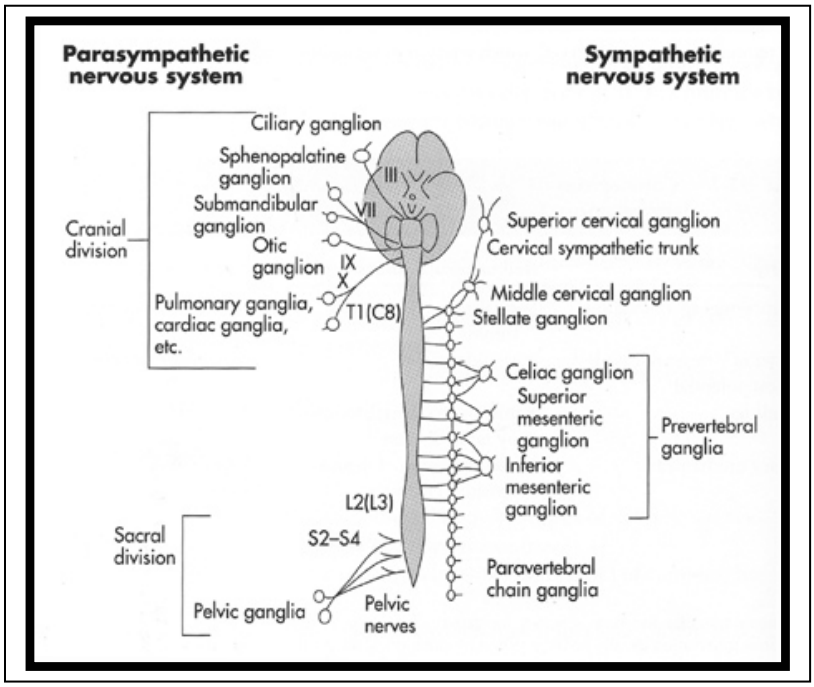


Two types of terminal innervation have been identified. The first involves neurotransmitter release from **varicosities** present along the length of the nerve axon. SNARE proteins involved in vesicular release are present in the varicosities. In some cases the varicosities lie in close proximity to the effector cell and neurotransmitter does not traverse a significant distance to find a receptor. Effector cells may be organized in a nexus such that transmitter interacts directly with surface cells which are coupled by gap junctions to underlying cells. Thus, the neurotransmitter has indirect effects on these underlying cells via electronic coupling with the surface cells. The underlying cells are said to be "indirectly coupled". Thus **diffuse innervation** can lead to wide spread activation of a field of cells. The neurotransmitter release is stimulated in a similar manner as the classical neurotransmission first described in the skeletal muscle neuromuscular junction except that synapses are arranged in series along the length of the axon terminal. The neurotransmitter is said to be released **en passage** as the depolarization is propagated along the length of the axon to more distal varicosities.

In other types of autonomic innervation, axons are bundled together in **Remak bundles** by **unmyelinated Schwann cells** which interdigitate between individual axons. The Schwann cell covering is lost at the terminal varicosities exposing regions where neurotransmitter can be released. In this configuration, the effector cell is typically much farther away from the axon. The neurotransmitter release is concentrated however, which may facilitate the generation of a junctional potential in the effector cell.



Overview of the Autonomic Nervous system Anatomy



Pre-ganglionic fibers of the autonomic nerves originate from the brainstem and segments of the spinal cord. Pre-ganglionic fibers of the parasympathetic system that innervate all but the lower most parts of the body originate from the brainstem and travel to their respective ganglia via the cranial nerves. Pre-ganglionic fibers of the parasympathetic nervous system that innervate the lower pelvic region originate from sacral spinal segments.

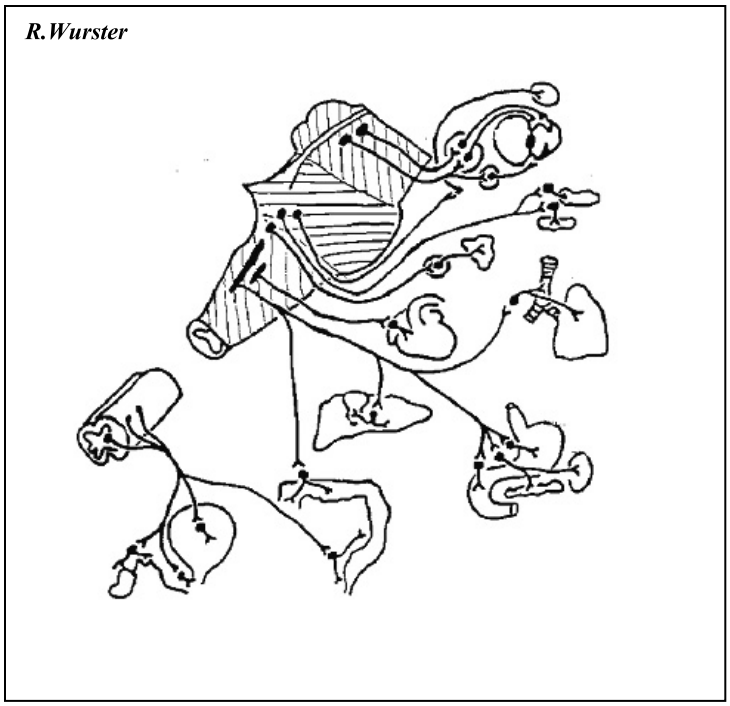
Sympathetic pre-ganglionic fibers originate from spinal segments T1 (C8) through L2 (L3). They travel through the dorsal root to reach the spinal nerve and eventually synapse with their target in either paravertebral or pre-vertebral ganglia or the adrenal medulla.

Comparison of Autonomic and Neuromuscular Terminal Innervation

Property	Neuromuscular Junction	Autonomic Junction
Post-junctional specialization	Specialized Junctional Folds	No obvious specialization
# of vesicles released/AP	150-200 vesicles	1-2 vesicles
Transmitter Release	Rapid, large increase followed by rapid decline	Low, gradual change related to frequency
Receptor Mechanism	Direct activation of ligand-sensitive channels	Slow activation of G-protein coupled receptors

The Parasympathetic Nervous System

Two main divisions- cranial and sacral. Pre-ganglionic cells originate in the brain stem or sacral spinal cord. Ganglion cells are relatively close to effector organ compared to the sympathetic system. This system provides more specific innervation to specific effector organs. **The main neurotransmitter released from pre- and post-ganglion cells is acetylcholine, which acts on nicotinic receptors of post-ganglionic fibers and muscarinic receptors of the effector organs.**



Parasympathetic innervation of Effector Organs.
The figure below indicates the innervation of the major effector organs targeted by the parasympathetic system. Recognize the names of the central nervous system cell bodies (nuclei) that give rise to the pre-ganglionic fibers, the name of the nerves they travel through to get to their post-ganglionic target, the name of the ganglia, the end effector organ and the effect that is produced when the organ is activated by the parasympathetic system.

Neurotransmitters released by the parasympathetic system

The most significant neurotransmitter released from post-ganglionic parasympathetic nerves is **acetylcholine** which acts on muscarinic receptors to mediate end organ responses. Five main muscarinic receptor subtypes have been identified, 3 of which are known to mediate specific functions.

M_1 predominantly couples to the Gq/G11 alpha subunit of the heterotrimeric G-proteins to activate inositoltrisphosphate (IP3) and diacylglyceride (DAG). M_1 receptors are the predominant muscarinic receptor in the myenteric plexus and mediate smooth muscle contraction of the gut.

M_2 receptors are expressed in the **sinoatrial node** and **atrioventricular node** of the cardiac conduction system. They are also G-protein coupled receptors that **activate K+ channels** leading to hyperpolarization of excitable cells and **delayed action**

potential generation (in the SA node) or delayed propagation of an action potential (AV node).

M_3 receptors also couple to Gq/G11 alpha proteins leading to IP3 and DAG formation and subsequent increases in calcium. These receptors are expressed in ciliary muscles of eye to **promote pupillary constriction and near-vision accommodation**. They are also expressed in **bronchiole smooth muscle where they promote constriction**. In endothelial cells lining vascular smooth muscle, increased intracellular calcium **activates nitric oxide synthase** leading to NO production, cGMP activation and **relaxation of adjacent vascular smooth muscle**. M_3 receptor activation also **generates fluids of the digestive system and secretions of the eccrine sweat gland** (the latter is a sympathetic response mediated by acetylcholine).

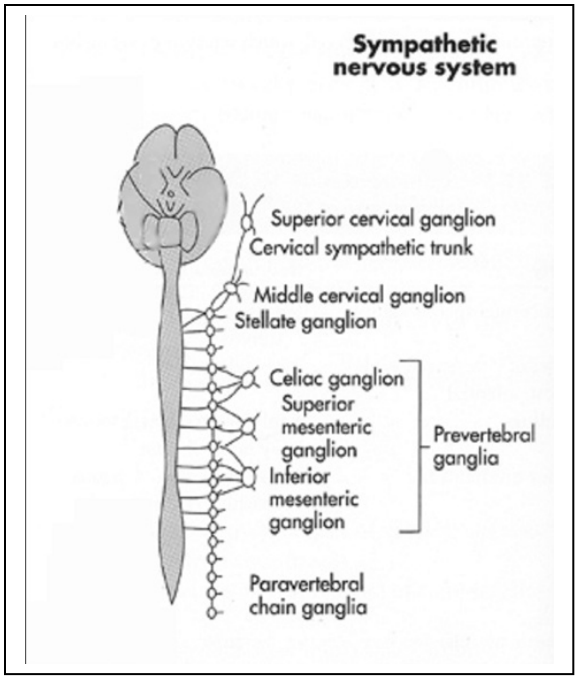
Additional neurotransmitters released from parasympathetic nervous system

Adenosine triphosphate (ATP) is a nucleotide neurotransmitter that co-localizes with acetycholine in post-ganglionic parasympathetic nerves. It mediates its actions through purinergic P2X ionotropic receptors which innervate the smooth muscle of the bladder detrusor muscle to cause contraction. Initial fast responses of the bladder to parasympathetic activation are mediated via ATP-sensitive, ligand-gated ion channels that are permeable to calcium and sodium. These currents mediate the more rapid contractile effects that are then followed by the slower muscarinic effects of acetylcholine.

Vasoactive intestinal peptide (VIP), first identified in neurons of the enteric nervous system, is also co-localized in a subset of parasympathetic neurons that innervate glands (e.g., pancreas) and blood vessels of the gut to **promote neural-mediated secretions and vasodilation**.

Nitric oxide (NO) is a gaseous neurotransmitter that is difficult to detect. NO is present in pre-ganglionic cells of both the sympathetic and parasympathetic system but only in the post-ganglionic cells of the parasympathetic system. In these cells it is commonly co-localized with VIP and acetylcholine. NO is prominent in the cardiovascular, urogenital, respiratory and gastrointestinal systems. It **promotes vasodilation** through activation of guanalyl cyclase and cGMP production. It is the main neurotransmitter responsible for **parasympathetic-dependent penile erection**. NO is also involved in parasympathetic mediated **vasodilation of cerebral vessels**. In the enteric nervous system it is important in **smooth muscle relaxation, particularly in sphincteric regions**. Reduced NO neurotransmission is implicated in impotence among diabetics, as well as in pyloric stenosis and other GI disorders associated with excessive smooth muscle constriction.

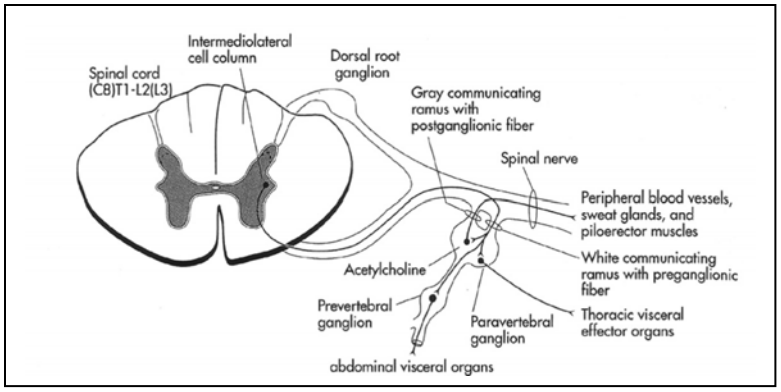
Sympathetic Nervous System



Post-ganglionic sympathetic fibers that originate in the **paravertebral** ganglia innervate targets of the **body wall**, e.g., vessels and sweat glands of the skin. The paravertebral ganglia run in two chains parallel to the spinal cord

Post-ganglionic sympathetic fibers that originate from **prevertebral** ganglia innervate **visceral organs.** These ganglia are situated on the ventral surface of the aorta. Pre-ganglionic fibers that synapse in the prevertebral ganglia course through the paravertebral ganglia before reaching their target.

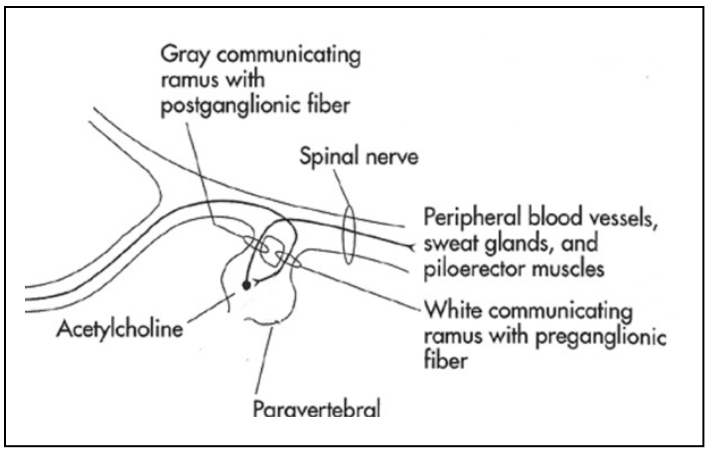
General scheme of sympathetic innervation



of Pre-ganglionic fibers emerge from the intermediolateral cell column of spinal segments T1 - L2. Some individuals vary and may have sympathetic nerves emanating from C8 or L3. The axons of the cells course through the ventral horn and join with the spinal nerve associated with the particular spinal segment from which the pre-ganglionic fiber emerges. The fiber courses into the distal white communicating ramus, so called because of the light myelination of the fibers. The fiber enters the paravertebral ganglion and either forms synapses near post-ganglionic fibers at that spinal level, travels up or down the sympathetic chain to another paravertebral ganglion to form synapses, or passes through the ganglion to other pre-vertebral ganglia without forming synapses. **Post-ganglionic fibers that originate in the paravertebral ganglia then travel through the more medial gray communicating ramus and back out toward the body wall** via the spinal nerve to innervate peripheral blood vessels, sweat gland and piloerrector muscles of the

Sympathetic Nervous System

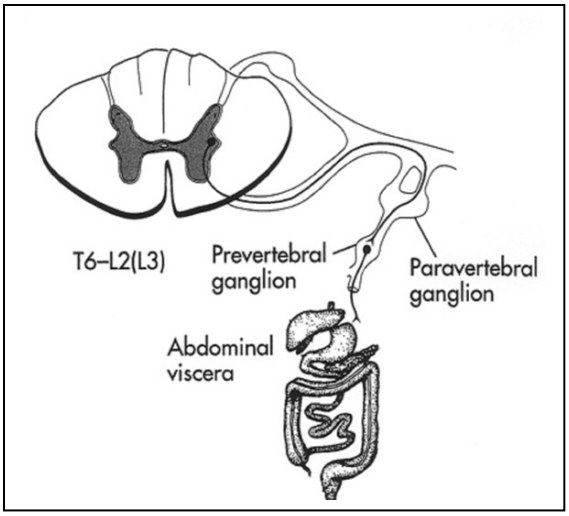
- Pre-ganglionic cell bodies in T1(C8) to L2(L3) spinal cord
- Two types of ganglia- paravertebral and prevertebral
- Short pre-ganglionic fibers and relatively long post-ganglionic fibers
- Differential control of different effector organs - normal conditions
- Mass excitation of different organs- extreme conditions



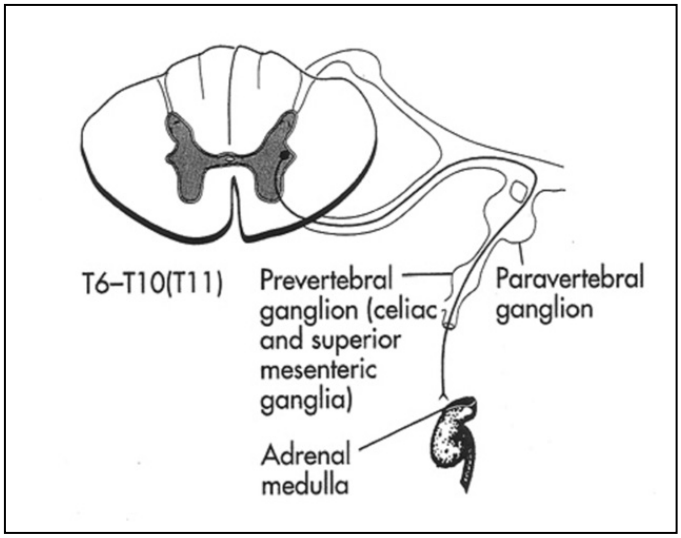
body wall. Pre-ganglionic cells that pass through the paravertebral ganglion course through various nerves to achieve their target in the pre-vertebral ganglia located on the anterior surface of the aorta. The **post-ganglionic cells that emerge from the prevertebral ganglion go on to innervate their target visceral organs.**

Innervation trajectories of specific targets

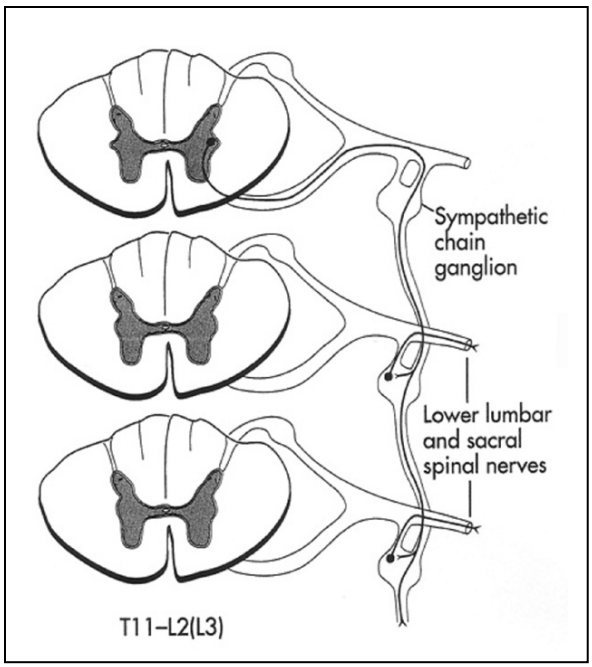
Sympathetic pre-ganglionic nerves that target the body wall emerge from their spinal segment of origin into the spinal nerve where they then either form synapses near post-ganglionic fibers within the associated paravertebral ganglion or travel rostrally or caudally to form synapses near post-ganglionic fibers in alternative paravertebral ganglia. One pre-ganglionic fiber can form synapses near several different post-ganglionic fibers at multiple levels. Very rarely do the axons split and go in both directions.



Sympathetic nerves that target the abdominal viscera emerge from multiple spinal levels. Their axons course through the associated paravertebral ganglia without forming synapses and project to one of the major pre-vertebral ganglia. They project through one of the major splanchnic nerves eventually forming synapses near post-ganglionic fibers located in one of the prevertebral ganglia. In this case, the fibers DO NOT course back into the spinal nerve via the gray communicating ramus but continue more anteriorly (ventrally) to find their target.

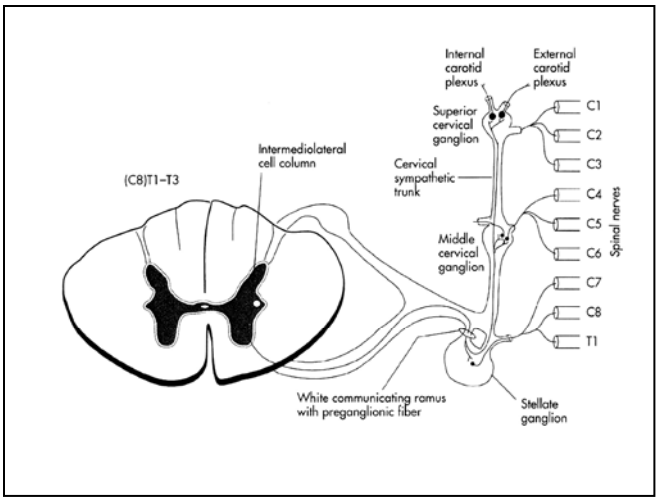


Sympathetic innervation of the adrenal gland is unique in that pre-ganglionic fibers do not form synapses in either paravertebral or pre-vertebral ganglia but course through both to reach their destination in the chromaffin cells of the adrenal medulla



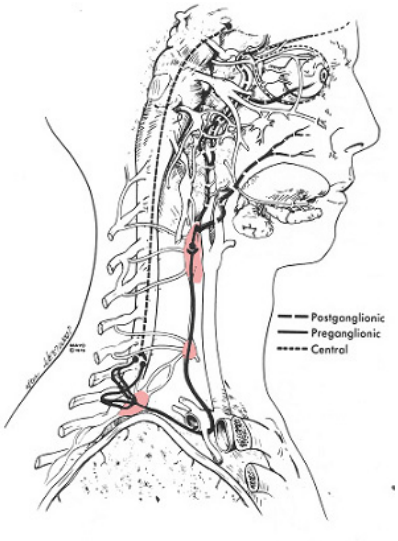
which are themselves modified post-ganglionic fibers that contain the enzymes necessary to produce epinephrine. Sympathetic activation of these fibers leads to release of epinephrine into the peripheral circulation.

Because sympathetic nerves do not emerge from spinal segments lower than L2 or L3, **sympathetic innervation of the lower extremities** requires that pre-ganglionic fibers from the lower lumbar segments enter the paravertebral chain and course caudally down to the lower paravertebral ganglia to form synapses near post-ganglionic fibers which then exit through the spinal nerve associated with the lower spinal segment lateral to the paravertebral ganglion which the fiber targets.



Similarly, **sympathetic pre-ganglionic nerves that innervate the head** emerge from the intermedolateral cell columns of T1-T2 and C8. In order to reach their more rostral synaptic connections they must either synapse in the associated paravertebral ganglion or pass through it to reach more rostral paravertebral ganglia closer to the effector organ target. Four prominent ganglia are associated with sympathetic innervation of the upper limbs, head and neck. **The stellate ganglion receives pre-ganglionic fibers that originate in C7,C8, T1 and T2 spinal segments. Ganglia associated with T1 and T2 often fuse with the inferior cervical ganglion to form the stellate ganglion**. However, in some individuals the stellate ganglion can be differentiated from **the inferior cervical ganglion** which itself is a**ssociated with spinal nerves emanating from C7 and C8**. **The middle cervical ganglion is associated with spinal nerves originating from cervical segments of C4, C5 and C6, while spinal nerves of C1, C2 and C3 connect to the superior cervical ganglion.** The **upper thoracic pre-ganglionic fibers synapse with post-ganglionic fibers in the stellate ganglion and middle cervical ganglia.** These fibers can, in turn, project through the vertebral nerve to C7 and C8 spinal nerves in order to reach their target in the upper arms and shoulders. **Post-ganglionic fibers in the middle cervical ganglion also project to**

C5 and C6 to reach the lower neck. Pre-ganglionic fibers of the upper thoracic segments can also project through the stellate and middle cervical ganglia to synapse on to post-ganglionic fibers in the **superior cervical ganglion**. **Post-ganglionic fibers in turn course along the internal and external carotid arteries to reach their targets in the upper neck head and eyes**. In the figure above, please note that the white ramus is shown medial to the gray ramus. This is done for clarity. The cervical ganglia have numerous fibers that emanate from them, not all of which travel to their destination through the spinal nerves.



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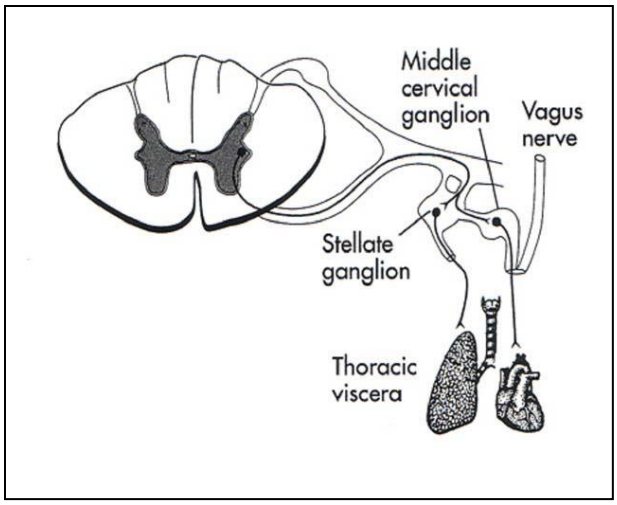
For instance **sympathetic innervation of the eye** originates from the upper thoracic pre-ganglionic fibers. These fibers must pass through the stellate ganglion and wrap around the aorta to reach the middle cervical ganglion. They continue through the middle cervical ganglion without forming synapses, but project further to the superior cervical ganglion where they form synapses near post-ganglionic fibers that innervate pupillary dilator muscles as well as the skin of the face, scalp and neck.

Sympathetic innervation of the thoracic viscera originate from the upper 5 or 6 thoracic spinal segments. Pre-ganglionic fibers synapse in various places including the thoracic paravertebral ganglia where they enter the rami communicans and pass upwards into the sympathetic trunk, these fibers then exit at various levels and form thoracic cardiopulmonary nerves that innervate the lung and heart. Some synapse in the stellate ganglion or ascend up to the middle cervical ganglion where they synapse with post-ganglionic fibers. Post-ganglionic fibers then form cervical cardiac nerves, which descend back into the thorax to innervate the heart. The figure to the right demonstrates a stylized picture, but there are numerous and varied pathways for innervation of the lungs and heart.



Sympathetic innervation of the target organs is topographically oriented such that rostral projection sites receive in put from pre-ganglionic fibers that arise from more rostral spinal segments. However, as mentioned before there is significant overlap and targets receive input from several different spinal segments. **Clinically it is important to recognize which spinal segments contribute to innervation of the target organs.** This can help the clinician diagnose the extent of spinal cord lesion or help anticipate what types of organ dysfunction that will result from spinal cord lesions at a specific site. The table to the right outlines the origin of pre-ganglionic fibers, their ganglion targets, the end organ target and the response of the end organ. Students should be prepared to identify functional deficits in autonomic function that could be expected from lesion at specific spinal cord levels, e.g., urinary incontinence can develop with spinal cord injury above T11 due to loss of tonic sympathetic control of bladder sphincter constriction.

TABLE 31-4 Sympathetic Innervation of Effector Organ

Organ	Preganglionic spinal level	Postganglionic cell	Effect
Tarsal muscle	C8-T1 to T2	Superior cervical ganglion	Eyelid elevation
Iris muscle	C8-T1 to T2	Superior cervical ganglion	Pupillary dilation
Salivary glands	C8-T1 to T2	Superior cervical ganglion	Thick salivation
Lungs	T1 to T5	Middle cervical and stellate ganglion	Bronchodilation and increased pulmonary vascular resistance
Heart	T1 to T5	Middle cervical and stellate ganglion	Increased heart rate, contraction, AV conductance, and cardiac output
Stomach and small intestines	T6 to T10	Celiac ganglion	Decreased motility, blood flow, and secretion
Spleen	T6 to T10	Celiac ganglion	Contraction and red blood cell release
Liver and pancreas	T6 to T10	Celiac ganglion	Increased blood glucose
Adrenal medulla	T6 to T10	None	Epinephrine release
Colon	T8 to L2	Superior and inferior mesenteric ganglion	Decreased motility, blood flow, and secretion
Urinary bladder and ureter	T11 to L2	Inferior mesenteric ganglion and hypogastric plexus	Inhibition of bladder ureter contraction and increased internal sphincter tone
Head and neck sweat glands and blood vessels	C8 to T3	Superior and middle cervical ganglion	Sweating and vasoconstriction
Glands and blood vessels of upper extremity and upper chest sweat glands	C8 to T5	Stellate ganglion and T2-T5 paravertebral ganglion	Sweating and vasoconstriction
Sweat glands and blood vessels of lower chest and abdomen	T6 to L2	T6 to L2 paravertebral ganglion	Sweating and vasoconstriction
Sweat glands and blood vessels of lower extremities	T10 to L2	L1 to S4 paravertebral ganglion	Sweating and vasoconstriction

Sympathetic Neurotransmitters include norepinephrine, acetylcholine, ATP, and neuropeptide Y, among others. **Norepinephrine is of course the major neurotransmitter of the sympathetic system.** Receptors sensitive to norepinephrine are known as "adrenergic receptors" There are 5 main classes including alph1-, alpha2-, beta1-, beta2- and beta3-adrenergic receptors. They have significant affinity for various endogenous neurotransmitters and hormones including norepinephrine, dopamine and epinephrine. They are all coupled to G-

Receptor type	Intracellular signal	Target and effect
Adrenergic Receptors		
Alpha-1	Increased IP3, DAG and $[Ca^{2+}]$, activates L type Ca^{2+} channels	Contracts smooth muscle of blood vessels (vasoconstriction and increases blood pressure), iris (radial muscles—pupillary dilation), GI sphincters, piloerection ("goose bumps"), uterus, and seminal vesicles (ejaculation) Inhibits myenteric plexus (decreases GI motility), activates apocrine sweat glands (emotional underarm sweating), increases liver glucose production
Alpha-2	Decreased cAMP	Inhibits sympathetic nerve terminal release of norepinephrine
Beta-1	Increased cAMP	Increases heart rate and force of contraction (increases cardiac output), increases renal renin release (leads to increased angiotensin and increased aldosterone production, increased renal NA^+ reabsorption, and increased blood pressure) Increased breakdown of fat cells (lipolysis) leading to increased fatty acid levels
Beta-2	Increased cAMP	Relaxes skeletal muscle blood vessels, bronchiolar muscle, uterine muscle, GI smooth muscle, and bladder detrusor muscle

proteins and so tend to have a slower onset of action due to the intervening activation of enzymes to achieve functional responses. In some cases, the G-proteins may be directly coupled to ion channels in which case, the functional response may be faster than classic G-protein coupled responses requiring a second messenger, but not quite as fast as responses to drugs that activate ligand-gated ion channels. The table above indicates the most well recognized coupling of each adrenergic receptor type, their target tissue and the response that is typically elicited by their activation. Beta3 receptors which are not indicated in the table are probably also coupled to Gαs proteins leading to increased cAMP. These receptors are expressed primarily in adipose tissue and are involved in lipolysis.

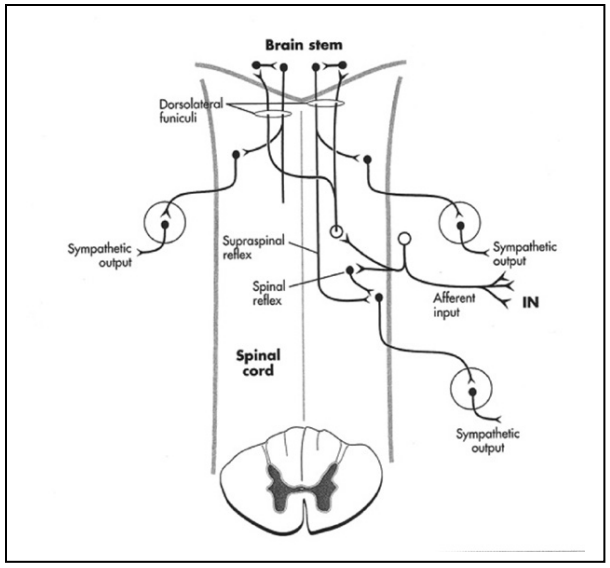
Acetylcholine is the main neurotransmitter **released by post-ganglionic sympathetic fibers that innervate eccrine sweat glands**, i.e., those sweat glands, located over the entire surface of the body, regulate temperature. They should not to be confused with apocrine sweat glands, which are the human scent glands of the axillary and groin regions.

Neuropeptide Y is a common co-transmitter found with norepinephrine in post-ganglionic sympathetic fibers that innervate vascular smooth muscle. The peptide is packaged in dense core vesicles that require more sustained activation of the neuron to dock and release their contents. The peptide binds to specific receptors termed Y1-Y6. NPY mediates vasoconstriction as well as inhibition of norepinephrine from the pre-synaptic nerve terminal. Vasoconstriction is mediated probably by activation of the Y1 receptor, which through an unknown mechanism leads to increased intracellular calcium.

ATP is packaged in synaptic vesicles with norepinephrine in post-ganglionic sympathetic fibers that innervate the peripheral vasculature. ATP binds to P2X purinergic receptors that are ligand-gated cation channels. The resulting increase in Na+ leads to depolarization of membranes and increased extracellular calcium influx into the vascular smooth muscle cell and consequently increased contraction. The response is very fast and produces the first phase of the vasoconstrictor response to sympathetic nerve stimulation. Norepinephrine produces the second phase, with its slower onset of action, while neuropeptide Y produces a slower, longer lasting constriction. The co-release of several different neurotransmitters means that the vasoconstrictor response to sympathetic stimulation is much different in intensity and duration than the response to a single vasoconstrictor agonist.

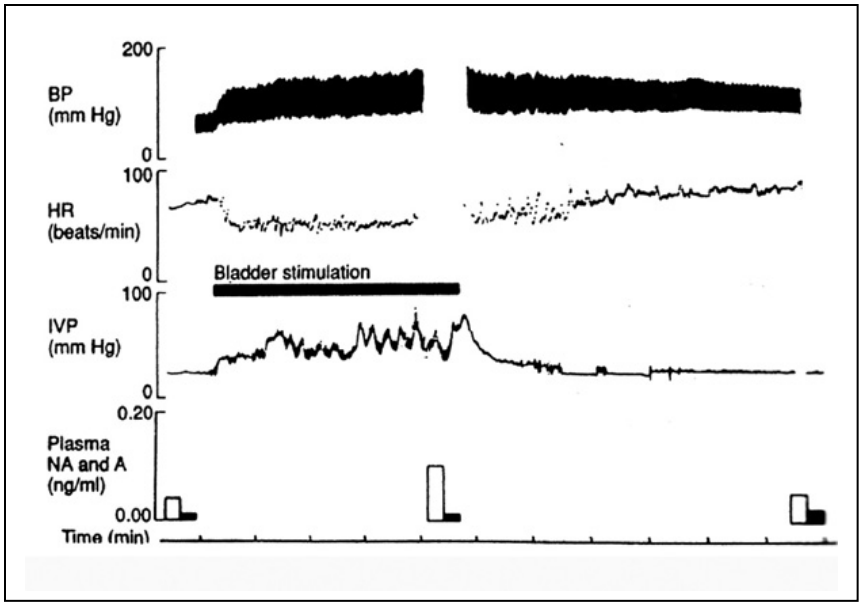
The role of **dopamine** as a neurotransmitter in the peripheral autonomic nervous system is controversial. It is **present in large quantities in the kidney and gut where it regulates sodium excretion and bicarbonate secretion respectively.** While it had been speculated that these sources of dopamine were derived from incomplete conversion of dopamine to norepinephrine in the sympathetic neuron, denervation of sympathetic nerves was shown to have no effect on peripheral dopamine levels. Dopamine instead is derived from local synthesis inside cells that take up L-dopa, an

intermediary metabolite of tyrosine. The dopamine that is released acts in a paracrine or autocrine manner to mediate its response.



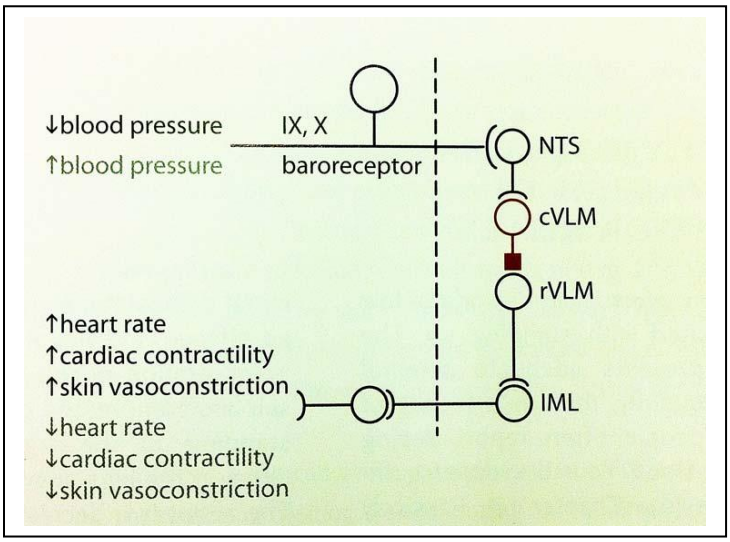
Autonomic afferent fibers are so named because they piggy back on autonomic motor neurons as they travel back to the CNS. One example is the vagus nerve which is composed of both sensory afferent fibers (90 %) and parasympathetic efferents. In addition, sensory afferents may synapse with interneurons that influence pre-ganglionic autonomic motor neurons in the IML. As a result, sensory input can cause reflex activation of the sympathetic nervous system. The schematic to the right demonstrates the anatomical connections between sensory afferents, sympathetic efferent and descending input. Normally, sensory afferent reflexes produce specific sympathetic activation under specific circumstances, e.g., sweat gland activation during heat sensation. Sensory afferent reflexes may also influence sympathetic efferents at the supraspinal level. In this case the effect is typically more wide spread bilateral activation of the autonomic reflex response. Normally afferent stimulation produces only limited sympathetic activation.

When descending input is disrupted as in a major spinal cord lesion, sympathetic efferents located below a complete lesion become supersensitive and sensory afferent sprouting can occur resulting in the development of inappropriate synaptic contacts. As a result activation of sensory neurons below the lesion can stimulate an inappropriately larger population of sympathetic efferents resulting in excessive sympathetic drive below the level of the lesion. A prime example observed clinically occurs when patients with a relatively



high spinal cord lesion with disruption of descending inhibitory input to sympathetic nerves below T5 develop bladder infections or significant bladder distention. Sensory afferent activation can cause profound sympathetic activation through aberrant spinal afferent reflexes below the lesion. When the lesion is high, bladder sensory afferents can reflexively activate a large population of the sympathetic fibers to cause a wide spread vasoconstriction that can lead to hypertensive crises. This is termed **autonomic dysreflexia**, a serious problem that may incur significant morbidity. Sympathetic efferents above the lesion continue to receive descending inhibitory input. If the lesion is low in the spinal cord, the sensory afferents from the bladder do not have much influence sympathetic efferents above the lesion resulting in sympathetic activation that is limited to the lower extremities. The limited vasoconstriction is typically not sufficient to cause a major change in blood pressure. Symptoms of autonomic dysreflexia include: pounding headache (caused by the elevation in blood pressure), goose pimples and profuse sweating below the injury (activation of sympathetic reflexes below the lesion). Nasal congestion, slow pulse, and red blotches of the skin (erythema) develop due to reflex sympathetic withdrawal above the lesion in response to high blood pressure. Restlessness may develop due to excessive circulating epinephrine release if the lesion is above spinal projections to the adrenal gland. The figure above right shows a typical example of this reflex during bladder stimulation in a patient with a full spinal cord lesion at T5.

Syncope or fainting is also a common clinical manifestation of autonomic dysregulation. It may result from autonomic failure due to peripheral neuropathy of autonomic nerves or from transient autonomic failure that is readily reversed. In both cases, inadequate reflex sympathetic-mediated peripheral vasoconstriction leads to pooling of blood and reduced venous return, which in turn, reduces cerebral blood flow leading to faint. The faint is initially adaptive in that it reduces the pressure required to perfuse the brain. However, with chronic neuropathy, patients experience chronic orthostatic intolerance. The orthostatic response is mediated by **arterial baroreflex** control of sympathetic drive in response to blood pooling. Specifically, **baroreceptors** of the aortic arch and carotid sinus detect loss of pressure upon standing. Peripheral baroreceptors respond to increased pressure. Therefore upon reduced pressure during standing baroreceptors are "unloaded" and their afferent activity declines. These sensory neurons normally provide excitatory projects to the medulla where they activate excitatory neurons in the nucleus tractus solitarius (NTS), the medullary brain region receiving the first sensory input from



peripheral visceral organs. The NTS sends excitatory projects to inhibitory interneurons in the caudal ventrolateral medulla (CVLM), which turn, inhibit cells of the rostral ventrolateral medulla (RVLM) which normally provide tonic excitatory out put to the pre-ganglionic sympathetic cells of the IML. Therefore, **during the pooling of blood that initially develops upon standing, barororeceptor unloading leads to a decrease in afferent activity.** NTS activity is consequently reduced leading to declines in the CVLM and disinhibition of the RVLM and increased sympathetic drive to blood vessels. The resulting vasocostriction contributes to increased venous return and helps the individual maintain cerebral perfusion pressure and upright position. **Patients with frank autonomic failure due to peripheral neuropathy cannot develop the reflex responses to blood pooling that should normally occur upon standing, or upon head up tilt.** Patients with **neurogenic syncope** do not have frank autonomic failure, but will instead show a sudden paradoxical transient drop in sympathetic activity that may occur at any time. The response typically abates rapidly and the individual is able to stand normally. The cause of the paradoxical syncopal response can be anyone of numerous stimuli such as an acute emotional stimulus (sight of blood), acute pain, extreme heat, etc. However, the mechanism by which these stimuli lead to withdrawal of sympathetic tone is not known.

Autonomic Nervous System I and II

August 22, 2011

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Learning Objectives

Recognize the distinguishing features of the sympathetic and parasympathetic systems

Recognize the variable trajectories of sympathetic innervation of the head, upper and lower limbs, thoracic abdominal and pelvic viscera

Recognize the brainstem nuclei and parasympathetic ganglia that give rise to parasympathetic innervation of the viscera

Understand how autonomic reflexes are involved in certain clinical findings discussed in lecture

Autonomic Nervous System

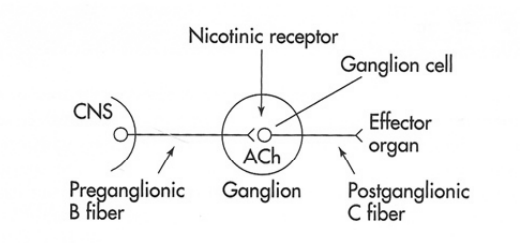
Definition - originally defined as an efferent motor system

- *Efferent innervation to smooth muscle. cardiac muscle, gland cells, fat cells and immune cells*
- *Autonomic nerves also contain afferent nerve fibers, e.g. vagus nerve contains 90% afferents*

Divisions of the ANS

- *Sympathetic or thoracolumbar division*
- *Parasympathetic or cranial-sacral system*
- *Enteric nervous system – sometimes considered part of parasympathetic nervous system*

Basic unit of sympathetic and parasympathetic systems



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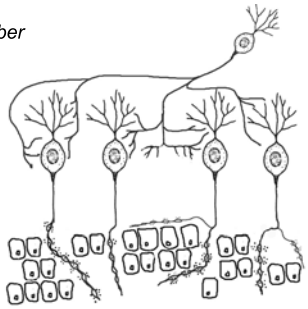
Synapses

Pre-ganglionic fiber

Ganglion

Post-ganglionic fibers

Effector cells



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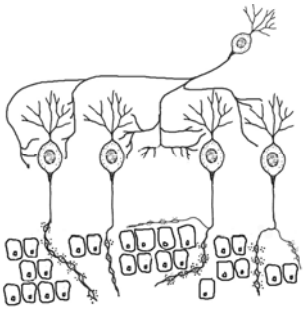
Ganglion Cells

- *One pre-ganglionic fiber affects one to several hundred ganglion cells, i.e., variation in divergence.*
- *Ganglion cells usually receive input from many different pre-ganglionic fibers (convergence).*

Divergence



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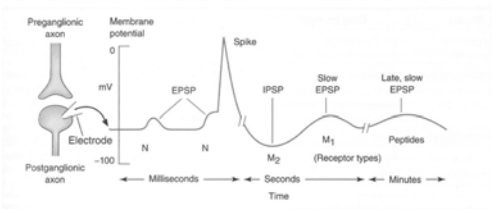
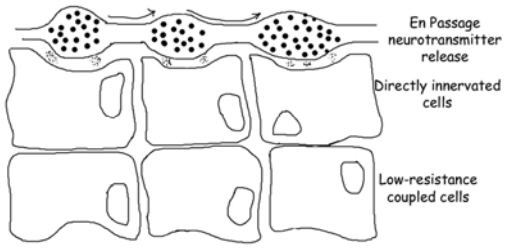
Ganglion cells (post-ganglionic cells) have numerous receptors, e.g., muscarinic receptors and many neuropeptide receptors.

Spatial and temporal summation of post-synaptic potentials contribute to generation of action potential



Neuroeffector Junction



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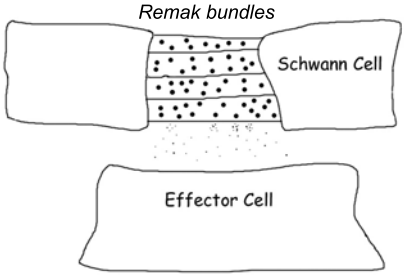
Remak bundles



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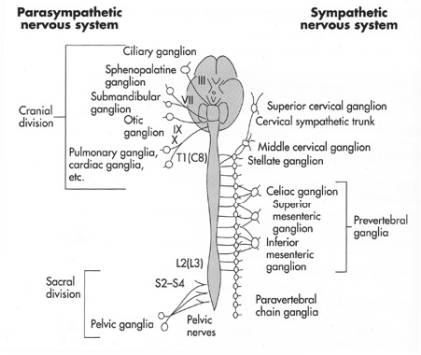
Comparison of Autonomic and Neuromuscular Terminal Innervation

Property	Neuromuscular Junction	Autonomic Junction
Post-junctional specialization	Specialized Junctional Folds	No obvious specialization
# of vesicles released/AP	150-200 vesicles	1-2 vesicles
Transmitter Release	Rapid, large increase followed by rapid decline	Low, gradual change related to frequency
Receptor Mechanism	Direct activation of ligand-gated channels	Slow activation of G-protein coupled receptors



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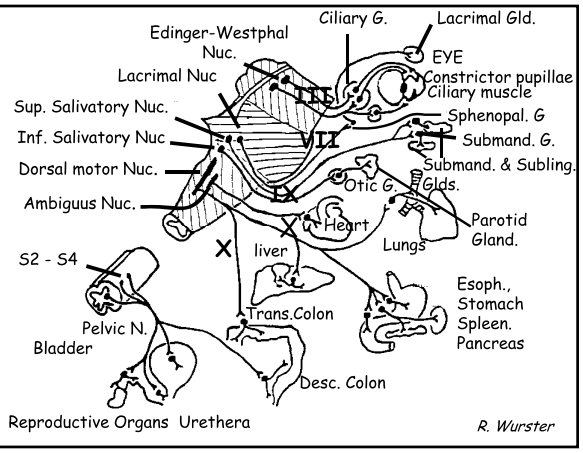
Parasympathetic Nervous System

Two main divisions- cranial and sacral, pre-ganglionic cells in brain stem or spinal cord.

Ganglion cells are relatively close to effector organ

Specific innervation to specific effector organs

Main post-ganglionic transmitter is acetylcholine which acts on muscarinic receptors of the effector organs



Neurotransmitters Released by Post-ganglionic Parasympathetic fibers

- Acetylcholine activates muscarinic receptors

Muscarinic Receptors		
M1	Increased IP3, DAG and $[Ca^{2+}]$	Activates myenteric plexus
M2	Opens K channels	Decreases heart rate and contraction (decreases cardiac output)
	Decreased cAMP, decreased Ca^{2+}	Inhibits norepinephrine release from sympathetic nerve terminals
M3	Increased IP3, DAG and $[Ca^{2+}]$	Contacts circular ciliary muscle (pupillary constriction), ciliary muscle (near-vision accommodation), bronchiolar muscle, GI smooth muscle, uterine muscle, and bladder detrusor muscle (micturition)
		Relaxes vascular muscle (via nitric oxide from endothelium)
		Stimulates secretions of GI tract, eccrine sweat glands,* tear glands, salivary glands, pancreas digestive fluids, and liver bile

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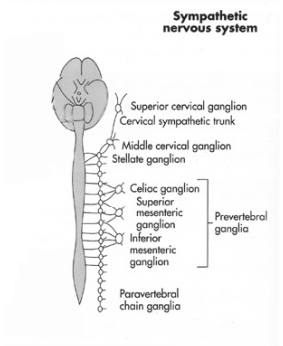
Additional Neurotransmitter in parasympathetic nerves

- *Adenosine triphosphate (**ATP**) activates **purinergic receptors** (e.g., urinary bladder has both Ach and purinergic receptors)*
- *Vasoactive intestinal peptide (**VIP**) activates peptidergic receptors in certain glands and blood vessels.*
- *Nitric oxide (**NO**) acts on **guanylyl cylcase** in the genitalia and gut to promote smooth muscle relaxation.*

Sympathetic Nervous System

- *Pre-ganglionic cell bodies in T1(C8) to L2(L3) spinal cord*
- *Two types of ganglia- paravertebral and prevertebral*
- *Short pre-ganglionic fibers and relatively long post-ganglionic fibers*
- *Differential control of different effector organs – normal conditions*
- *Mass excitation of different organs- extreme conditions*



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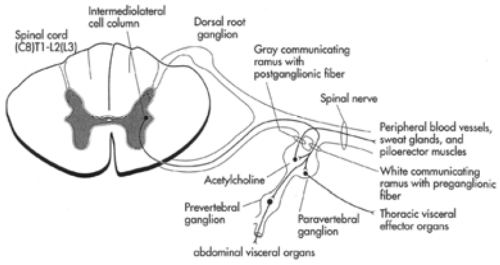
General scheme of pre and post-ganglionic sympathetic fiber innervation of various targets



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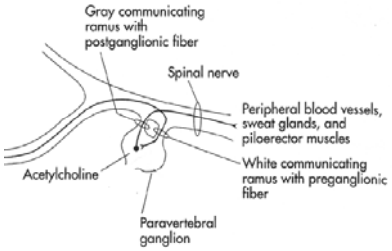
Specific Sympathetic Innervation

Skin and Muscle



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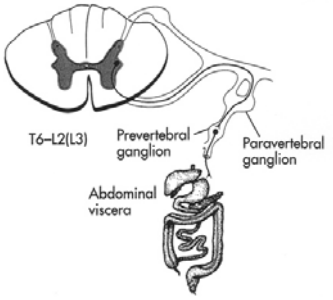
Sympathetic Innervation of Abdominal Viscera
(Also genitalia)



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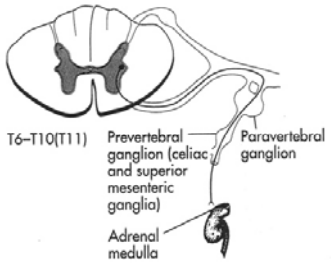
Sympathetic innervation of the Adrenal Medulla



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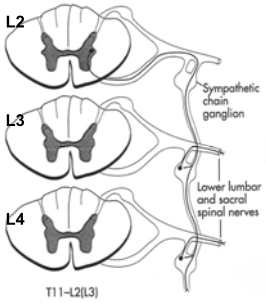
Sympathetic Innervation of Lower Abdomen And Lower Extremities



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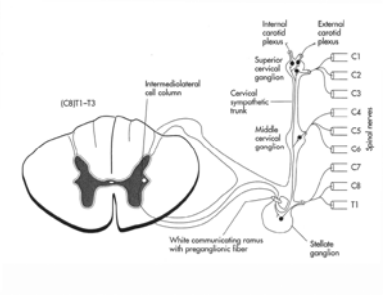
Sympathetic Innervation to head, neck and portions of upper limbs



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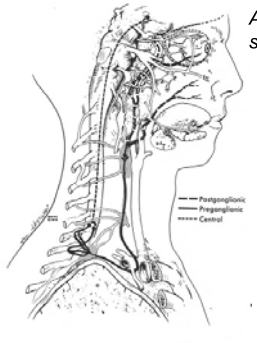

Anatomy of stellate, middle and superior cervical ganglia

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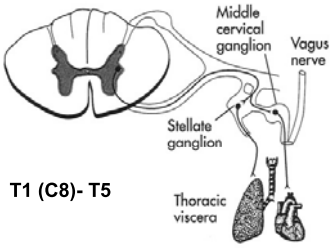
Sympathetic Innervation of Thoracic Viscera



T1 (C8)- T5

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Organ	Preganglionic spinal level	Postganglionic cell	Effect
Tarsal muscle	C8-T1 to T2	Superior cervical ganglion	Eyelid elevation
Iris muscle	C8-T1 to T2	Superior cervical ganglion	Pupillary dilation
Salivary glands	C8-T1 to T2	Superior cervical ganglion	Thick salivation
Lungs	T1 to T5	Middle cervical and stellate ganglion	Bronchodilation and increased pulmonary vascular resistance
Heart	T1 to T5	Middle cervical and stellate ganglion	Increased heart rate, contraction, AV conductance, and cardiac output
Stomach and small intestines	T6 to T10	Celiac ganglion	Decreased motility, blood flow, and secretion
Spleen	T6 to T10	Celiac ganglion	Contraction and red blood cell release
Liver and pancreas	T6 to T10	Celiac ganglion	Increased blood glucose
Adrenal medulla	T6 to T10	None	Epinephrine release
Colon	T8 to L2	Superior and inferior mesenteric ganglion	Decreased motility, blood flow, and secretion
Urinary bladder and ureter	T11 to L2	Inferior mesenteric ganglion and hypogastric plexus	Inhibition of bladder ureter contraction and increased internal sphincter tone
Head and neck sweat glands and blood vessels	C8 to T3	Superior and middle cervical ganglion	Sweating and vasoconstriction
Glands and blood vessels of upper extremity and upper chest sweat glands	C8 to T5	Stellate ganglion and T2-T5 paravertebral ganglion	Sweating and vasoconstriction
Sweat glands and blood vessels of lower chest and abdomen	T6 to L2	T6 to L2 paravertebral ganglion	Sweating and vasoconstriction
Sweat glands and blood vessels of lower extremities	T10 to L2	L1 to S4 paravertebral ganglion	Sweating and vasoconstriction

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Main neurotransmitter - norepinephrine

Receptor type	Intracellular signal	Target and effect
Adrenergic Receptors		
Alpha-1	Increased IP3, DAG and $[Ca^{2+}]$, activates L type Ca^{2+} channels	Contracts smooth muscle of blood vessels (vasoconstriction and increases blood pressure), iris (radial muscles—pupillary dilation), GI sphincters, piloerection ("goose bumps"), uterus, and seminal vesicles (ejaculation) Inhibits myenteric plexus (decreases GI motility), activates apocrine sweat glands (emotional underarm sweating), increases liver glucose production
Alpha-2	Decreased cAMP	Inhibits sympathetic nerve terminal release of norepinephrine
Beta-1	Increased cAMP	Increases heart rate and force of contraction (increases cardiac output), increases renal renin release (leads to increased angiotensin and increased aldosterone production, increased renal NA^+ reabsorption, and increased blood pressure) Increased breakdown of fat cells (lipolysis) leading to increased fatty acid levels
Beta-2	Increased cAMP	Relaxes skeletal muscle blood vessels, bronchiolar muscle, uterine muscle, GI smooth muscle, and bladder detrusor muscle

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Other important sympathetic neurotransmitters:

Acetylcholine *– eccrine sweat glands*
some vascular smooth muscle

Neuropeptide Y *– common co-transmitter with norepinephrine in sympathetic nerve terminals innervating vascular smooth muscle*

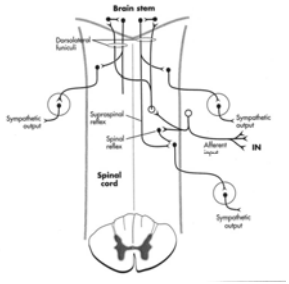
ATP

Dopamine *(?)*

Autonomic Afferent Fibers

- *Autonomic nerves carry many afferent fibers, e.g., vagus is 90% afferent*
- *Visceral afferents, including those that mediate pain, are carried by autonomic nerves*
- *Afferent cell bodies are located in sensory ganglia, e.g., dorsal root ganglia (sympathetic afferents) or cranial nerve sensory ganglia (e.g., nodose ganglion for vagal afferents).*

Sympathetic reflexes



Spinal Afferent input

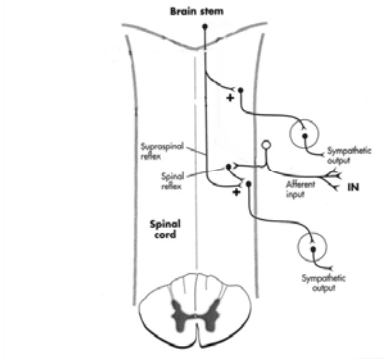
*reflex activity via **spinal** or **supraspinal** pathways*

spinal reflex segmental and ipsilateral (e.g., sweating)

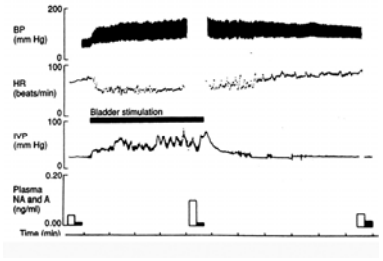
Supraspinal reflexes run in dorsolateral funiculus.

*Can evoke **hyperactive sympathetic reflexes** in chronic phase of spinal cord injury*

From Castro, Merchut, Nearsey and Wurster, In: Neuroscience, an outline approach Mosby Inc., St. Louis, 2002



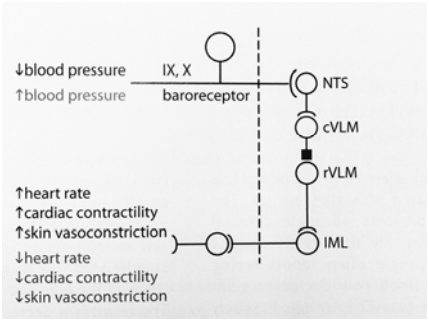
Autonomic dysreflexia



From Robertson, Biaggioni, Burnstock and Low, Figure 81.4 In: Primer on the Autonomic Nervous System, 2nd Ed. Elsevier, San Diego, 2004

Syncope

Arterial baroreflex



CORTEX I, II AND II

Date: August 23, 24 & 26, 2011
Reading Assignment: Mason (2011). *Medical Neurobiology*, Chapter 13.

Be able to answer the following questions.

1. How may cellular layers are typical found in the cerebral cortex?
2. What are connections of each cortical layer?
3. What is basis of Brodmann's cytoarchtectonic divisions?
4. What cortex is supplied by middle cerebral artery? anterior cerebral artery? posterior cerebral artery?
5. What is corpus callosum? anterior commissure?
6. What is the internal capsule? its subdivisions?
7. What are five major categories of cortical function?
8. What is basic organization of somatosensory cortex?
9. How many body maps are found in somatosensory cortex?
10. What is basic organization of motor cortex?
11. Where is primary auditory cortex located?
12. What feature of sound are auditory cortex neurons tuned to?
13. Where is primary visual cortex?
14. How do peripheral visual fields map onto primary visual cortex?
15. What is a hypercolumn in primary visual cortex?
16. What is an ocular dominance column in primary visual cortex?
17. What is an orientation column in primary visual cortex?
18. What is an orientation “pinwheel”?
19. What are dorsal and ventral streams of visual processing and what does each do?
20. What is blindsight?
21. What is prosopoagnosia?
22. What is Wernicke's area? Broca's area?
23. What are symptoms of two major types of aphasia?
24. What cortex is related to eye movements and attention?
25. What cortex is related to visceral autonomic responses and emotion?

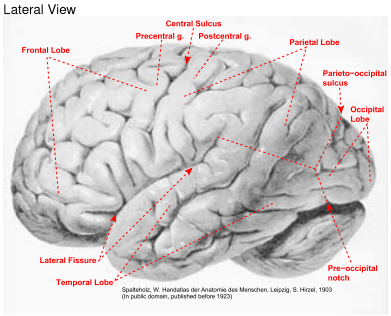
FINAL COPY RECEIVED: 7/11

Cortex123

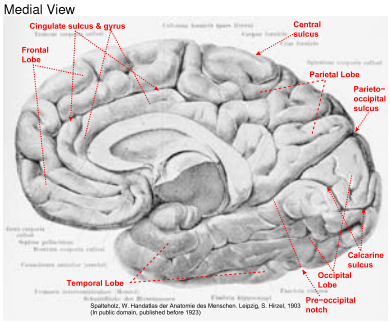
E.J. Neafsey, Ph.D.

1 Lobes and Sulci: Key Sulci=Central, Lateral, Calcarine, Cingulate

Lateral View

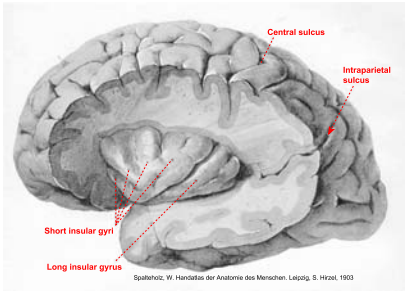


Medial View

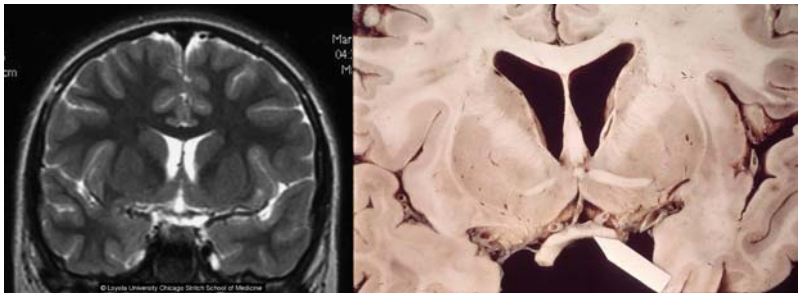


1. **Frontal lobe**
   (a) Movement
   (b) Language Production
   (c) Attention
   (d) Emotion
2. **Parietal lobe**
   (a) Somatic sensation
   (b) Integration of somatosensory, visual, and auditory information
3. **Occipital lobe**
   (a) Vision
4. **Temporal Lobe**
   (a) Hearing
   (b) Language Perception
   (c) Vision
   (d) Memory formation
5. **"Limbic Lobe"**
   (a) Attention
   (b) Emotion

2 Insular Cortex

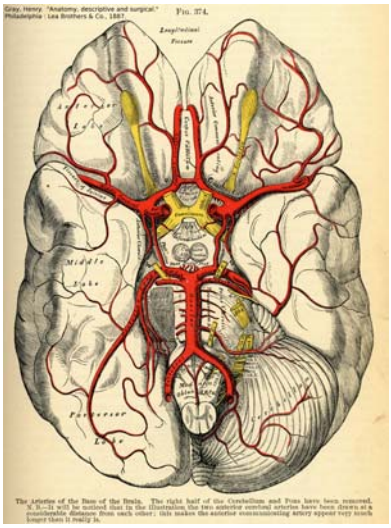


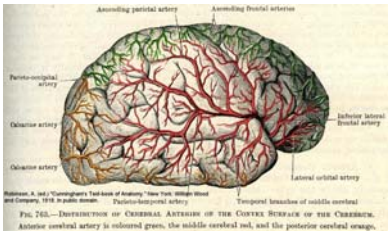
Insular cortex is "buried" inside the lateral (Sylvian) fissure beneath overhanging parts of the frontal, parietal, and temporal lobes.

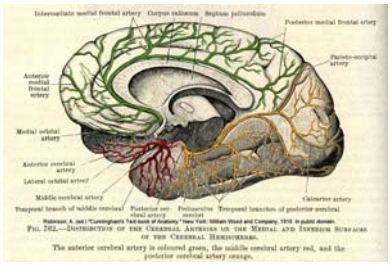


Where is the lateral fissure?
Where is the insular cortex on this MRI?
What blood vessel do you see near it?
Where is the temporal lobe?

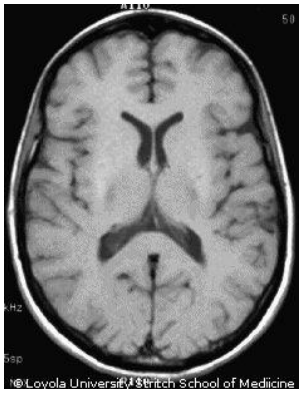
3 Cortical Blood Supply: ACA, MCA, PCA

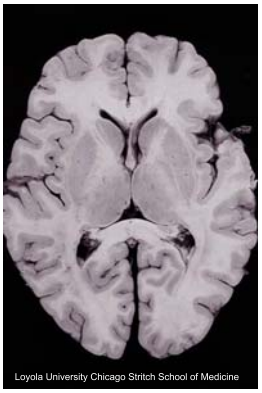


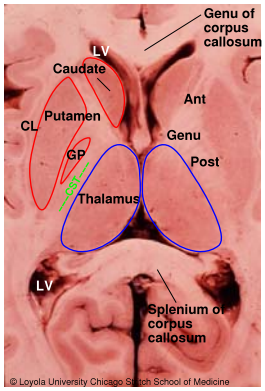




4 Horizontal (Axial) MRI: Internal Capsule, Thalamus, BG, etc.

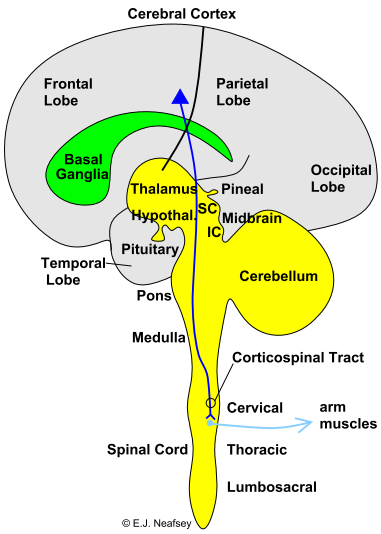


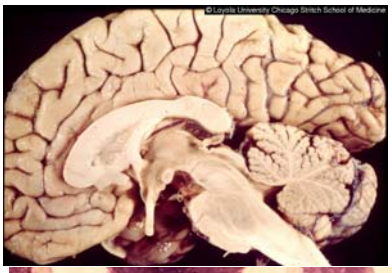


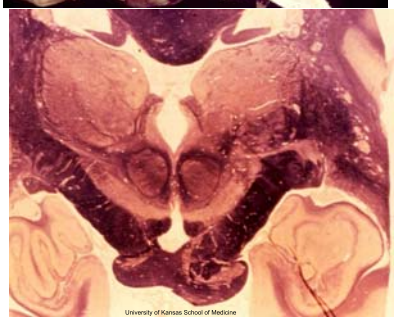


1. Lateral Ventricles
2. Basal Ganglia
3. Thalamus
4. Insula
5. Corpus Callosum
6. Internal Capsule
   (a) Anterior limb
   (b) Genu
   (c) Posterior limb
   (d) corticospinal fibers
   (e) thalamocortical fibers

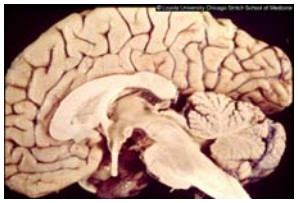
5 Where is thalamus?

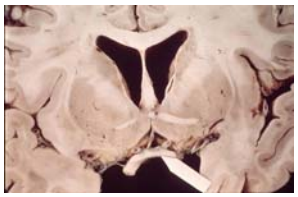






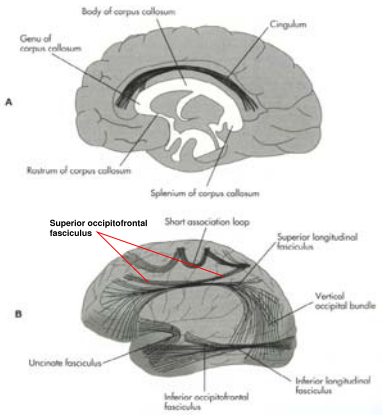
6 Contralateral Cortical Association Commissures





1. **Commissures** arise from pyramidal neurons in **layer III** and cross midline
   (a) **corpus callosum** (300,000,000 fibers) interconnects corresponding (homologous) areas in hemispheres, e.g., left hand somatosensory cortex with right hand somatosensory cortex
      - **"split brain" patients** had corpus callosum cut to prevent spread of epilepsy from one hemisphere to the other
   (b) **anterior commissure** interconnects temporal lobes and olfactory bulbs
   (c) The corpus callosum is very susceptible to **"diffuse axonal injury"** that takes place because of **axonal "shearing"** that occurs during violent head decelerations or accelerations that take place during falls, motor vehicle accidents, or explosions. Such injuries are hard to visualize with brain imaging but can lead to **major changes in cognition and mood.**

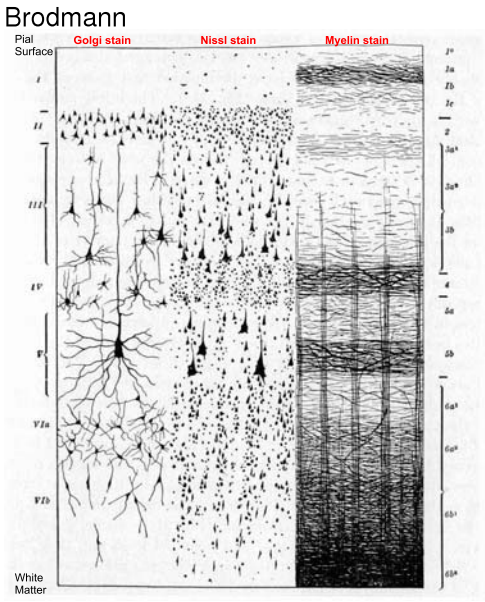
7 Ipsilateral Cortical Association Bundles



1. arise from pyramidal neurons in **layer II**
   (a) **cingulum** interconnects parietal and occipital lobes with frontal lobe
   (b) **inferior occipitofrontal fasciculus**
   (c) **SUPERIOR LONGITUDINAL FASCICULUS (ARCUATE FASCICULUS)** interconnects temporal and frontal lobe language areas; damage in dominant hemisphere results in **conduction aphasia (great difficulty repeating heard words)**
   (d) **uncinate fasciculus** interconnects temporal and frontal lobes
   (e) **superior occipitofrontal fasciculus**; damage to it in parietal lobe of non-dominant hemisphere results in **contralateral neglect syndrome**
   (f) short association bundles connect adjacent gyri
   (g) These ipsilateral white matter tracts are also susceptible to **"diffuse axonal injury"**

See also Diffusion Tensor Imaging of Cerebral White Matter: A Pictorial Review of Physics, Fiber Tract Anatomy, and Tumor Imaging Patterns by Jellison BJ, Field AS, Medow J, Lazar M, Salamat MS, and Alexander AL. *American Journal of Neuroradiology* 25:356-369, 2004.

8 NeoCortex = 6 Layers of Cells and Fibers



(Fig. 19.1 of *Neuroscience: An Outline Approach*)

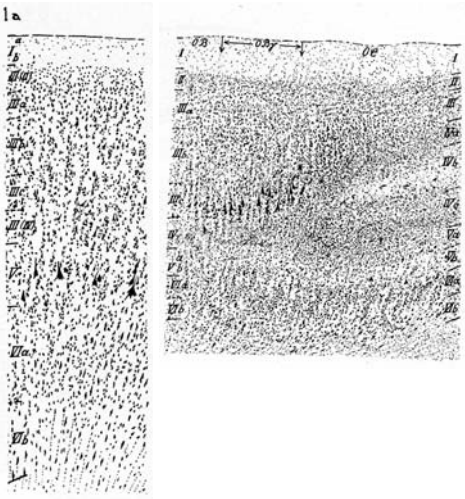
Two basic cell types:

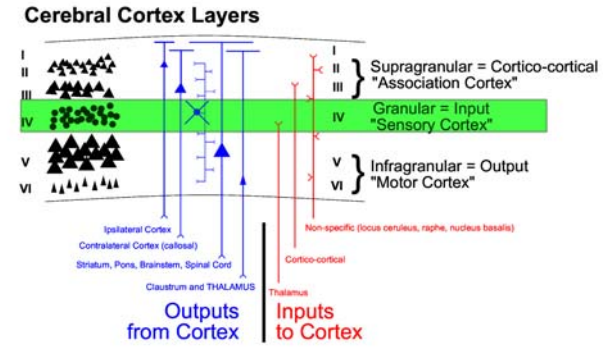
1. **Pyramidal cells** in layers II, III, V, VI (**long axon** projection neurons)
2. **Stellate or granule cells** in layer IV (**short axon** "local circuit" neurons)

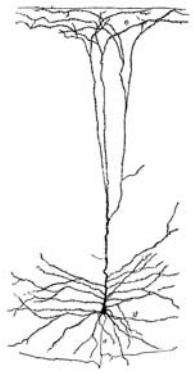
6 Layers:

1. Layer I is mostly dendrites and axons, with few cell bodies
2. Layers II and III are **supragranular** layers composed mainly of pyramidal cells
3. **Layer IV is granule cell layer where thalamocortical afferents terminate**
4. Layers V and VI are **infragranular** layers, also composed mainly of pyramidal cells

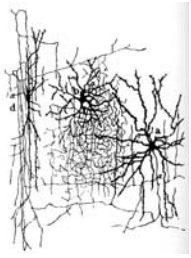
9 Layers Vary in Thickness, Have Different Connections, and Function as Vertical “Columns”



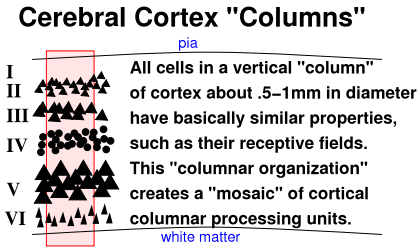


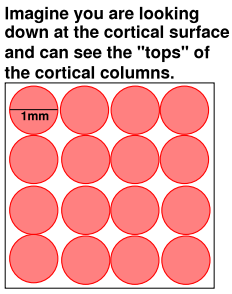


pyramidal cell
layers II, III, V, VI
Cajal



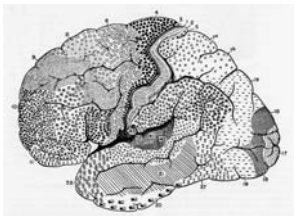
stellate cells
layer IV
Cajal

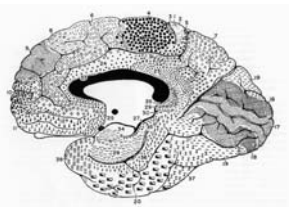




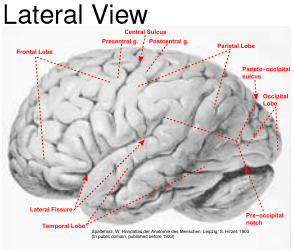
10 Cytoarchitecture and Lobes

Brodmann’s Cytoarchitectonic Maps Based on Variations in Cortical Cell Layering

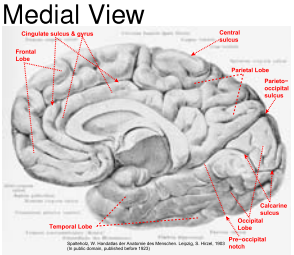




Lateral View



Medial View



4, 6	**Motor**	**17, 18, 19**	**Visual**
3, 1, 2	**Somatosensory**	**41, 42**	**Auditory**

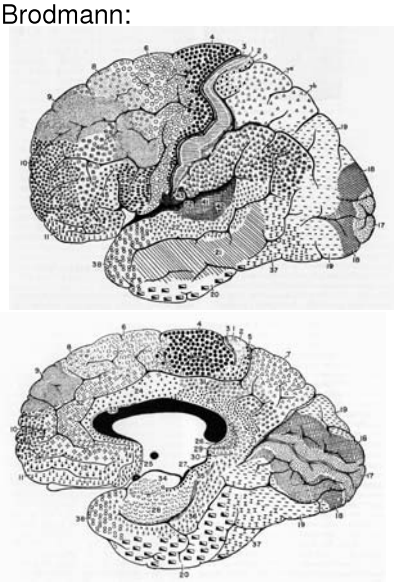
Brodmann, K. 1909. Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Leipzig: Barth JA.

11 Why is Cortical Localization Important?

1. The **same areas** of cortex that respond **during sensory stimulation or movement** are also active **when remembering or thinking about** that type of experience and **when observing** another person having the same type of experience!
2. **Remembering = Encoding/Feeling = Observing**
   (a) **"mirror neurons"** in frontal cortex fire BOTH when you move **AND** when you **observe** another person make same type of movement
   (b) Likewise, feeling disgust from smelling a bad odor **AND observing** disgust in another person activates the **same part of the insular cortex**
   (c) The "mirror neuron system" provides us with a direct "internal" experience that allows us to understand the actions and intentions of others
   (d) A malfunctioning mirror neuron system has been proposed as an explanation for some symptoms of **autism**, in which "high functioning autistic children may understand the intentions of others cognitively but lack the mechanism for understanding them experientially." (Cattaneo *et al.* PNAS 104:17825-17830, 2007.)

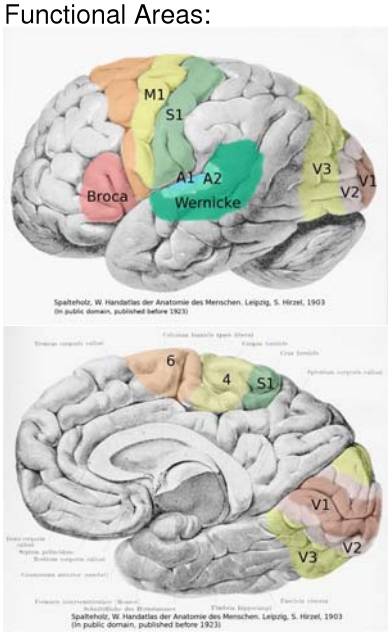
12 Function and Cytoarchitecture: Big Six: S1, M1, V1, A1, Broca, Wernicke

Brodmann:

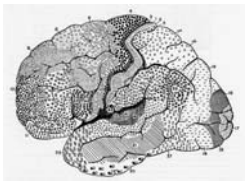
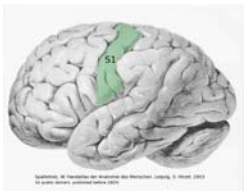


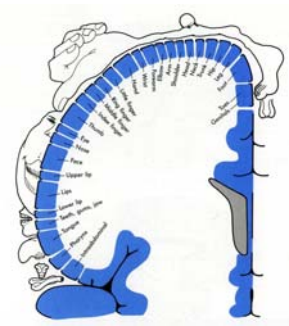
(Fig. 19.1 of *Neuroscience: An Outline Approach*)

Functional Areas:



13 Body: Primary Somatosensory Cortex (S1) = BA3,1,2

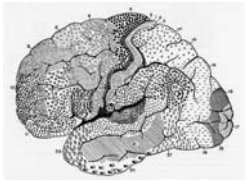
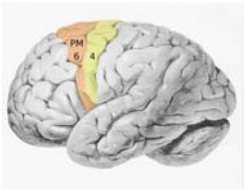


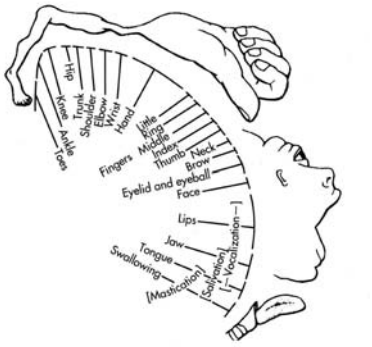

Wilder Penfield, M.D.

Fig. 19-3 of *NAOA*

1. S1 is in postcentral gyrus
2. dense lamina IV
3. thalamic afferents from **VPL and VPM**
   (dorsal column/medial lemniscal and spinothalamic tr.)
   (a) skin tactile receptors
   (b) joint receptors
   (c) muscle spindle receptors
   (d) **localization of pain** but not pain affect
4. Penfield's somatotopic sensory "homunculus" (foot fetish?)
5. lesions
   (a) contralateral deficits
   (b) **inability to discriminate size, texture, and shape**
   (c) **loss of limb position sense**
   (d) loss of pain localization

14 Body: Primary Motor Cortex (M1): BA4, 6

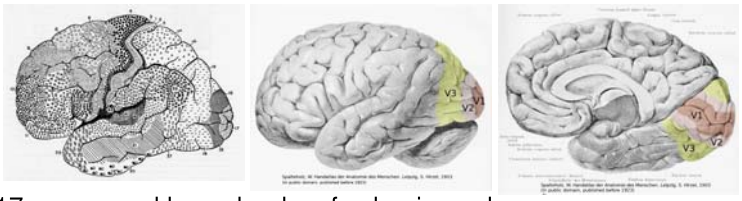





Penfield's motor homunculus
Fig. 19-5 of *NAOA*

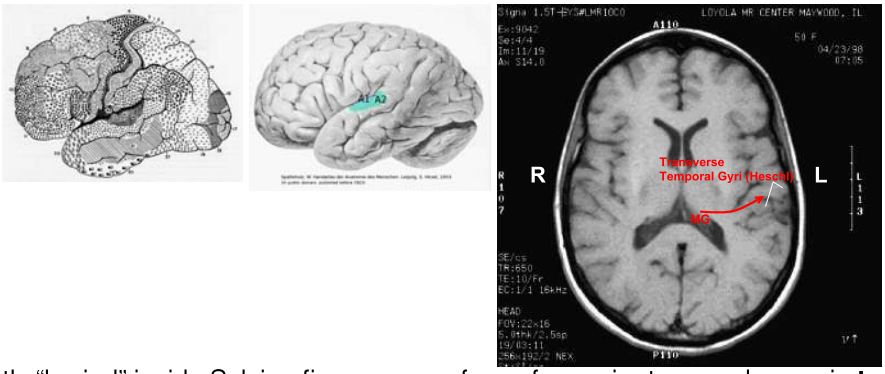
1. motor homunculus that is almost a mirror image of sensory homunculus in somatosensory cortex on other side of central sulcus
2. Prominent layer V with "Betz cells" and hardly any layer IV
3. Afferents from **ventral lateral nucleus** of thalamus (VL) **relay cerebellar output**; other afferents from other motor and somatosensory cortices
4. Efferents include corticospinal, corticobulbar, corticopontine, corticostriate, and corticothalamic
5. Location of cell bodies of **"upper motor neurons"**; lesions, as in a stroke, lead to upper motor neuron signs such as paralysis, hypertonia, and hyperreflexia.

15 Retinas: Primary Visual Cortex (V1) = BA17



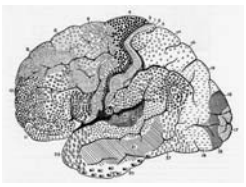
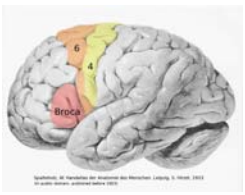
1. area 17: upper and lower banks of calcarine sulcus
2. area 17: striate cortex or calcarine cortex or V1
3. afferents from **lateral geniculate** of thalamus
4. complete map of contralateral visual hemifield
5. **macular retina** projects to **posterior third** of calcarine cortex
6. efferents to superior colliculus (tectum) and pretectum are involved in generating **eye movements in visual tracking**; area 17 or V1 is thus also the "occipital eye field."
7. lesions lead to **cortical blindness**
8. complete unilatateral lesions cause "contralateral homonymous hemianopsia" (complete blindness in contralateral visual field)

16 Inner Ears: Primary Auditory Cortex (A1, A2) = BA41,42



1. mostly "buried" inside Sylvian fissure on surface of superior temporal gyrus in **tranverse temporal gyri** (of Heschl)
2. afferents from **medial geniculate nucleus** of thalamus relay auditory signals from both ears
3. **"Tonotopic" frequency maps** are found in which cells are tuned to different frequency ranges, with low frequencies found rostrally and high frequencies caudally
4. both cochleas project bilaterally, so unilateral cortical lesion does NOT lead to deafness.

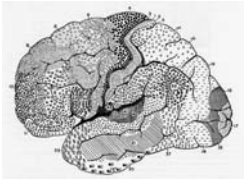
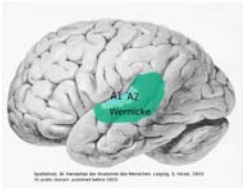
17 Broca's Area (BA44, 45)

Paul Broca

1. Broca's area is a higher order cortical region in the language dominant (usually LEFT) hemisphere related to **speech production**
2. Lesions of Broca's area cause **Broca's aphasia**, in which the production of speech is lost or impaired. The patient's speech is effortful and is sometimes described as "telegraphic" because only a few, essential words are used.
3. Located just in front of primary motor cortex

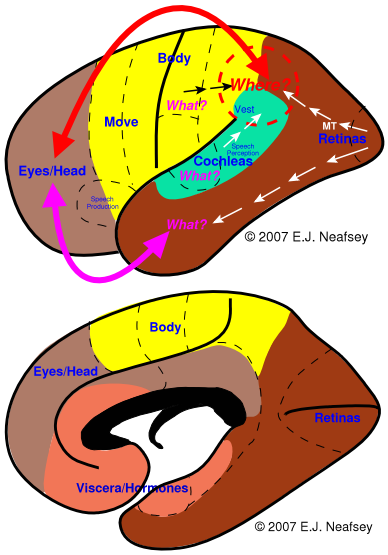
18 Wernicke's Area (BA22)

Carl Wernicke

1. Wernicke's area is a higher order cortical region in language dominant (usually LEFT) hemisphere related to **language perception or understanding**
2. Lesions of Wernicke's area cause **Wernicke's aphasia**, in which the understanding or perception of speech is lost or impaired and the patient's speech has characteristics of a "word salad" that makes little sense.
3. Located next to primary auditory cortex

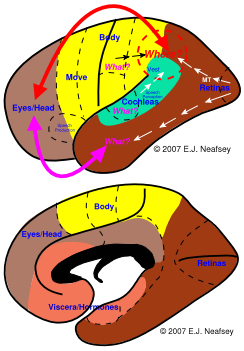
19 The Five Major Functional Regions of Cortex

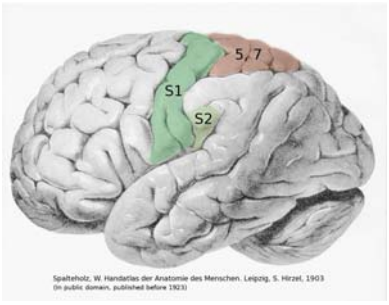


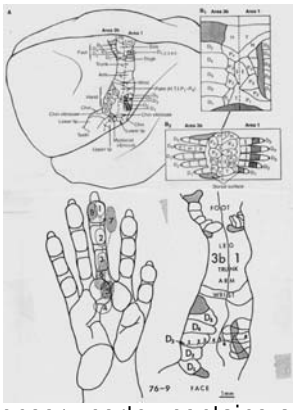
Only Five Major Functional Areas:

Sensory Input	Thalamic Relay	**"Motor" Output**	**Function**
Retinas	LG, PUL-LP, ANT-LD	Superior Colliculus	Seeing
Inner Ears	MG	Inferior Colliculus, Superior Olive	Hearing, Balance
Body	VP, VL, VA	Spinal Cord, Brain Stem	Feeling, Moving
Eyes-Head	MDl-ILN	Superior Colliculus	Looking, Attending
Viscera-Hormones	MDm-Mid	Hypothalamus, PAG, ANS	ANS arousal, Emotions

20 Body: S1 Has Multiple Maps of Contralateral Body

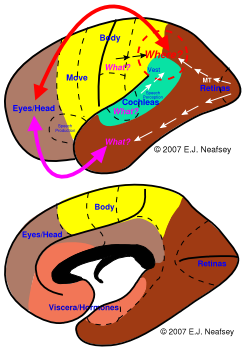


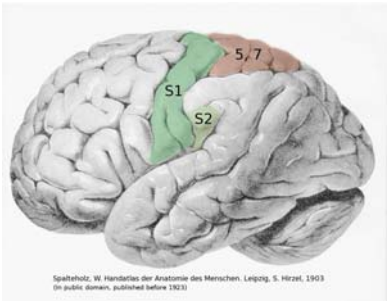




1. Note that each cytoarchitectonic area in primary somatosensory cortex contains a separate and complete representation or "homunculus" of contralateral body.
   (a) area **3a** maps contralateral **muscle spindle afferents**
   (b) areas **3b and 1** map contralateral **cutaneous afferents**
   (c) area **2** maps contralteral **joint afferents**
2. Somatosensory cortex sends strong descending projections to dorsal column nuclei and the dorsal horn, allowing control over its input.

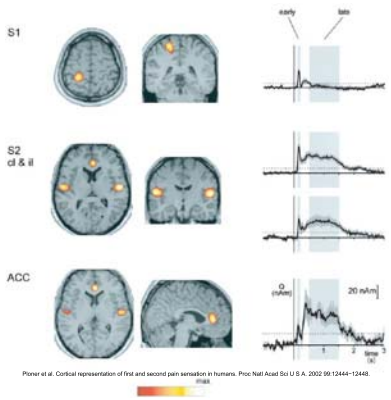
21 Body: Secondary Somatosensory Cortex (S2) = BA40 Another Map





1. Mostly buried in upper bank of lateral (Sylvian) fissure
2. caudal to S1, contains **a separate body map** or representation
3. body map is not as detailed as that in S1
4. thalamic afferents from VPL/VPM as well as posterior and intralaminar nuclei
5. cortical afferents from S1 are very important
6. **S2 responds to painful stimuli** as well as other types of somatic stimuli; the adjacent insula and anterior cingulate cortex on medial surface are also activated by painful stimuli

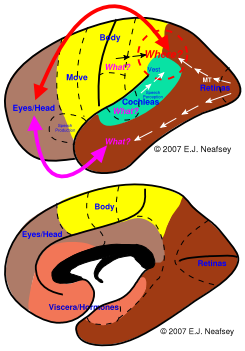
22 Body: Pain in the Cortex = S1, S2, and Ant Cingulate

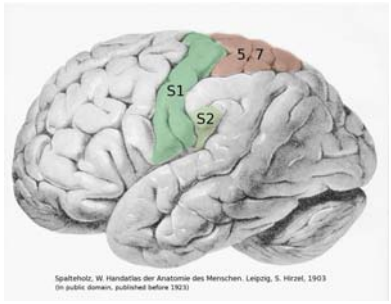


Locations and time courses of early or first (Aδ fiber, relayed by lateral spinothalamic tract) and late or second (C fiber, relayed by anterior spinothalamic tract) pain-evoked activations (**magnetoencephalography**) in S1, S2, and ACC (anterior cingulate cortex) after laser heat pulse to back of right hand.

1. S1 only activated by first pain pathway
2. S2 activated by both first and second pain pathways
3. ACC only activated by second pain pathway.

23 Body: Posterior Parietal Cortex = BA5,7, More Maps



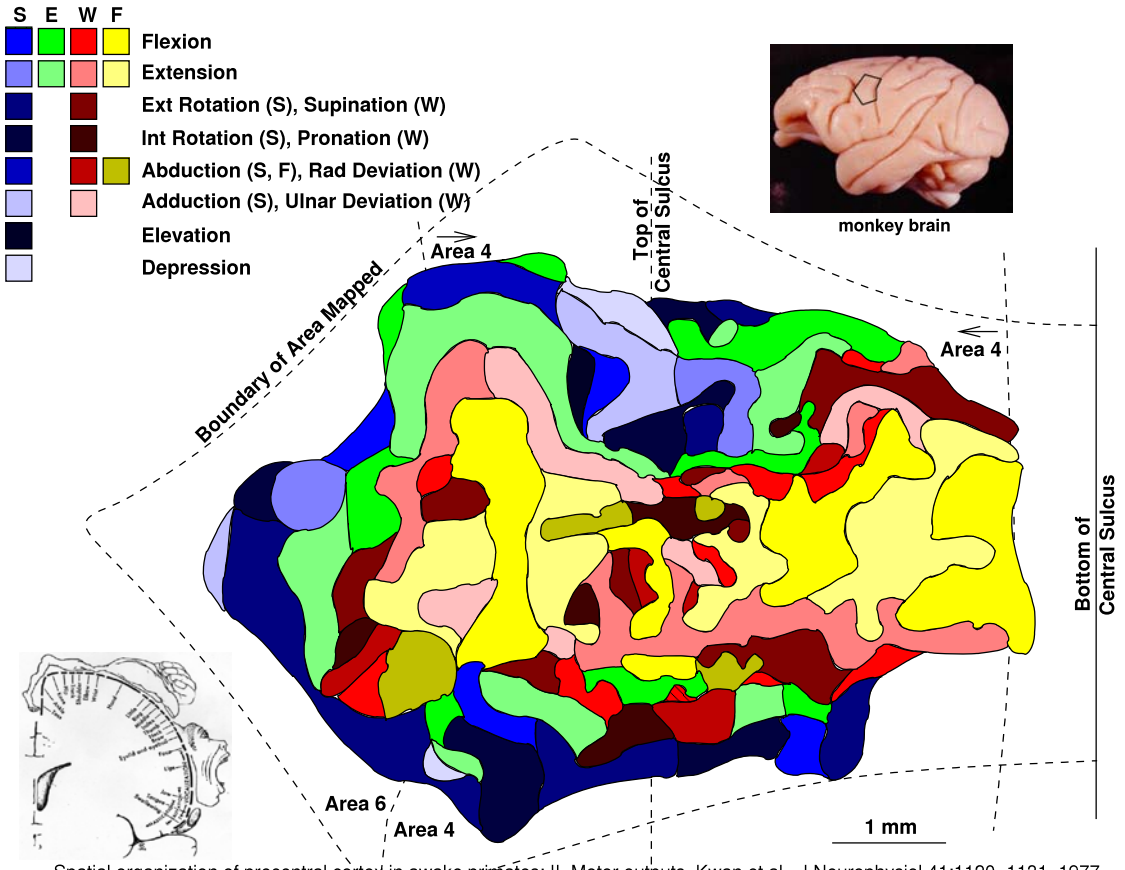


1. located in superior parietal lobule above intraparietal sulcus
2. afferents from SI and SII and from pulvinar nucleus of thalamus
3. inputs also from visual and auditory cortex
4. integration of various senses leading to orientation of body to stimuli; involved in **visual attention**
5. lesions can produce **astereognosis** in which patient is **unable to recognize objects by touch** even though sensory pathways are intact
6. lesions of this area in **right hemisphere** can also produce a **neglect** syndrome where contraleral body and even contralateral space are “neglected”

24 Summary of Somatosensory Cortex Lesions

1. A VPL/VPM lesion would produce complete numbness of entire contralateral side of body, along with associated deficits in position sense and in discrimination of texture, size, and shape (astereognosis).
2. A complete S1 cortical lesion would produce similar deficits, but such a lesion would be highly unlikely because of its large size and involvement of both MCA and ACA territories.
3. A complete S2 lesion produces severe impairments in the discrimination of both shape and texture and prevents learning of new tactile discriminations based on shape; it would also impair pain localization.
4. A lesion of areas 5+7 produces complex sensorimotor deficits related to body image.

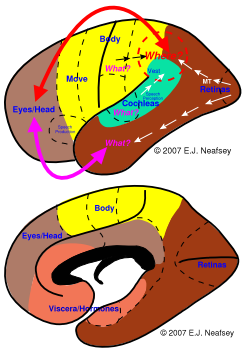
25 Body: Motor Cortex for Arm and Hand

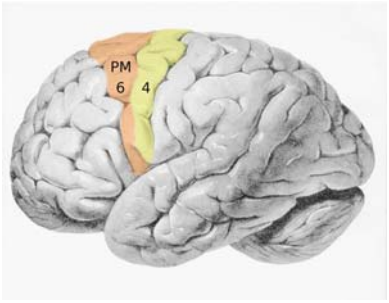


Spatial organization of precentral cortex in awake primates: II. Motor outputs. Kwan et al., J Neurophysiol 41:1120–1131, 1977

1. Motor cortex contains **multiple representations** of contralateral muscle groups (S=shoulder, E=elbow, W=wrist, F==fingers).
2. Motor cortex has strong descending connections to brain stem and spinal cord ventral horn via corticobulbar and corticospinal tracts (**"upper motor neurons"**).

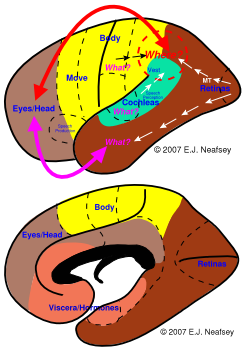
26 Body: Premotor Cortex (PM) = lateral BA6

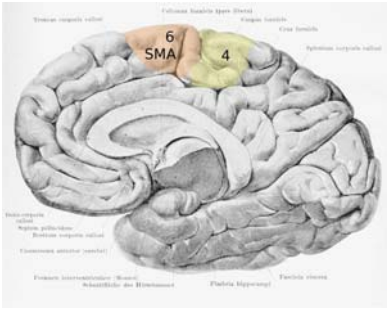




1. involved in **preparation for movement**
2. Afferents from **ventral anterior nucleus** of thalamus (VA) relay **basal ganglia** output
3. **Corticocortical afferents** from other motor and somatosensory cortices
4. **Efferents** include corticospinal, corticobulbar, corticopontine, corticostriate, and corticothalamic

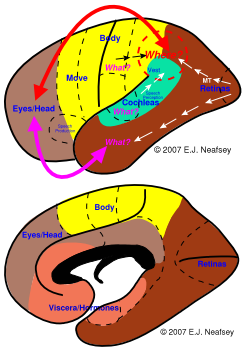
27 Body: Supplementary Motor Cortex (SMA) = midline BA6

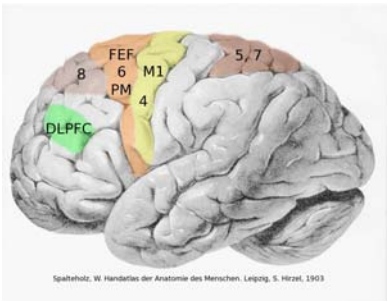




1. another motor map or representation of contralateral body
2. involved in **preparation for movement and coordinating posture**
3. Afferents from **ventral anterior nucleus** of thalamus (VA) relaying **basal ganglia** output and from other motor and somatosensory cortices
4. **Efferents** include corticospinal, corticobulbar, corticopontine, corticostriate, and corticothalamic

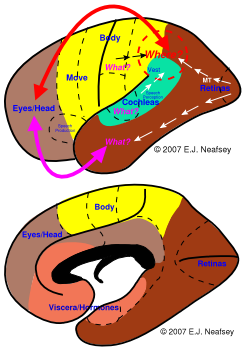
28 Eyes/Head: Frontal Eye Field (FEF) = medial BA6

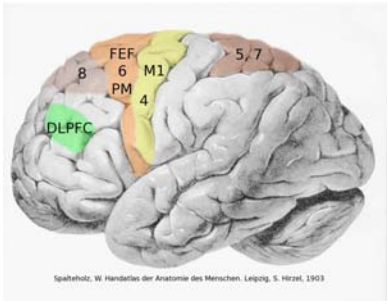


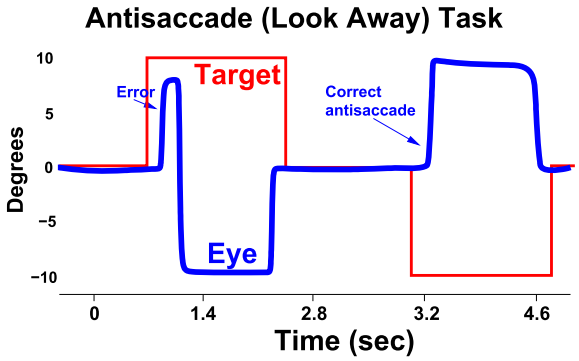


1. involved in generating **saccadic eye movements**
2. stimulation produces eye and head movements to **opposite or contralateral side**
3. Recent studies have **redefined its location** as **superior BA6** (not BA8)
4. **Afferents** from **mediodorsal nucleus of thalamus** (MD) relay input from superior colliculus and from posterior parietal cortex (BA7) and dorsolateral prefrontal cortex (DLPFC, BA46), which are both also involved in eye movements and visual attention
5. **Efferents** include corticotectal projections to **superior colliculus** and corticobulbar projections to **PPRF**

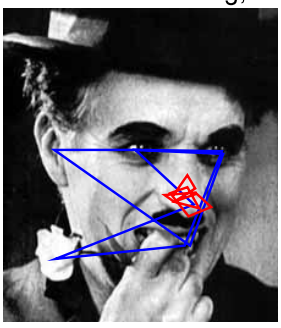
29 Eyes/Head: Dorsolateral Prefrontal Cortex Lesions Greatly Increase Antisaccade Task ("Don't Look") Errors





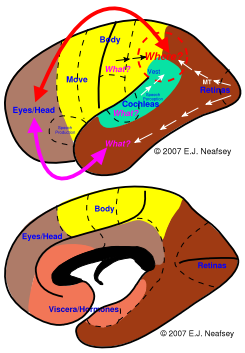


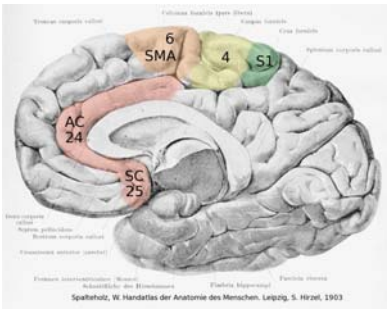
1. Dorsolateral prefrontal cortex (DLPFC) has strong projections to FEF and also directly to superior colliculus that can **inhibit** the superior colliculus's normal output of orienting reflex eye and head movements towards stimuli that would cause errors in the antisaccade (Look Away) task. This seriouslly impair the capacity to **pay attention**.
2. Increased antisaccade errors (can't "not look") are also seen in both **schizophrenia** and **ADHD**, which both also show decreased metabolic activity in the dorsolateral frontal cortex known as **hypofrontality**.
3. More generally, **prefrontal lesions impair the ability to INHIBIT BEHAVIOR** (looking, saying, doing, etc.), often resulting in inappropriate or embarrassing behaviors in social situations.
4. Hypofrontality (low blood flow in frontal lobes) in schizophrenia may cause abnormal eye movement scanning, as seen in picture below.

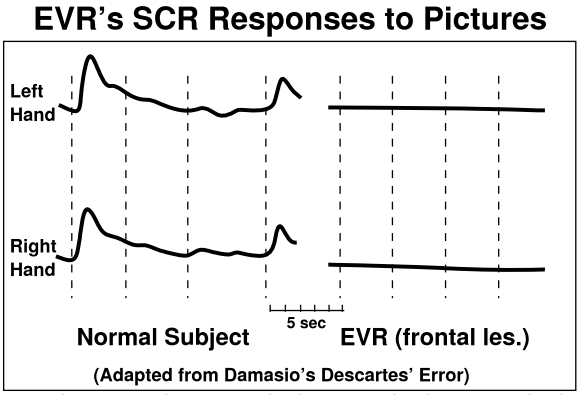


Eye Movements

30 Viscera/Hormones: Ventromedial Frontal Cortex Lesions of Anterior Cingulate (AC, BA24) and Subcallosal Cortex (SC, BA25) Reduce Emotion and "Gut Feelings"





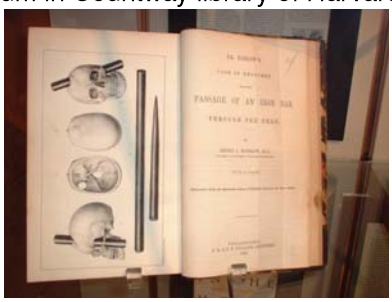


1. Patient EVR suffered bilateral ventromedial frontal cortex damage during surgical removal of a brain tumor. Postoperatively, even though all his cognitive abilities (intelligence, memory, etc.) were still superior, he nonetheless consistently misjudged real life situations, leading to loss of his job and inability to hold another, failure of his marriage, and bankruptcy brought on by foolish investments. Remarkably, the cause of his problems appears to be his loss of normal emotional physiological responses, such as skin conductance responses (SCR). Lacking these immediately felt bodily cues ("gut feelings"), EVR can no longer intuitively appreciate the personal and social consequences of his actions, even though he can correctly analyze and verbally explain each situation when asked. EVR is considered the modern Phineas Gage. (Damasio AR. *Descartes' Error: Emotion, Reason, and the Human Brain*. G.P. Putnam's Sons, New York, 1994.)
2. Ventromedial cortex controls the **autonomic nervous system** and is part of brain's system for emotion
3. **Afferents** include inputs from the **Mediodorsal nucleus** of the thalamus (MD), which relays visceral inputs from the solitary nucleus, among others
4. **Efferents** from the ventromedial prefrontal cortex include projections to the **hypothalamus, amygdala, and brain stem "autonomic" centers**
5. Ventromedial prefrontal cortex was a primary target of the **prefrontal lobotomy** surgery. (Valenstein, E. *Great and Desperate Cures: A History of Radical Treatments for Mental Illness*. HarperCollins, New York, 1987.)

31 Viscera-Hormones: Phineas Gage

From exhibit in Warren Anatomical Museum in Countway library of Harvard Medical School






SEPTEMBER 13, 1848: the accidental explosion of a charge Gage had just set blew his tamping iron out of the borehole and through the left side of his skull: it entered point first under this left cheek bone, exited through the top of his head and landed some 25 to 30 yards away. Gage was knocked over but may not have lost consciousness, according to some accounts. Most of the left frontal lobe was destroyed, but Gage was treated with such skill by Cavendish physician Dr. John Harlow that he returned to his home in Lebanon, New Hampshire ten weeks later.
Seven months later, Gage was strong enough to resume work, but despite exemplary work prior to the accident, his employer would not return him to his former position. He had become fitful, irreverent, and grossly profane, showing little deference for other workers. Impatient and obstinate yet capricious and vacillating, he was unable to settle on any of the plans he devised for future action. According to his friends, he was “No longer Gage.” Gage died in 1860.

32 Inner Ears (Hearing and Balance) Cortex

1. Will be covered later.

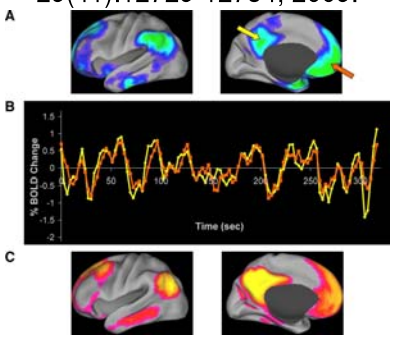
33 Retinas (Seeing) Cortex

1. Will be covered later.

34 The Default Mode Network

Your brain is very active when you’re doing nothing!

Figure from Raichle ME, J Neuroscience 29(41):12729-12734, 2009.



1. Brain regions of the **Default Mode Network** highlighted in A are **intrinsically active at rest** and show activity DECREASES during performance of goal-directed tasks. The spontaneous BOLD fluctuations (B) within the same network in the resting state derived from regions of interest placed in the posterior cingulate/precuneus (yellow arrow) or the medial prefrontal cortex (orange arrow). Note the remarkable degree of coherence between activities from these two distant loci within the same system. The degree of system-wide coherence within the DMN is shown in C when all voxels in the brain are examined for their correlation with a region of interest in the posterior cingulate/precuneus (yellow arrow in A).
2. What important areas are NOT in the DMN?

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Medical Neuroscience – 2011 –

Channelopathies

Learning Objectives:

1) To explain the basic mechanism that cause ion channel dysfunction in human diseases.

2) To explain how the malfunction in one or more of the basic properties of an ion channel in neurons or skeletal muscle fibers can explain pathologies of the neuromuscular system.

3) To understand the conceptual basis of drugs in improving symptoms of a mal-functioning channel.

4) To correlate, using a few well studied neurological disorders, the basic relationships between channel dysfunction, action potential alteration, synaptic transmission, and general patient symptoms.

5) To realize the inherent difficulties in extrapolating the behavior of an ion channel in an *in vitro* system to a nerve cell in the middle of a complex network of neurons.

1. Introduction.

Ultimately, neurophysiology is about ion channel gating:

- ❖ activation (closed state → open state)
- ❖ deactivation (open state → closed state)
- ❖ inactivation (open (or closed) state → inactivated)
- ❖ Recovery from inactivation (inactivated state → close state)

Channelopathies are caused by dysfunctional gating.

So far alterations in ionic permeability in dysfunctional channels have not been demonstrated.

Samuel Cukierman, M.D., Ph.D. (scukier@lumc.edu; Bldg. 102, Room 4626)

Ion channel gating alterations can occur in:

- ❑ Autoimmune diseases
- ❑ Mutation of channel protein (direct effect)
- ❑ Alterations in the modulation of ion channel protein:
  1) glycosylation,
  2) (de)-phosphorylation of channel protein,
  3) accessory subunits to ion channel,
  4) expression of a protein that inhibits normal channel gating.
- ❑ Intoxication (poisoning)

2. Autoimmune Diseases.

❑ **Myasthenia Gravis (MG)** is the classical example of neuro-autoimmune disease that has been studied since the 1970s.

❑ Antibodies generated against the nicotinic Ach-channel in skeletal muscle fibers prevent the binding of Ach. As such end-plate potentials are attenuated or non-existent. Thus, no or few action potentials occur in skeletal muscle fibers leading to muscle weakness and fatigue that can be identified in tests.

❑Diplopia, ptosis (drooping of eyelids) are common first symptoms. Choking and respiratory failure are life-threatening conditions.

❑ patients with MG may or not have antibodies generated against muscle nicotinic Ach-receptors.

❑ Thymus is almost abnormal in MG (25% thymomas);

❑ Inihibitors of acetylcholinesterases improve symptoms.

❑ **Lambert-Eaton** neuro-autoimmune disease.

❑ Antibodies generated against the Ca^{2+} channels in presynaptic terminals (end-plate region). Thus, no or little neurotransmitter release in the end plate, and no excitation of muscle fibers. Symptoms are similar to those in myasthenia gravis;

❑ Malignant tumors (lungs, thymus, T-cell lymphomas, Hodgkin's, and prostate) are quite common in those patients;

❑ Corticosteroids (anti-inflammatory) and 4-aminopyridine (4-AP) have limited success in improving muscle weakness and fatigue;

❑ 4-AP is an inhibitor of K-channels in the presynaptic nerve fiber. Channel blockade causes lengthening of membrane depolarization in the presynaptic terminal causing late openings of Ca^{2+} channels.

Table 1. Ion Channel and Related Targets in Antibody-Mediated Diseases

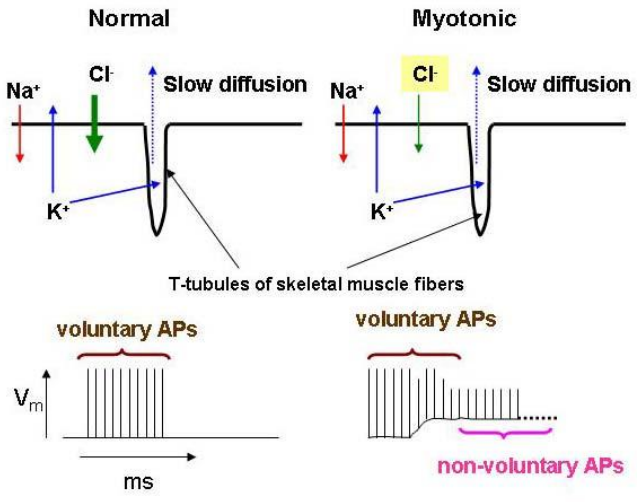
Ion Channel or Related Protein	Associated Autoimmune Disease(s)	Main Clinical Features	Location	Genetic Defects also Found?
α1 nicotinic acetylcholine receptor (AChR)	myasthenia gravis	muscle weakness and fatigue	neuromuscular junction	congenital myasthenic syndromes
Muscle-specific kinase (MuSK)	myasthenia gravis without AChR antibodies	muscle weakness and fatigue	neuromuscular junction	one case of congenital myasthenic syndrome
P/Q-type (α1A) voltage-gated calcium channel (VGCC)	Lambert Eaton myasthenic syndrome	muscle weakness	presynaptic nerve terminal at neuromuscular junction	congenital myasthenic syndrome not yet identified, but subtle defects in transmitter release in spontaneous mouse mutants and α1A knockouts
P/Q-type (α1A) voltage-gated calcium channel (VGCC)	lung cancer-associated cerebellar ataxia	ataxia	presynaptic nerve terminal at central synapses	familial hemiplegic migraine, episodic ataxia type 2, and spinocerebellar ataxia type 6
Voltage-gated potassium channel (VGKC) Kv1 subtypes	acquired neuromyotonia	muscle fasciculations, cramps, pseudomyotonia, hyperhydrosis	presynaptic nerve terminal at neuromuscular junction	epilepsy, episodic ataxia type 1 (Kv1.1) with myokymia
Voltage-gated potassium channel (VGKC) Kv1 subtypes	limbic encephalitis	memory loss, confusion, seizures, personality change, psychiatric features	presynaptic nerve terminal at central synapses	Kv1.1 knockout mice are seizure sensitive and have memory impairment
α3 nicotinic acetylcholine receptor (α3 AChR)	autoimmune autonomic neuropathy	orthostatic hypotension, impaired pupil responses, urinary retention	autonomic ganglia	knockout mice have marked autonomic dysfunction

3. Mutations of Ion Channels. *A few relatively well known clinical cases linked to channel mutations will be discussed in lecture.*

3.1. Myotonias

❑ Myotonia is defined as a series of involuntary contractions of skeletal muscles following one or more voluntary contractions.
❑ This is a clear indication that repetitive action potentials (APs) are being automatically generated after a train of voluntary APs (hyperexcitability).
❑ Only Cl^- and/or Na^+ channels were so far been found involved in myotonias.

A) Myotonias related to Cl^- channel mutations
Human dominant myotonia congenita (DMC, Thomsen's disease), recessive myotonia congenita. Low membrane g_{Cl} (CLC 1 channels).



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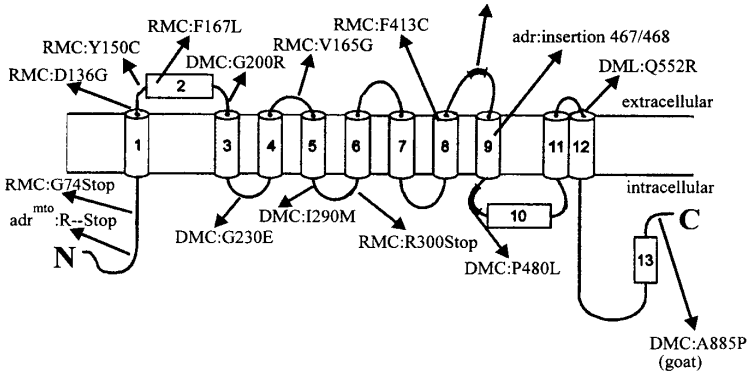
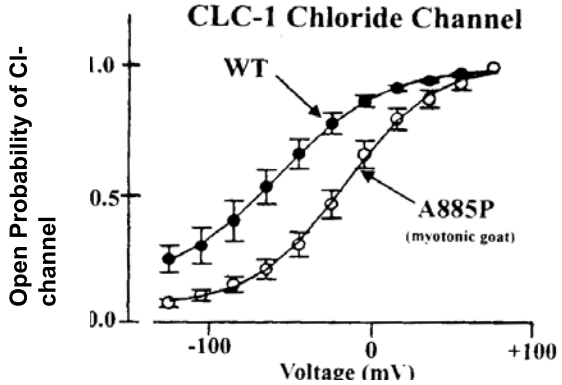


CLC-1 skeletal muscle Cl^- channels

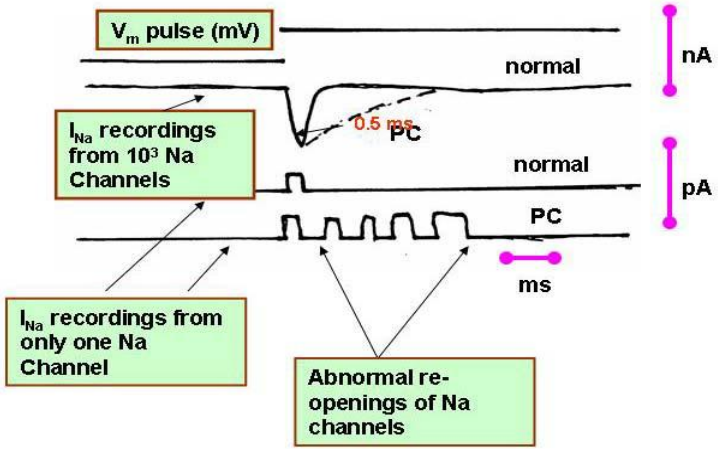
DMC = dominant myotonia congenita: single point mutations in position 230 (Gly instead of Glu).
RMC = recessive myotonia congenita: many distinct single point mutations. Moreover, dysfunctional Na channels also contribute in some types of RMC.

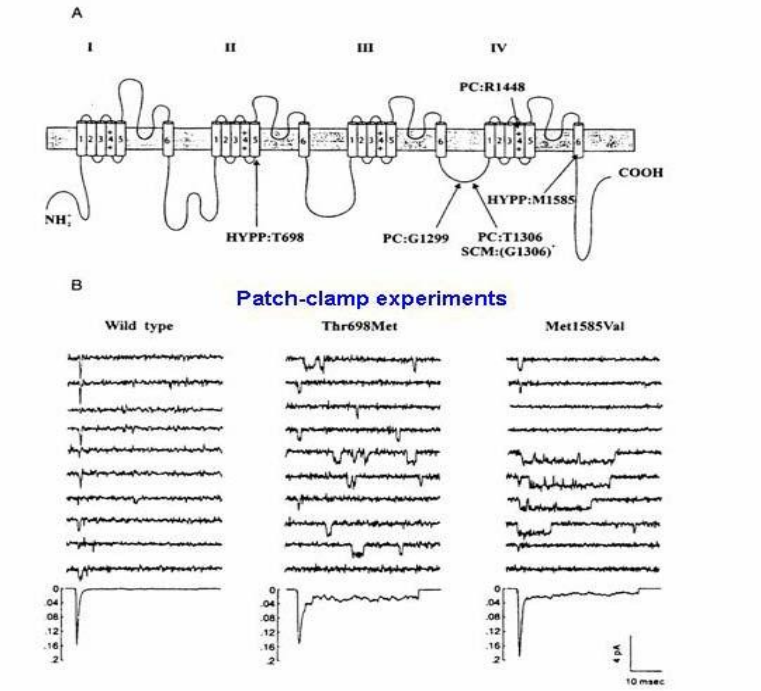


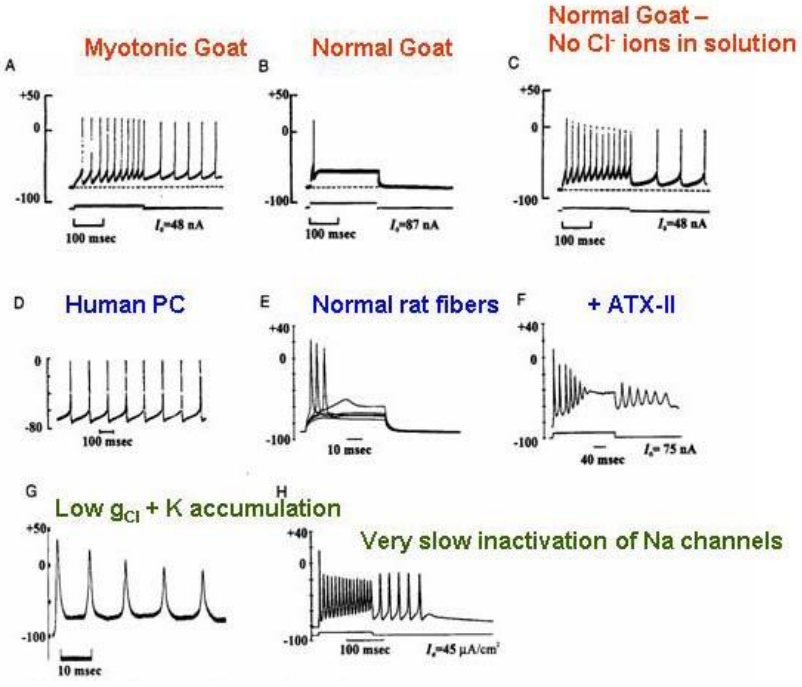
A) Myotonias related to Na^+ channel mutations
Hyperkalemic periodic paralysis (HYPP).

- ❑ Na^+ channel myotonia.
- ❑ The common physiological factor in this group of myotonia concerns an abnormal inactivation of Na^+ channels

Voltage and Patch-clamp Experiments with Na+ currents or channels:




A
I
II
III
IV
PC:R1448
COOH
NH2
HYPP:M1585
HYPP:T698
PC:G1299
PC:T1306
SCM:(G1306)
B
Patch-clamp experiments
Wild type
Thr698Met
Met1585Val
4 pA
10 msec


Myotonic Goat
Normal Goat
Normal Goat –
No Cl- ions in solution
A
B
C
+50
0
-100
100 msec
I_s=48 nA
I_s=87 nA
I_s=48 nA
D
Human PC
E
Normal rat fibers
F
+ ATX-II
-80
+40
10 msec
40 msec
I_s= 75 nA
G
Low g_{Cl} + K accumulation
H
Very slow inactivation of Na channels
I_s=45 µA/cm²

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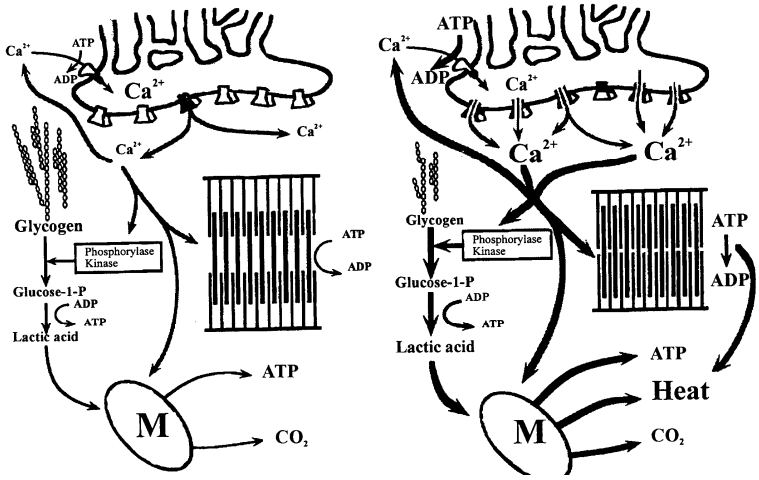
3.2. Malignant Hyperthermia.

❑ Some individuals when given halothaene anaesthesia in conjunction with a neuromuscular blocker (succinyl-choline for example) develop muscle rigidity, hypermetabolism, and very high fever. Muscles enter in a state of contracture. Patients die soon if not treated immediately.

Mutation of the **Ca^{2+}-release channel** in the skeletal muscle SR has been identified. In MH pigs, it is a single point mutation. In human, two single point mutations were identified. Some MH patients have normal genes.

There are several tests that indicate that a patient may be at high risk group for MH (http://www.mhaus.org).

Dantrolene Sodium blocks Ca^{2+}-release channels and is effective in controlling MH.



3.3. Epilepsy.

Table 1 | **Some of the genes that are involved in epilepsy**

Subtypes	Gene symbol	Phenotype
Ion channel genes in idiopathic epilepsy		
Nicotinic acetylcholine receptors	*CHRNA4/CHRNB2*	ADNFLE
Potassium channels	*KCNQ2/KCNQ3*	BFNC
Sodium channels	*SCN1A/SCN2A/SCN1B*	GEFS+
Chloride channels	*CLCN2*	IGE
$GABA_A$ receptors	*GABRG2/GABRA1*	GEFS+/IGE
Non-ion channel genes in idiopathic epilepsy		
Function unknown	*LGI1*	ADLTE
G-protein coupled receptors	*MASS1/VLGR1*	FS
Progressive myoclonus epilepsies		
Polyglucosan metabolism	*EPM2A/EPM2B(NHLRC1)*	Lafora disease
Cysteine protease inhibition	*CSTB*	Unverricht–Lundborg disease
Respiratory chain	*MTTK/MTTL1*	MERRF
Lipidoses	*PPT*	Infantile NCL
	CLN2	Late infantile NCL
	CLN3	Juvenile NCL
	CLN5	Late infantile NCL, Finnish variant
	CLN6	Late infantile NCL, Indian variant
	CLN8	Northern epilepsy
Glycopeptide/oligosaccharide	*NEU1*	Sialidosis metabolism

ADLTE, autosomal dominant lateral temporal lobe epilepsy; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; BFNC, benign familial neonatal convulsions; FS, febrile seizures; GEFS+, generalized epilepsy with febrile seizures plus; IGE, idiopathic generalized epilepsies; MERRF, myoclonic epilepsy with ragged red fibres; NCL, neuronal ceroid lipofuscinosis.

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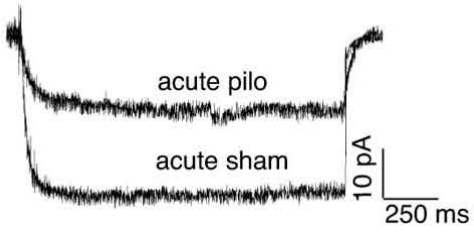
3.3.A. Downregulation of HCN channels in dendrites of CA1 hippocampal pyramidal neurons.

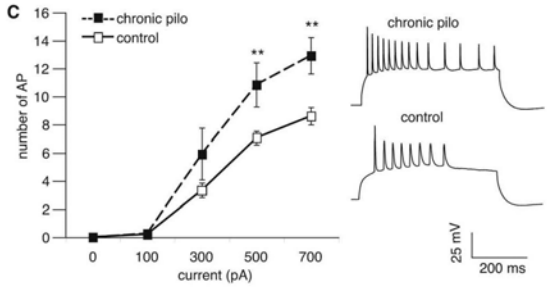
❑ Hyperpolarization-activated cation channel (HCN) has been found present in high densities in dendrites of neurons in hippocampal and neocortical pyramidal neurons;

❑ Pilocarpine (a muscarinic agonist) downregulates HCN expression and induce epileptic seizures in animal models. Blockers of HCN channels also cause seizures;

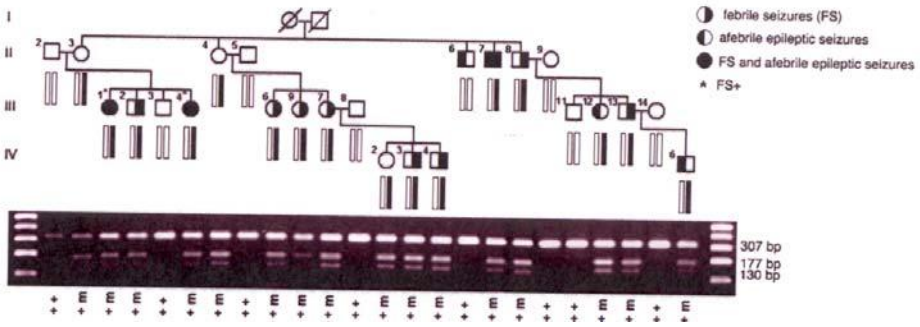
❑ HCN channels are K^+ channels that are activated by voltage and cyclic nucleotides.

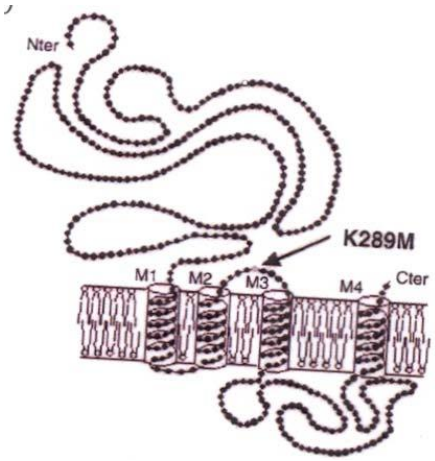
❑ HCN channels stabilize the resting potential in dendrites thus decreasing the amplitude of EPSPs. Downregulation or blockade of HCN channels increase EPSPs amplitude and frequency.

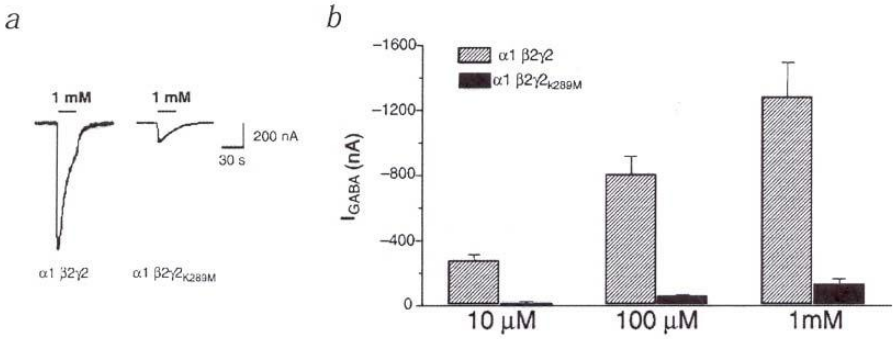




3.3.B. GABA single channel mutation in Epilepsy.







3.4. Hypokalemic Periodic Paralysis.

❑ Typical surge of muscle weakness and relaxation with a low serum [K] begins a few hours after a high carbohydrate meal (often when asleep) and can last for 4-24 hours.

❑Two distinct mutations were described in the skeletal muscle L-type Ca channels of patients.

❑ However, experimental mutations in this channel in the laboratory did not show dysfunction of Ca^{2+} currents .

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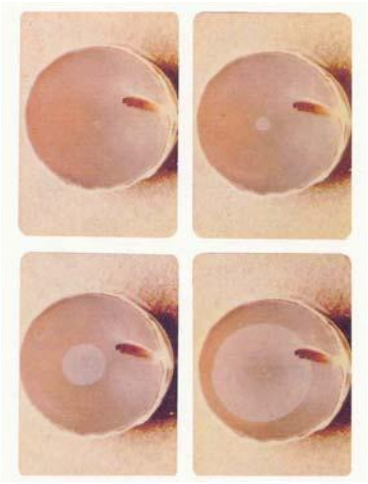
3.5. Familial Hempilegic Migraine (FHM) and Episodic Ataxia Type-2 (EP-2).

❑ FHM is a rare autosomal dominant form of migraine which combines the typical migraine with paralysis of one side of the body, and (sometimes) atrophy of cerebellum. EP-2 has the same symptoms of FHM but the cerebellar atrophy *is always* present. The episodic ataxia component in both FHM and EP-2 responds with a carbonic anhydrase blocker (acetazolamide).

❑Both diseases are often associated with mutations in the gene that codes for the P/Q-type Ca channels located in the presynaptic terminals throughout the brain. There is an increase in the P(open) of the channels as well as a consequent increase in the Ca currents flowing through these channels.

❑The phenomenon of cortical spreading depression (CSD) usually (but not always reported) precedes migraine development and causes the "aura" (subjective sensation of light). During CSD there is complete abolishment of all neuronal activity.

❑Enhancement of Ca currents in P/Q type channels could favor CSD and, FHM and EP-2.



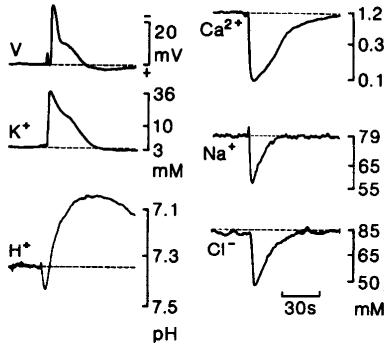
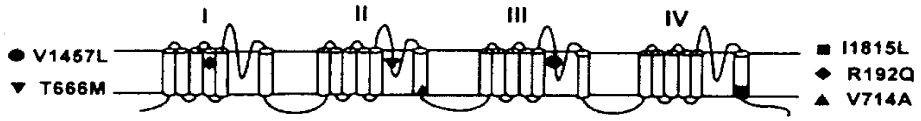
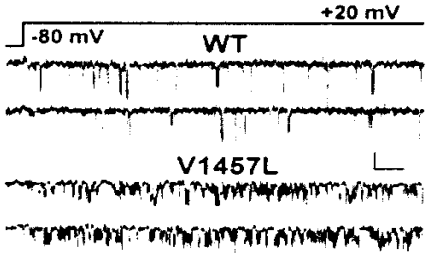
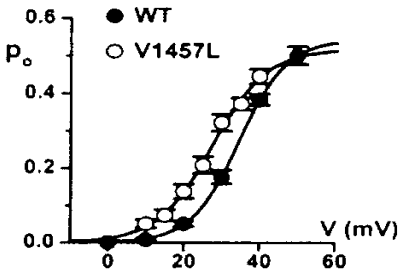


Fig. 10. Extracellular ionic changes during SD in rat cerebellum. All amplitude scales are logarithmic but magnitudes differ depending on ion. $[K^+]_e$ increases during SD, $[H^+]_e$ shows initial decrease (pH increase) then increases. $[Ca^{2+}]_e$, $[Na^+]_e$ and $[Cl^-]_e$ all fall. SD was induced by a brief train of local surface stimuli. In all cases, cerebellum was conditioned by reducing NaCl content; this accounts for reduced baseline in $[Na^+]_e$ and $[Cl^-]_e$ records. Based on Ref. [76].







Medical Neuroscience – 2011 –
Channelopathies

Learning Objectives:

1) To explain the basic mechanism that cause ion channel dysfunction in human diseases.

2) To explain how the malfunction in one or more of the basic properties of an ion channel in neurons or skeletal muscle fibers can explain pathologies of the neuromuscular system.

3) To understand the conceptual basis of drugs in improving symptoms of a mal-functioning channel.

4) To correlate, using a few better studied neurological disorders, the relationships between channel dysfunction, action potential alteration, synaptic transmission, and general patient symptoms.

5) To realize the inherent difficulties in extrapolating the behavior of an ion channel in an *in vitro* system to a nerve cell in the middle of a complex network of neurons.

1. Introduction.

Ultimately, neurophysiology is about ion channel gating:

❖ activation (closed state → open state)

❖ deactivation (open state → closed state)

❖ inactivation (open (or closed) state → inactivated)

❖ Recovery from inactivation (inactivated state → close state)

Channelopathies are caused by dysfunctional gating.

So far alterations in ionic permeability in dysfunctional channels have not been demonstrated.

1. Introduction.

Ion channel gating alterations can occur in:

❑ Autoimmune diseases

❑ Mutation of channel protein (direct effect)

❑ Alterations in the modulation of ion channel protein:

1) glycosylation.

2) (de)-phosphorylation of channel protein,

3) accessory subunits to ion channel,

4) expression of a protein that inhibits normal channel gating.

❑ Intoxication (poisoning)

2. Autoimmune Diseases.

❑ **Myasthenia Gravis (MG)** is the classical example of neuro-autoimmune disease that has been studied since the 1970s.

❑ Antibodies generated against the nicotinic Ach-channel in skeletal muscle fibers prevent the binding of Ach. As such, end-plate potentials are attenuated or non-existent. Thus, no or few action potentials occur in skeletal muscle fibers leading to muscle weakness and fatigue that can be identified in tests.

❑ Diplopia, ptosis (drooping of eyelids) are common first symptoms. Choking and respiratory failure are life-threatening conditions.

❑ patients with MG may or not have antibodies generated against muscle nicotinic Ach-receptors.

❑ Thymus is almost abnormal in MG (25% thymomas);

❑ Inihibitors of acetylcholinesterases improve symptoms.

❑ **Lambert-Eaton :** Neuro-autoimmune disease.

❑ Antibodies generated against the Ca^{2+} channels in presynaptic terminals (end-plate region). Thus, no or little neurotransmitter release in the end plate, and no excitation of muscle fibers. Symptoms are similar to those in myasthenia gravis;

❑ Malignant tumors (lungs, thymus, T-cell lymphomas, Hodgkin's, and prostate) are quite common in those patients;

❑ Corticoids (anti-inflammatory) and 4-aminopyridine (4-AP) have limited success in improving muscle weakness and fatigue;

❑ 4-AP is an inhibitor of K-channels in the presynaptic nerve fiber. Channel blockade causes lengthening of membrane depolarization in the presynaptic terminal allowing late openings of Ca^{2+} channels.

Table 1. Ion Channel and Related Targets in Antibody-Mediated Diseases

Ion Channel or Related Protein	Associated Autoimmune Disease(s)	Main Clinical Features	Location	Genetic Defects also Found?
α1 nicotinic acetylcholine receptor (AChR)	myasthenia gravis	muscle weakness and fatigue	neuromuscular junction	congenital myasthenic syndromes
Muscle-specific kinase (MuSK)	myasthenia gravis without AChR antibodies	muscle weakness and fatigue	neuromuscular junction	one case of congenital myasthenic syndrome
P/Q-type (α1A) voltage-gated calcium channel (VGCC)	Lambert Eaton myasthenic syndrome	muscle weakness	presynaptic nerve terminal at neuromuscular junction	congenital myasthenic syndrome not yet identified, but subtle defects in transmitter release in spontaneous mouse mutants and α1A knockouts
P/Q-type (α1A) voltage-gated calcium channel (VGCC)	lung cancer-associated cerebellar ataxia	ataxia	presynaptic nerve terminal at central synapses	familial hemiplegic migraine, episodic ataxia type 2, and spinocerebellar ataxia type 6
Voltage-gated potassium channel (VGKC) Kv1 subtypes	acquired neuromyotonia	muscle fasciculations, cramps, pseudomyotonia, hyperhydrosis	presynaptic nerve terminal at neuromuscular junction	epilepsy, episodic ataxia type 1 (Kv1.1) with myokymia
Voltage-gated potassium channel (VGKC) Kv1 subtypes	limbic encephalitis	memory loss, confusion, seizures, personality change, psychiatric features	presynaptic nerve terminal at central synapses	Kv1.1 knockout mice are seizure sensitive and have memory impairment
α3 nicotinic acetylcholine receptor (α3 AChR)	autoimmune autonomic neuropathy	orthostatic hypotension, impaired pupil responses, urinary retention	autonomic ganglia	knockout mice have marked autonomic dysfunction

3. Mutations of Ion Channels.

A few relatively well known clinical cases linked to channel mutations will be discussed in lecture.

3.1. Myotonias

❑ Myotonia is defined as a series of involuntary contractions of skeletal muscles following one or more voluntary contractions.

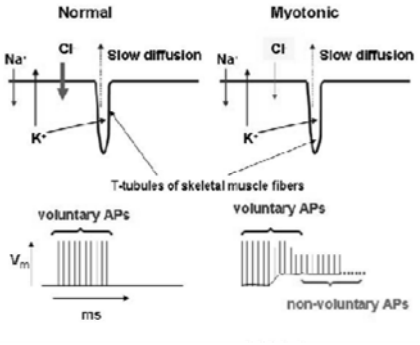
❑ That is a clear indication that repetitive action potentials (APs) are being automatically generated after a train of voluntary APs (hyperexcitability).

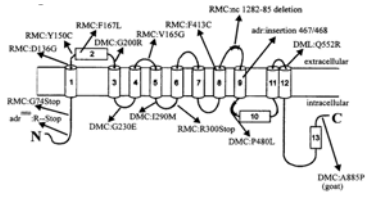
❑ Cl^- and/or Na^+ channels are the only channels that are involved in myotonias.

A) Myotonias related to Cl^- channel mutations

Human dominant myotonia congenita (DMC, Thomsen's disease), recessive myotonia congenita.

Low membrane g_{Cl} (CLC 1 channels).



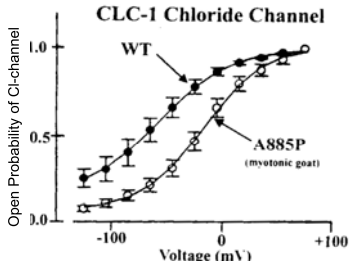


CLC-1 skeletal muscle Cl^- channels

DMC = dominant myotonia congenita: single point mutations in position 230 (Gly instead of Glu).

RMC = recessive myotonia congenita: many distinct single point mutations. Moreover, dysfunctional Na channels also contribute in some types of RMC.

Why can't the Cl channel deliver the Cl^- current necessary to stabilize the resting membrane potential?

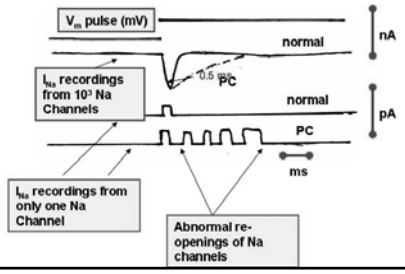


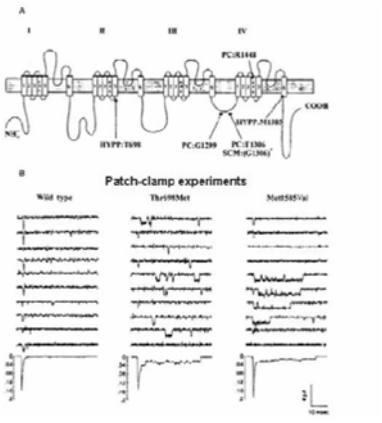
A) Myotonias related to Na^+ channel mutations

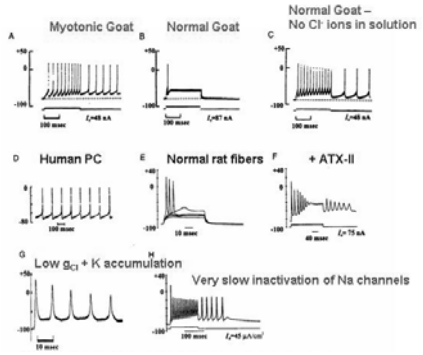
- Hyperkalemic periodic paralysis (HYPP).
- Na^+ channel myotonia.

The common physiological factor in this group of myotonia concerns an abnormal inactivation of Na^+ channels.

Voltage and Patch-clamp Experiments with Na+ currents or channels:







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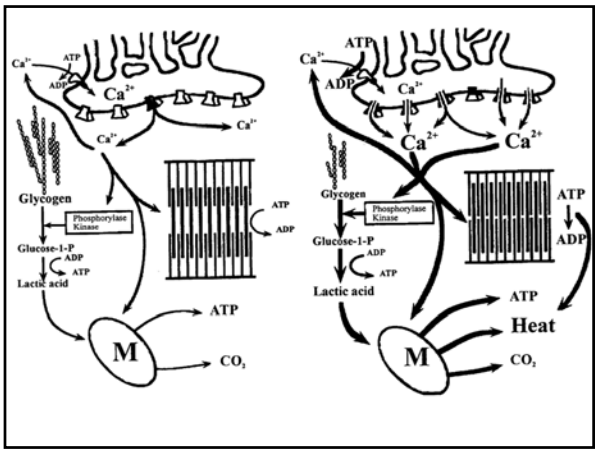
❑ Some individuals when given halothaene anaesthesia in conjunction with a neuromuscular blocker (succinyl-choline for example) develop muscle rigidity, hypermetabolism, and very high fever. Muscles enter in a state of contracture. Patients die soon if not treated immediately.

❑ Mutation of the **Ca^{2+}-release channel** in the skeletal muscle SR has been identified. In MH pigs, it is a single point mutation. In human, two single point mutations were identified. Some MH patients have normal genes.

❑ Dantrolene is a blocker of Ca^{2+}-release channels and is used to block MH.

❑ There are several tests that indicate that a patient may be at high risk group for MH (http://www.mhaus.org).



3.3. Epilepsy.

Several ion channels have been postulated to be present in altered states in epilepsy.

Table 1 | **Some of the genes that are involved in epilepsy**

Subtypes	Gene symbol	Phenotype
Ion channel genes in idiopathic epilepsy		
Nicotinic acetylcholine receptors	*CHRNA4/CHRNB2*	ADNFLE
Potassium channels	*KCNQ2/KCNQ3*	BFNC
Sodium channels	*SCN1A/SCN2A/SCN1B*	GEFS+
Chloride channels	*CLCN2*	IGE
$GABA_A$ receptors	*GABRG2/GABRA1*	GEFS+/IGE
Non-ion channel genes in idiopathic epilepsy		
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G-protein coupled receptors	*MASS1/VLGR1*	FS
Progressive myoclonus epilepsies		
Polyglucosan metabolism	*EPM2A/EPM2B(NHLRC1)*	Lafora disease
Cysteine protease inhibition	*CSTB*	Unverricht–Lundborg disease
Respiratory chain	*MTTK/MTTL1*	MERRF
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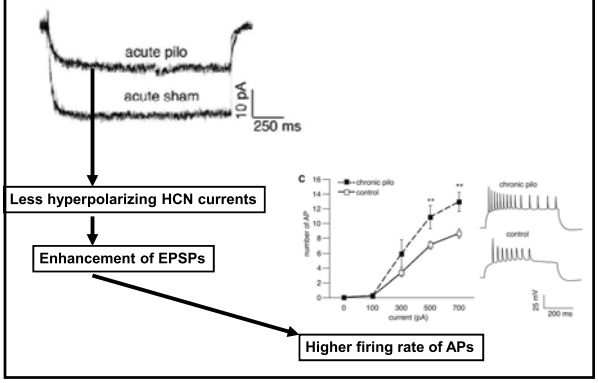
	CLN2	Late infantile NCL
	CLN3	Juvenile NCL
	CLN5	Late infantile NCL, Finnish variant
	CLN6	Late infantile NCL, Indian variant
	CLN8	Northern epilepsy
Glycopeptide/oligosaccharide	*NEU1*	Sialidosis metabolism

ADLTE, autosomal dominant lateral temporal lobe epilepsy; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; BFNC, benign familial neonatal convulsions; FS, febrile seizures; GEFS+, generalized epilepsy with febrile seizures plus; IGE, idiopathic generalized epilepsies; MERRF, myoclonic epilepsy with ragged red fibres; NCL, neuronal ceroid lipofuscinosis.

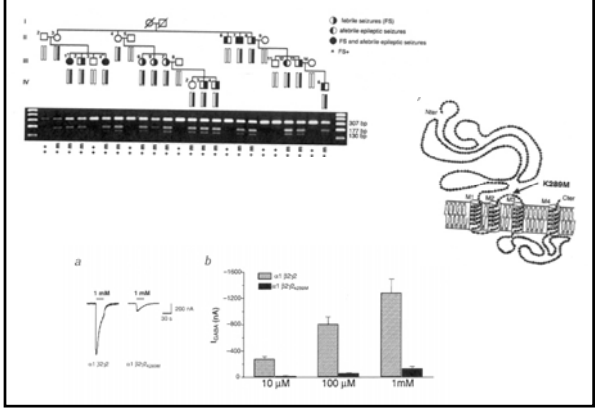
3.3. Epilepsy.

- ❑ Hyperpolarization-activated cation channel (HCN) has been found in high densities in dendrites in hippocampal and neocortical pyramidal neurons;
- ❑ Pilocarpine (a muscarinic agonist) downregulates HCN expression and induce epileptic seizures in animal models. Blockers of HCN channels also cause seizures;
- ❑ HCN channels are K^+ channels that are activated by voltage and cyclic nucleotides.
- ❑ HCN channels stabilize the resting potential in dendrites thus decreasing the amplitude of EPSPs. Downregulation or blockade of HCN channels increase EPSPs amplitude and frequency.

3.3.A. Downregulation of HCN channels in dendrites of CA1 hippocampal pyramidal neurons.



3.3.B. GABA single channel mutation in Epilepsy.



3.4. Hypokalemic Periodic Paralysis.

- Typical surge of muscle weakness and relaxation with a low serum [K] begins a few hours after a high carbohydrate meal (often when asleep) and can last for 4-24 hours.
- Two mutations were described in the skeletal muscle L-type Ca channels of patients.
- However, experimental mutations in this channel in the laboratory did not show dysfunction of Ca^{2+} currents .

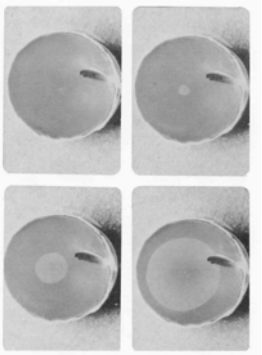
3.5. Familial Hempilegic Migraine (FHM) and Episodic Ataxia Type-2 (EP-2).

❑ FHM is a rare autosomal dominant form of migraine which combines the typical migraine with paralysis of one side of the body, and (sometimes) atrophy of cerebellum. EP-2 has the same symptoms of FHM but the cerebellar atrophy *is always* present. The episodic ataxia component in both FHM and EP-2 responds with a carbonic anhydrase blocker (acetazolamide).

❑ Both diseases are often associated with mutations in the gene that codes for the P/Q-type Ca channels located in the presynaptic terminals throughout the brain. There is an increase in the P_{open} of the channels as well as a consequent increase in the Ca currents flowing through these channels.

❑ The phenomenon of cortical spreading depression (CSD) usually (but not always reported) precedes migraine development and causes the "aura" (subjective sensation of light). During CSD there is complete abolishment of all neuronal activity.

❑ Enhancement of Ca currents in P/Q type channels could favor CSD and, FHM and EP-2.



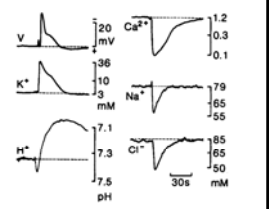
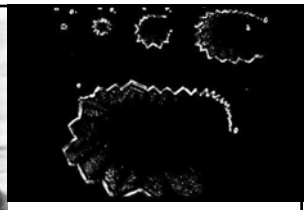
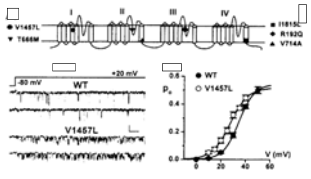
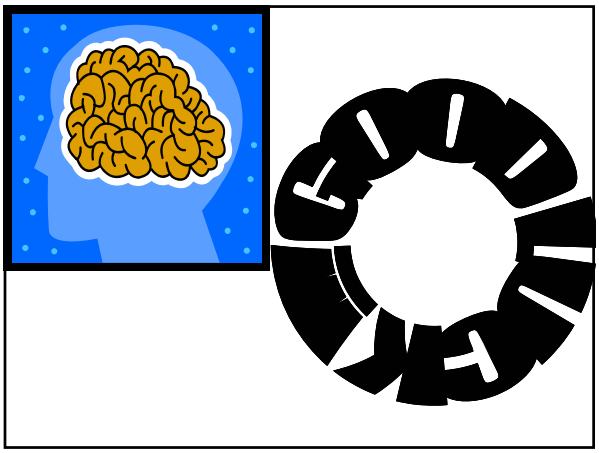


Fig. 10. Extracellular ionic changes during SD in rat cerebellum. All amplitude scales are logarithmic but magnitudes differ depending on ion. $[K^+]_e$ increases during SD, $[H^+]_e$ shows initial decrease (pH increase) then increases. $[Ca^{2+}]_e$, $[Na^+]_e$ and $[Cl^-]_e$ all fall. SD was induced by a brief train of local surface stimuli. In all cases, cerebellum was conditioned by reducing NaCl content; this accounts for reduced baseline in $[Na^+]_e$ and $[Cl^-]_e$ records. Based on Ref. [76].






CHILD

CLINICAL CORRELATION: MULTIPLE SCLEROSIS

Date: August 25, 2011 - 10:30 AM
Reading Assignment: Refer to posted handout in LUMEN

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Recognize that multiple sclerosis (MS) is an autoimmune, demyelinating disorder of the central nervous system.

2. List the risk factors for MS regarding age of onset, gender, family history, and geography.

3. Explain the more frequent signs and symptoms of MS.

4. Explain how the clinical diagnosis of MS is made, and how various ancillary tests support the diagnosis.

5. List the available treatments for MS, particularly for severe, acute attacks and for long-term disease modification.

Multiple Sclerosis (MS)

Michael P. Merchut, MD

(lecture slides with Frank Netter slides, copyrighted materials, videos and patient material removed)

CNS "white matter diseases"

- **Demyelinating CNS diseases involve destruction of normal myelin**
  - **multiple sclerosis (MS), others**
- **Dysmyelinating disorders involve varied hereditary metabolic defects, leading to abnormal myelin production: leukodystrophies**
  - **metachromatic leukodystrophy (CNS and PNS myelin affected), others**

Slide
"Metachromatic Leukodystrophy"
Frank Netter Collection
Vol 1, Part II, p. 20

Pathophysiology of MS

- **Immune-mediated destruction of normal CNS myelin with secondary loss of axons**
- ***White matter plaques*** **are seen postmortem in optic nerves, spinal cord and brain**
  - **plaque inflammation, demyelination, axon loss and gliosis (scarring) varies with its age**
  - **plaques are often periventricular in location**

Pt slide

MS white matter plaques, typically periventricular, appear beige or gray in unfixed tissue;

(far left) plaques appear pale in myelin stain preparations;

(left) dark areas reflect gliosis in MS plaques;

Pt slide

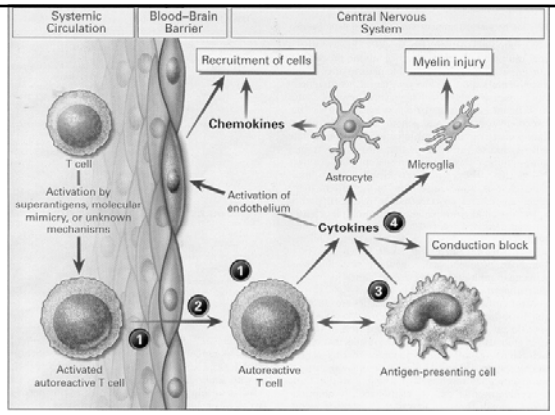
MS plaques appearing pale in the optic nerve and chiasm (myelin stain)

Pt slide

Asymmetric MS plaques appearing pale in the (L to R) pons, medulla and cervical spinal cord (myelin stain)

Pathophysiology of MS

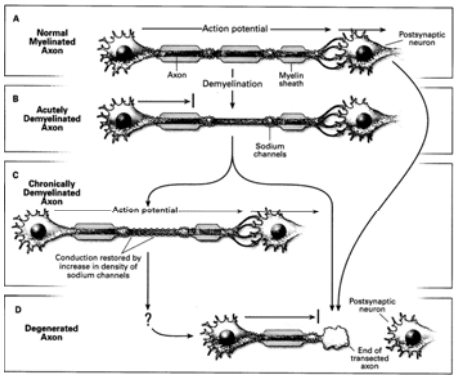
- **Unknown initial (multiple?) triggers or events**
- **Adhesion molecules of circulating (T-cell) lymphocytes attach to vascular endothelial receptors in the brain**
- **T-cells & monocyte-derived macrophages penetrate blood-brain-barrier (BBB) tight junctions**
- **Cytokines & antibodies are produced within the brain, more inflammatory cells activate and pass the BBB**
- **An autoimmune "cascade" to destroy myelin occurs**
- **The process repeats during the life of the patient at variable times, to different degrees, in different areas of the CNS**



Oversimplified **hypothetical pathogenesis of MS.** ***NEJM*** **337:1604, 1997**

Pathophysiology of MS

- In MS plaques, axonal conduction locally slows or fails, causing symptoms that may improve or recover spontaneously over days to weeks
- Significant recovery usually occurs only early in the disease course
- Permanent neurological disability develops if plaques with axonal loss accumulate



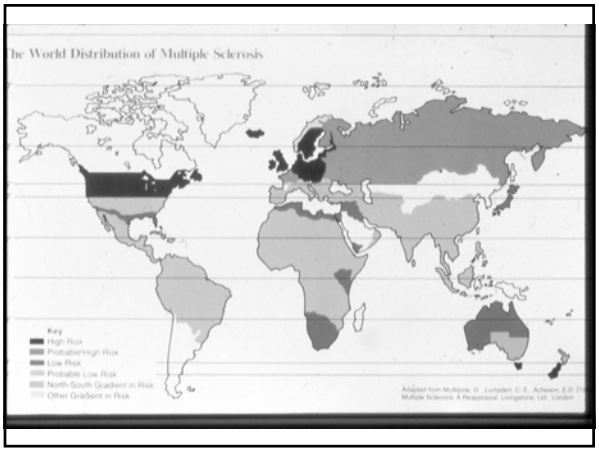
MS: myelin and axon damage. NEJM 338:323, 1998

Variable MS plaque pathophysiology

- If predominant inflammation, relatively preserved myelin and axons---
  - inflammation quickly subsides to normal state, best prognosis, full recovery
- If significant demyelination with preserved axons---
  - remyelination slowly occurs, or sodium channels develop to allow suboptimal transmission over demyelinated segments, intermediate prognosis, partial recovery
- If significant demyelination and axonal loss or transection---
  - no transmission occurs with irreparable axonal loss, worst prognosis, no recovery

Do viruses initiate or trigger MS?

- **Infection with a virus which antigenically resembles or alters myelin may start autoimmune myelin destruction by "molecular mimicry"**
  - **Growing up in temperate zones allows an environmental factor (viral exposure?) to increase your risk of MS**
  - **Postinfectious encephalomyelitis involves inflammatory white matter lesions after a viral infection, but does not reoccur**
  - **No single virus has yet been identified as the trigger of MS**



What else initiates or triggers MS?

- **Epidemiological research has failed to prove several common factors as triggers of MS (head trauma, mercury dental fillings, others)**
- **A positive family history of MS is a known risk factor**
- **The immune system in a genetically susceptible patient reacts improperly to CNS myelin (or other neural antigens) following early life exposure to various or multiple unknown factors**

Risk factors for MS

- **Onset in young adults 20-40 yrs old (range of 15-60 years)**
- **Female:male ratio is about 2:1**
- **20x greater risk if MS is present in first degree relative**
- **Certain HLA types**
- **Growing up in urbanized, temperate zones**

Clinical features of MS

- **The longer myelinated fiber tracts (for lower limbs) are more statistically prone to acquire MS plaques over time**
- **Development of an MS plaque in "noncritical" cerebral white matter may produce no overt symptoms**
- **A tiny MS plaque may be very symptomatic in "critical" areas like the optic nerve(s)**

Slide
"Multiple Sclerosis: Clinical Manifestations"
Frank Netter Collection, Vol 1, Part II, pp. 174-5

Most common initial symptoms & signs of MS: sensory or motor deficits in lower limbs, optic neuritis. **Typical (nonspecific) features: Lhermitte's sign, trigeminal neuralgia, internuclear ophthalmoplegia.**

Pt slide

Acute, left optic neuritis:

*** sudden, complete or patchy blindness in left eye;**

*** swollen, blurred left optic disc;**

*** impaired pupillary light reflex;**

Pt slide

*** optic neuritis may improve with partial to nearly complete visual recovery;**

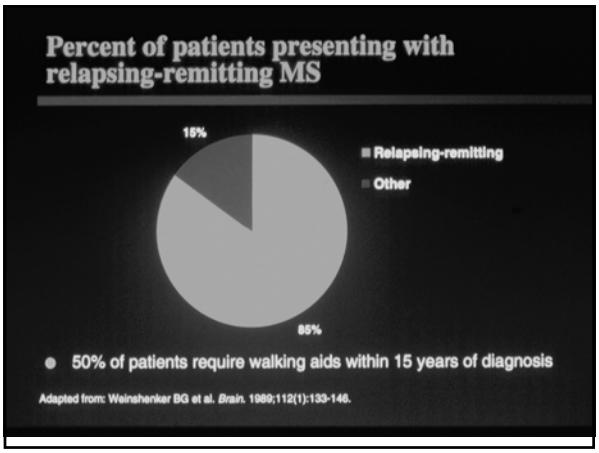
*** the optic disc now appears sharply outlined and paler ("optic atrophy");**

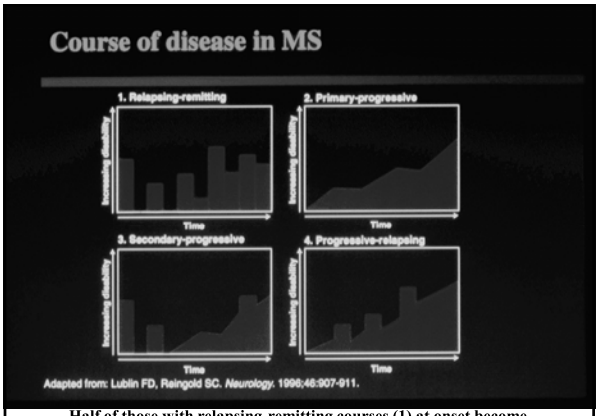
Pt slide

Bilateral internuclear ophthalmoplegia (MLF syndrome):

*** MS in younger patient;**

*** brain stem ischemia in older patient;**





Half of those with relapsing-remitting courses (1) at onset become secondarily progressive later (3) & (4).

MS diagnosis: *signs & symptoms disseminated in time & space*

- **Two or more symptomatic episodes, related to two or more distinct CNS lesions, occurring at different times (not monophasic), without better alternative diagnosis**
- **Lab tests exclude other disorders, support MS**
- **Dilemma: errors plague early diagnosis, but earliest treatment is desirable**

Pt slide

Ancillary tests for MS:

* **more sensitive than specific;**
* **show symptomatic and asymptomatic lesions;**

MRI scans of brain & spinal cord:

Pt slide

MRI brain scan:

* **multiple, peri-ventricular white matter lesions;**
* **lesions may or may not enhance with contrast;**
* ***overall, the most sensitive test for MS*;**

Pt slide

MRI brain scan of patient with MS

Ancillary tests for MS:

*** visual-evoked potential (VEP)**

Slide
"Multiple Sclerosis: Diagnostic Tests"
Frank Netter Collection
Vol 1, Part II, pp. 176-7

Somatosensory evoked potential (SSEP)

Slide
"Multiple Sclerosis: Diagnostic Tests"
Frank Netter Collection
Vol 1, Part II, pp. 176-7

CSF analysis, to show an immune process in the CNS (increased IgG production, oligoclonal bands)

Treatment of MS

- **No current curative therapy**
- **Some acute or chronic treatments may hasten recovery, lessen severity of attacks, or reduce long-term disability**
- **Some patients respond, others do not**

Treatment of an acute MS flare-up, relapse or "attack"

- Brief bedrest, then physical therapy as needed
- Treat any infection, keep afebrile
- If a disabling deficit, use IV methylprednisolone, 0.5-2 gms daily for 3-10 days, with or without oral prednisone taper $\leq$ 14 days
- Oral prednisone alone may be ineffective or worsen subsequent course (Acute Optic Neuritis Trial, Beck et al, NEJM 1993; 329:1764-69)

Symptomatic treatment of MS

- Spasticity
  - oral baclofen or tizanidine, or intrathecal pump baclofen
- Bladder dysfunction
- Fatigue
  - amantidine, pemoline or modafinil
  - 4-aminopyridine (blocks inhibitory K+ channels)
- Immobility
  - assistive devices, physical therapy

Disease-modifying treatment of relapsing/remitting MS

- Beta-interferons
  - natural proteins which enhance suppressor T-cell function, decrease lymphocyte entry into CNS, lessen cytokine production & antigen presentation
  - manufactured by recombinant DNA technique
- Glatiramer acetate
  - synthetic polypeptide mimic of myelin basic protein, a breakdown product of myelin
  - binds to antigen-presenting inflammatory cells, decreasing their binding to myelin targets, with other favorable effects on lymphocytes and cytokines
- Others (with significant side effect profiles)

Disease-modifying treatment of relapsing/remitting MS

- 1990s research trials with beta-interferons or glatiramer showed some treated patients had MS attacks which were less severe or less frequent
  - progression of disability often delayed
  - reduced disease burden (plaques) on MRI
- These drugs are given by subcutaneous or intramuscular injection
- Common side-effects: local skin reactions, flu-like symptoms

Disease-modifying drugs for relapsing/remitting MS

- Betaseron (beta-interferon 1b)
  - alternate day subcutaneous injection
- Avonex (beta-interferon 1a)
  - weekly intramuscular injection
- Rebif (beta-interferon 1a)
  - thrice weekly subcutaneous injection
- Copaxone (glatiramer)
  - daily subcutaneous injection