NEUROTRANSMITTERS

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Membrane potential

- Membrane potentials are always expressed as intracellular relative to extracellular potential.
- Resting membrane potential is primarily determined by K^+.
- When K^+diffuses from intracellular to extracellular fluid down its concentration gradient, the inner membrane potential becomes negative relative to the outer membrane potential.
- The Na^+-K^+ pump is responsible for maintaining the K^+ concentration gradient that is responsible for the resting membrane potential.

Ion transport

- Cl^- moves down its concentration gradient (extracellular fluid to intracellular fluid).
- However, Cl^- moves against an electrical gradient (on the Na^+-K^+-Cl^- co-transporter).
- Energy is required to move Cl^-.
- Low extracellular Ca^{2+} levels alter the resting potential.
- 3 Na^+ are pumped out for every 2 K^+ (or 1 Ca^{2+}) pumped in.

Action potential

- The nerve action potential consists of a transient self-propagated reversal of charge on the membrane.
- When Na^+ channels open, Na^+ diffuses down its concentration gradient (outside to inside).
- An action potential is generated.
- At the peak of the upstroke, the inner membrane potential becomes positive relative to the outer membrane potential.

Action potential

- The internal potential goes from a negative value, through zero potential, to a slightly positive value primarily through increases in Na^+ permeability and then returns to resting values by an increase in K^+ permeability.

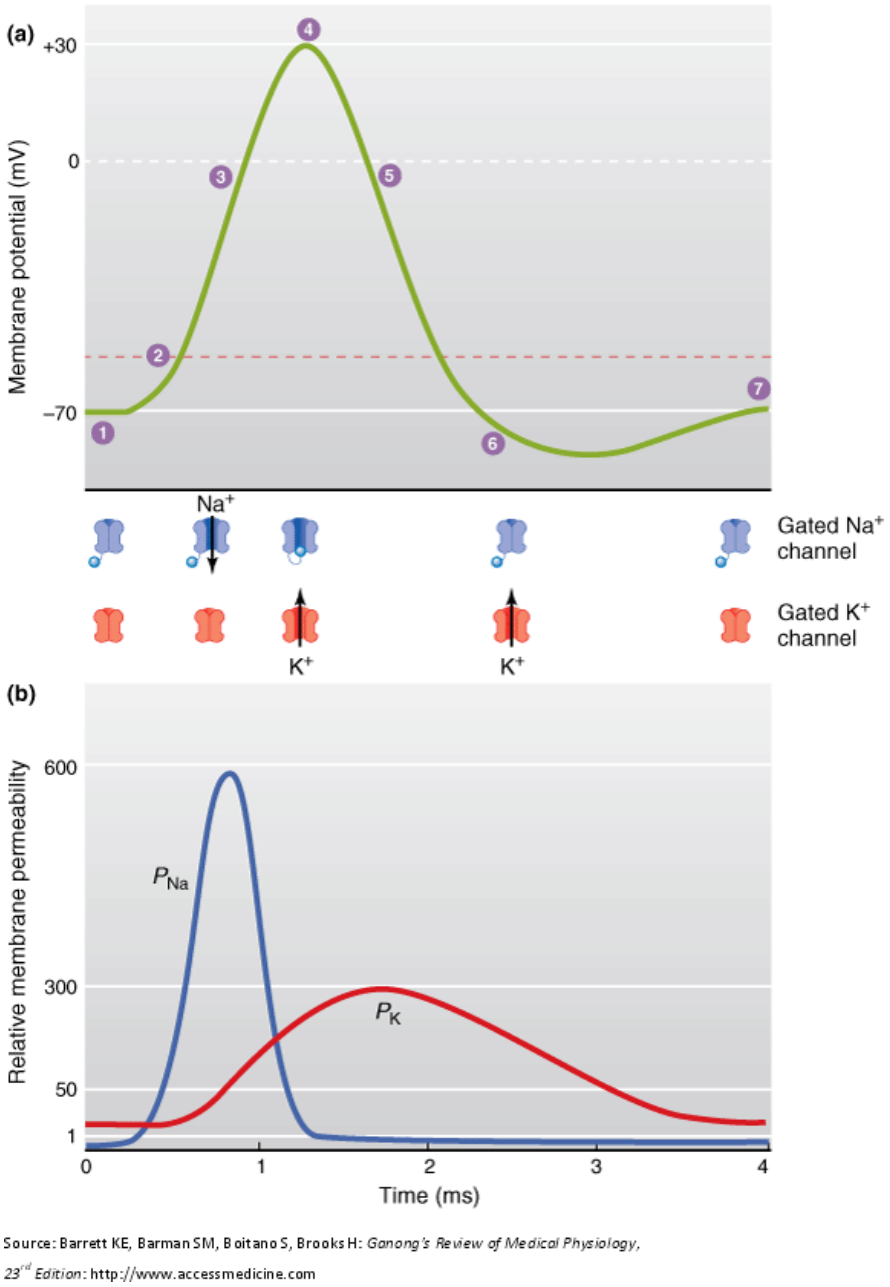
Action potential

- The Na^+/K^+ pump (Na^+/K^+-ATPase) tends to extrude Na^+ from the interior of the cell, but it carries K^+ ions inward.
- The Na^+-K^+ pump is responsible for maintaining the Na^+-concentration gradient that is responsible for the upstroke.
- Activation of voltage-dependent Ca^{2+} channels contributes to the depolarizing phase.
- Depolarization opens K^+ channels, resulting in outward movement of K^+
- Repolarization, closure of the Na^+ channel, and hyperpolarization.

Action potential

- A depolarizing current pulse directly activates a series of unitary action potentials for as long as the input remains above the threshold; this is the tonic mode of firing.
- When the action potential arrives at the pre-synaptic terminal, it initiates release of the excitatory or inhibitory transmitter.
- Depolarization at the nerve ending and entry of Ca^{2+} initiate docking and then fusion of the synaptic vesicle with the membrane of the nerve ending.
- Lead (>10µg/dL) interferes with Ca^{2+} homeostasis, altering nerve depolarization as well as inhibiting neurotransmitter release

Action potential



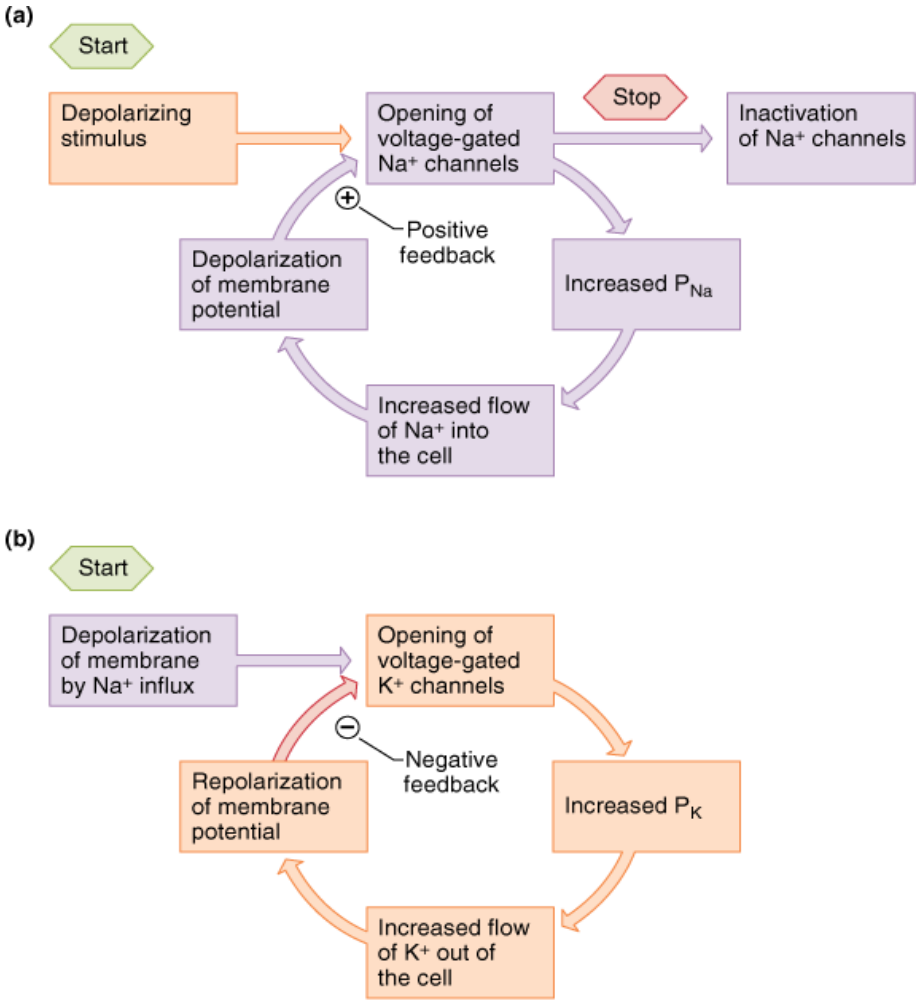
Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

The changes in (a) membrane potential (mV) and (b) relative membrane permeability (P) to Na+ and K+ during an action potential.

(From Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology.* McGraw-Hill, 2008.)

Fig. 4-6 Accessed 03/01/2010

Feedback control



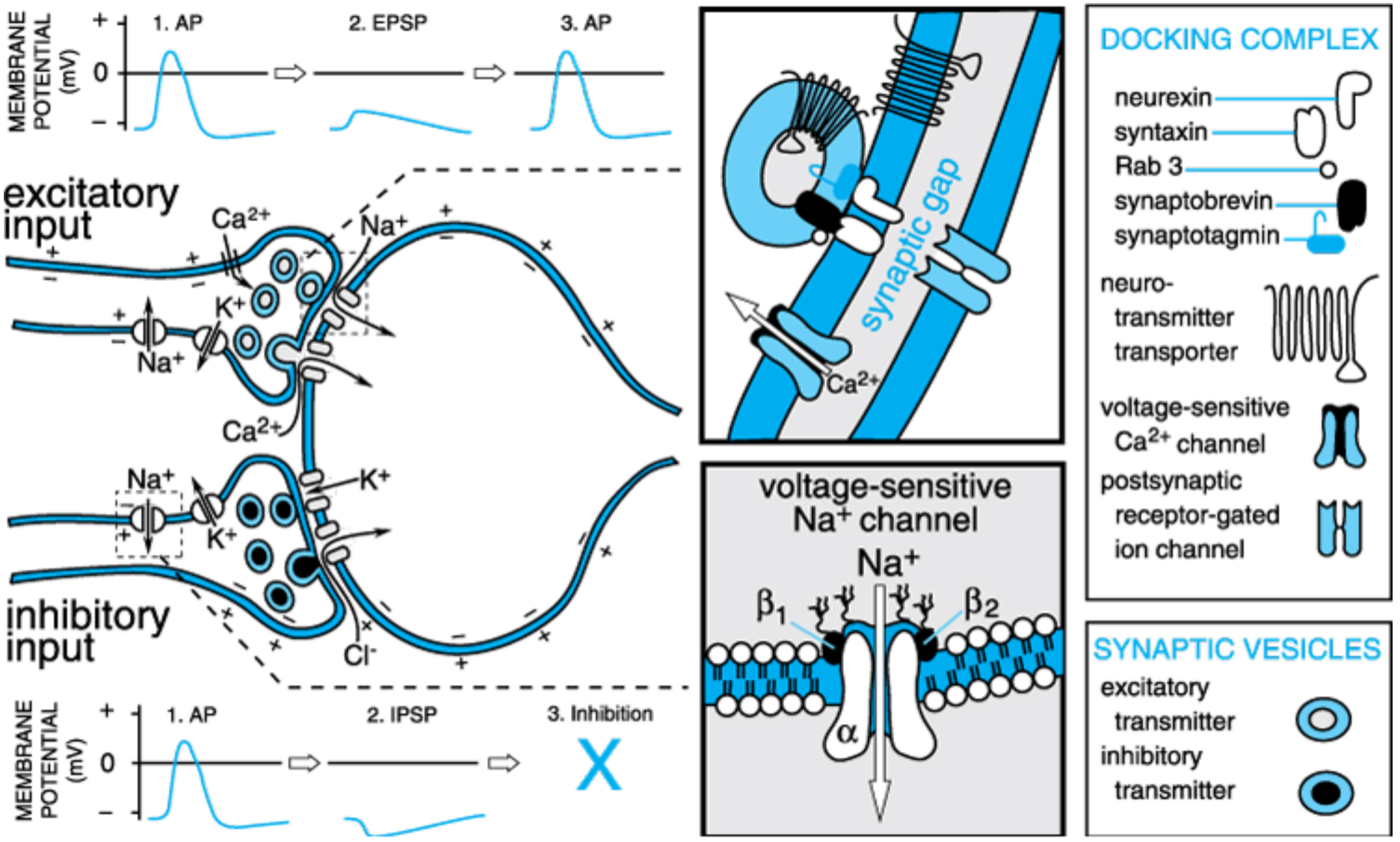
Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

(a) Na^+ channels exert positive feedback. (b) K^+ channels exert negative feedback.

(From Widmaier EP, Raff H, Strang KT: *Vander's Human Physiology.* McGraw-Hill, 2008.)

Fig. 4-7 Accessed 03/01/2010

Synapse



(Modified from Eccles, 1964, 1973; Katz, 1966; Catterall, 1992; Jahn and Südohorf, 1994.)

Fig. 6-2 Accessed 02/01/2010

Synapses

Electrical	Chemical
3-4nm between pre and post synaptic membrane bridged by gap junctions	40nm wide synaptic cleft
Pre and post ganglion cytoplasm continuous Open after engagement by neurotransmitter	Interact with G proteins
Signals transmitted by ions	Signal transmitted by chemicals
No synaptic delay	1-5ms synaptic delay across cleft
Ion/electrical conduction may occur in either direction	Usually unidirectional

Synapse

- Ligand gated channels open.
- Entering ions depolarize immediate region.
- Adjacent voltage gated channels open propagating action potential.
- Action potential reaches terminal.
- Voltage gated Ca^{2+} channels open.
- Ca^{2+} binds to proteins on vesicles permitting fusion with terminal membrane.
- Neurotransmitter is released.

Synapse

- Voltage gated K^+ channels open to repolarize axon
- May see reuptake of neurotransmitter.
- Nicotine upregulates N1 and N2 receptors.
- Pufferfish toxin (tetradotoxin) blocks Na^+ channel.
- Botulinum toxin blocks acetylcholine release.

Neurotransmitters

Neurotransmitter	Areas of Concentration
Acetylcholine (ACh)	Neuromuscular junction, autonomic ganglia, parasympathetic neurons, motor nuclei of cranial nerves, caudate nucleus and putamen, basal nucleus of Meynert, portions of the limbic system
Norepinephrine (NE)	Sympathetic nervous system, locus ceruleus, lateral tegmentum
Dopamine (DA)	Hypothalamus, midbrain nigrostriatal system
Serotonin (5-HT)	Parasympathetic neurons in gut, pineal gland, nucleus raphe magnus of pons
Gamma-aminobutyric acid (GABA)	Cerebellum, hippocampus, cerebral cortex, striatonigral system
Glycine	Spinal cord
Glutamic acid	Spinal cord, brain stem, cerebellum, hippocampus, cerebral cortex

Neurotransmitters

Acetylcholine (basal forebrain to cortex; motor neurons to neuromuscular junction; interneurons in striatum)
- subtypes M1, N excitatory
- subtype M2 inhibitory

Dopamine (D1,D2) inhibitory (substantia nigra to striatum, to limbic system)

GABA (A,B) inhibitory (cortical neurons, long projection pathways.)

Glutamate (NMDA, ACPD, AMPA) excitatory
- ligand gated Calcium ion channel (Magnesium dependent)

Glycine inhibitory (spinal cord)

Serotonin (pontine raphe nuclei; medulla/pons to dorsal horn of spinal cord)
- subtypes 5HT2A, 3, 4 excitatory
- subtype 5HT1A inhibitory
- cAMP as second messenger

Norepinephrine (locus ceruleus to limbic system; medulla to locus ceruleus, spinal cord)
- subtypes α1, β1 excitatory
- subtypes α2, β2 inhibitory

Transmission

- G-protein coupled inward rectifying K^+ (GIRK) activated by muscarinic AChR (bind β, γ of G_i)
- Hyperpolarize (heart tissue), leading to diminished rate of firing
- Nicotinic receptor is the substrate for PKA (α, δ), PKC, tyrosine kinase (β, γ, δ).
- Phosphorylation of AChR desensitizes
- Na^+ transport channel
- Acetylcholine is found at motor synapses, preganglionic and parasympathetic postganglionic synapses, as well as in the nucleus basalis
- <u>Ion channels regenerative (all or none firing)</u>

Transmission

- The extent of phosphorylation of inhibitor-1 by PKA reduces phospholipoprotein phosphatase controlled by calcineurin
- Ca^{2+} activated phosphatase dephosphorylates inhibitor-1
- Ca^{2+} leads to neurotransmitter release in quantal packets
- L-type channel is not a fast responder and is not at active zone
- T-type channel is low voltage activated
- P/Q, N, R type channels permit fast synaptic transmission

Second messengers

- G-receptors: adrenergic, $GABA_B$, odorants, rhodopsin, neuropeptides
- NE binds receptor, activates G_s; adenyl cyclase second messenger; cAMP activated; cAMP dependent protein kinase is effector
- ACh binds muscarininc receptor, activates G_q; PLC second messenger; IP3/Ca^{2+} and DAG/PKC are effectors
- Histamine binds receptor, activates G; PLA_2 second messenger; arachidonic acid effectors are 5-Lipoxygenase, 12-lipoxygenase, cyclo-oxygenase

G-protein linked second messengers

Receptor	G-protein class
α_1	q
α_2	i
β_1, β_2	s
M_1, M_3	q
M_2	i
D_1	s
D_2	i
H_1	q
H_2	s
V_1	q
V_2	S

G_q activates phospholipase C, leading to generation of PIP_2 with resulting increase in intracellular Calcium or protein kinase C depending upon later pathway.

G_s activates adenylyl cyclase, leading to a rise in cAMP, and, protein kinase A.

G_i blocks adenylyl cyclase, leading to a fall in cAMP, and, protein kinase A.

Neurotransmitter receptors

Type	**Second messenger**
N-N, N-M	Open Na^+, K^+ channels
M1, M3	Increase IP3, DAG, intracellular Ca^{2+}
M2	Opens K^+ channel, inhibits adenyl cyclase
α1	Increases IP3, DAG, intracellular Ca^{2+}
α2	Decreases cAMP or decreases intracellular Ca^{2+} or closes K^+ channels
β (all)	Stimulate adeny cyclase, increase cAMP
D1 D2	Stimulates adenyl cyclase, increases cAMP Inhibits adenyl cyclase, opens K^+channels

Pre-synaptic inhibition

- Pre-synaptic inhibition is a mechanism that permits the "gain" at a particular synaptic input to be reduced without reducing the efficacy of other synapses that impinge on that neuron.
- The reduction in neurotransmitter is caused either by:
- A decrease in the size of the action potential in the pre-synaptic terminal as a result of activation of K^+ or Cl^- channels
- OR
- By reduced opening of Ca^{2+} channels in the pre-synaptic terminal

Pre-synaptic inhibition

- Binding of neurotransmitters to the receptors mediating pre-synaptic inhibition leads to a reduction in the amount of neurotransmitter secreted by the post-synaptic axon.
- Synaptic conduction can be strengthened or weakened on the basis of past experience.

Pre-synaptic inhibition

- Habituation is a simple form of learning in which a neutral stimulus is repeated many times.
- Non-associative learning.
- The first time it is applied it is novel and evokes a reaction.
- As it is repeated, the stimulus evokes lesser responses as intracellular Ca^{2+} is decreased as Ca^{2+} channels are deactivated.
- Release of neurotransmitter from the pre-synaptic terminal is decreased.

Enhanced post-synaptic potentiation

- Post-tetanic potentiation is the production of enhanced post-synaptic potentials in response to stimulation.
- This enhancement lasts up to 60 seconds and occurs after a brief (tetanizing) train of stimuli in the pre-synaptic neuron that causes Ca^{2+} to accumulate in the pre-synaptic neuron as the intracellular Ca^{2+} binding sites swamped.
- This involves a Na^{+}-K^{+} ligand gated channel.

Enhanced post-synaptic potentiation

- Long-term potentiation is a rapidly developing persistent enhancement of the postsynaptic potential response to pre-synaptic stimulation after a brief period of rapidly repeated stimulation of the pre-synaptic neuron.
- It is initiated by an increase in intracellular Ca^{2+} in the post-synaptic rather than the pre-synaptic neuron.
- It may persist for days.
- Associative learning.

Enhanced post-synaptic potentiation

- Sensitization is the prolonged occurrence of augmented post-synaptic responses after a stimulus to which one has become habituated is paired once or several times with a noxious stimulus.
- Pre-synaptic facilitation may occur.
- Sensitization is due to a Ca^{2+}-mediated change in adenylyl cyclase that leads to a greater production of cAMP.

Enhanced post-synaptic potentiation

- Long-term depression is the opposite of long term potentiation.
- It is characterized by a decrease in synaptic strength and is produced by slower stimulation of pre-synaptic neurons (with a smaller rise in intracellular Ca^{2+}).
- Phosphorylation of the GluR2 subunit of the AMPA receptors is required.
- Glutamate neurotransmission.
- It may be involved in the mechanism by which learning occurs in the cerebellum.

Post-synaptic inhibition

- Binding of excitatory neurotransmitter with post-synaptic receptors initiates a conducted action potential in the post-synaptic neuron (the excitatory post-synaptic potential)
- Opening of Na^+ or Cl^- channels or the closing of K^+ channels produces depolarization.
- This can be prevented, however, by the hyper-polarization induced by a concurrent inhibitory post-synaptic potential.

Enhanced post-synaptic potentiaion

- The inhibitory transmitter causes a selective increase in permeability to Ca^{2+} or Cl^{-}
- Results in a localized hyper-polarization, the inhibitory post-synaptic potential.
- Glycine facilitates.
- The NMDA receptor-linked Ca^{2+} channels open only when both sets of synapses are activated.
- These synapses sense the "pairing" of two synaptic inputs.
- Mg^{2+} blocks these channels.

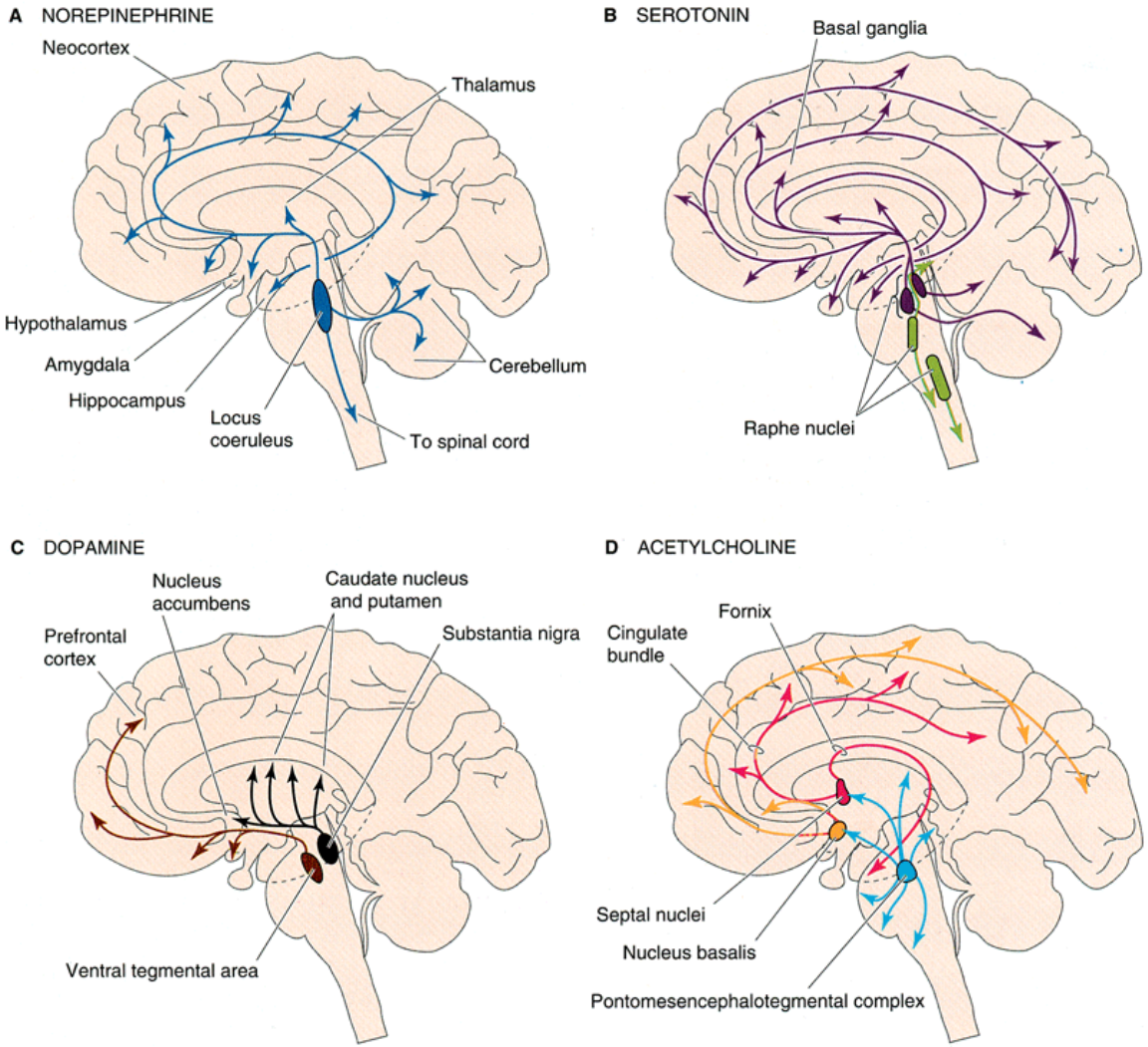
Enhanced post-synaptic potentiaion

- As a result of increased Ca^{2+} admitted into post-synaptic cells by this mechanism, protein kinases are activated and alter the synapse so as to strengthen it.
- Memory formation occurs.

Synapses

- Axo-somatic synapses terminate on neuronal cell bodies and tend to be inhibitory.
- Axo-dendritic synapses terminate on dendrities or mushroom-shaped "dendritic spines," and tend to be excitatory.
- Denditric-dendritic synapses may be excitatory or inhibitory.
- Axo-axonal synapses terminate on an axon, often close to synaptic terminals, and modulate the release of neurotransmitters (presynaptic inhibition).

Neurotransmitters and pathways



Source: Barrett KE, Barman SM, Boitano S, Brooks H: *Ganong's Review of Medical Physiology, 23rd Edition*: http://www.accessmedicine.com

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Fig. 7-2 Accessed 02/01/2010

Central autonomic network

- Nucleus of the solitary tract receives visceral input from CN VII, IX, X.
- Relayed to forebrain via parabrachial nucleus
- Surrounds superior cerebellar peduncle in upper pons
- Provides input to hypothalamus, periacqueductal gray matter, amygdala, ventroposterior parvocellular nucleus of the thalamus, anterior insula and infralimbic area of the anterior cingulate cortex
- The periacqueductal gray receives inputs from hypothalamus, nucleus of the solitary tract, and parabrachial nucleus
- Projects to medullary reticular formation.

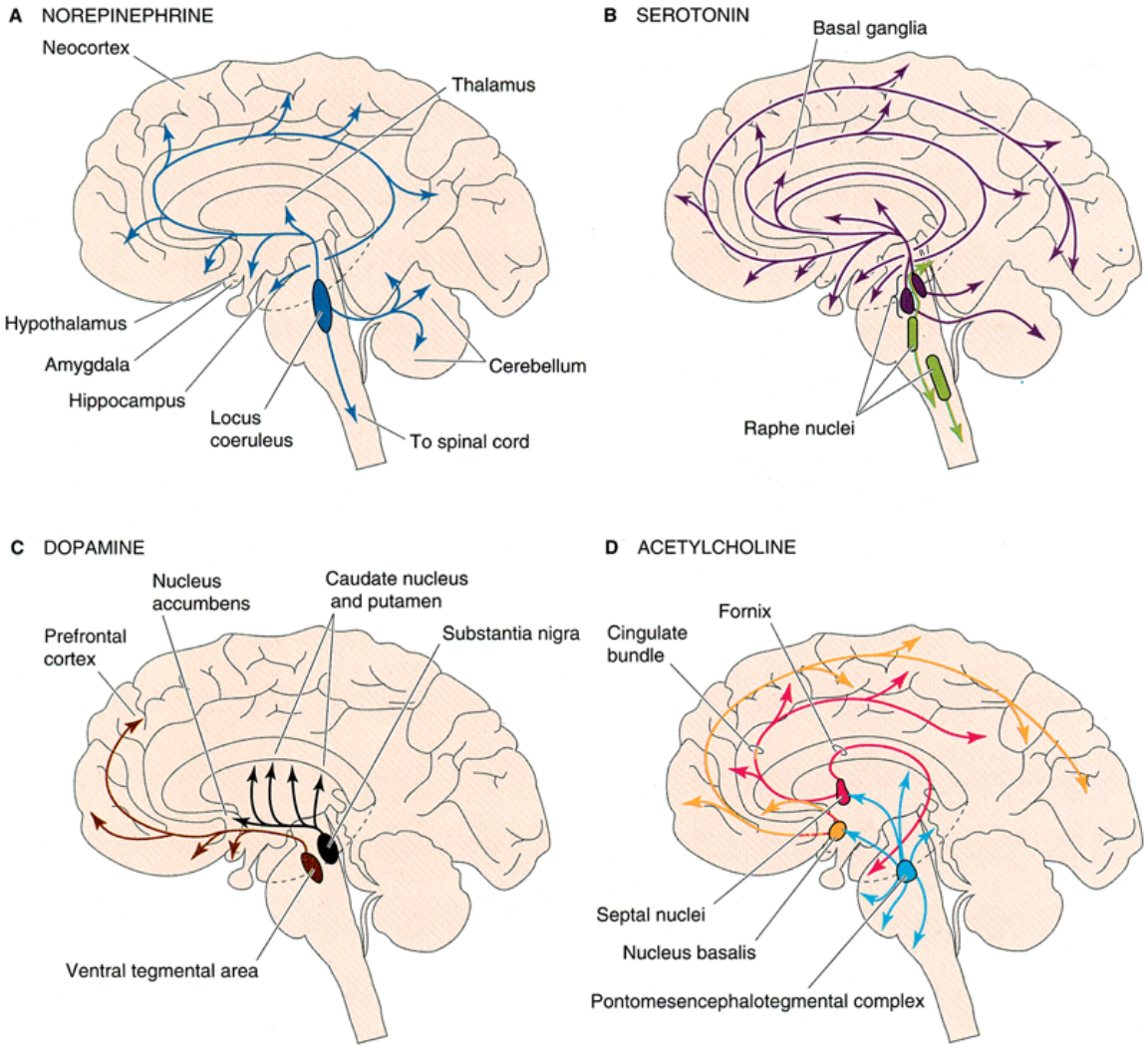
Central autonomic network

- Hypothalamus integrates autonomic and endocrine functions with behavior.
- Compares sensory information with set points.
- Medial forebrain bundle.
- Periventricular fiber system links hypothalamus to periacqueductal gray
- Sterotyped behavioral patterns
- Axons from parvocelluar neurons (releasing hormones) as well as paraventricular and arcuate nuclei conveyed to median eminence for control of anterior pituitary; axons from the magnocellular neurons (oxytocin, vasopressin)
- Continue down the pituitary stalk also meet in the median eminence.

Central autonomic pathways

- Central autonomic pathways descend beside the intermediate gray matter.
- Originate in part from the hypothalamus and in part from nuclear groups in the brainstem.
- Terminate in the intermediolateral cell columns that give rise to the preganglionic sympathetic and parasympathetic fibers of the peripheral autonomic system.
- The central sympathetic system is required for normal baroceptor reflex activity.
- The central parasympathetic pathway is required for bladder and bowel function.

Neurotransmitters and pathways



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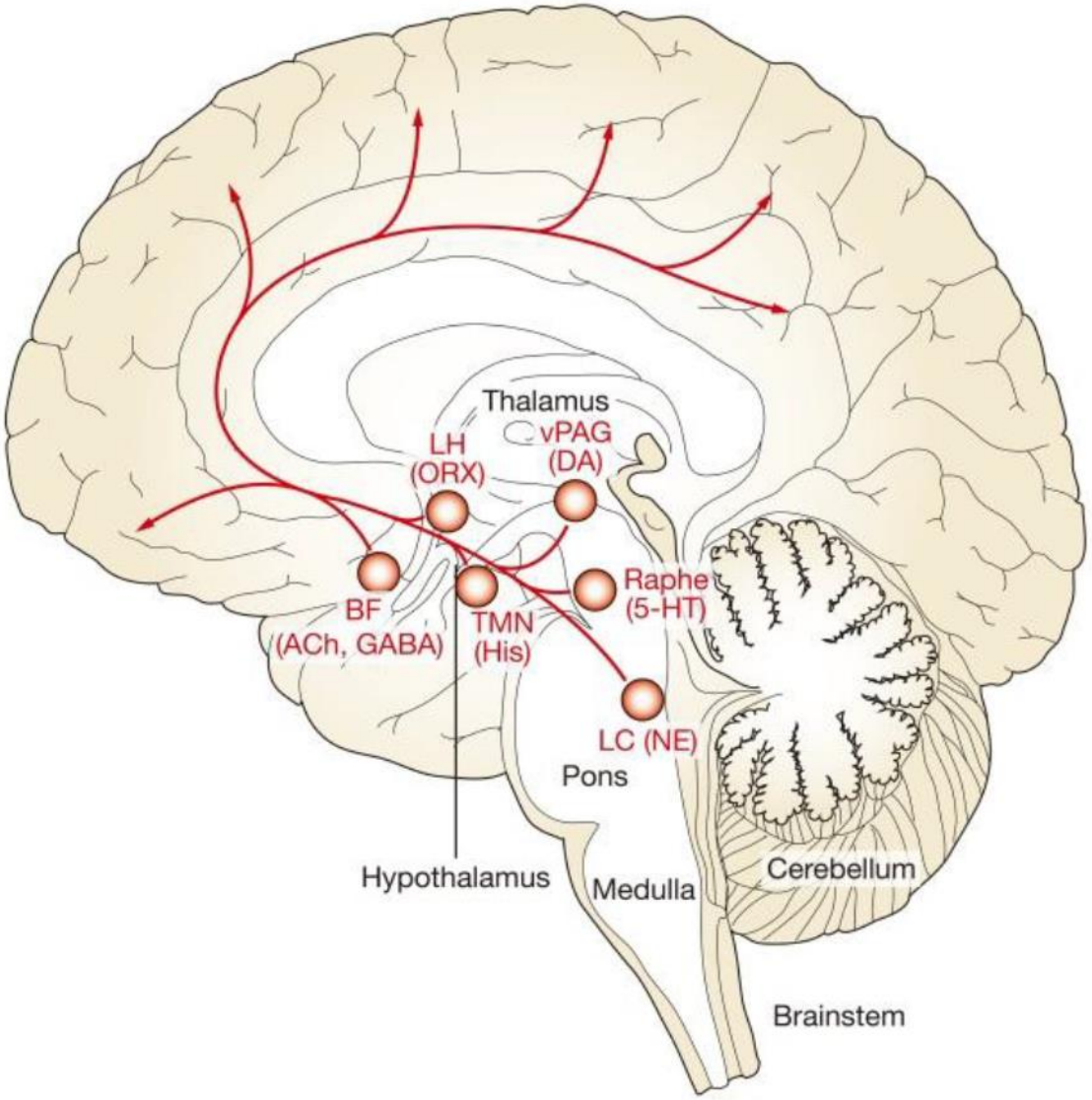
Thalamus
LH
(ORX)
vPAG
(DA)
BF
(ACh, GABA)
TMN
(His)
Raphe
(5-HT)
LC (NE)
Pons
Hypothalamus
Medulla
Cerebellum
Brainstem

Adrenergic cell groups

- Noradrenergic neurons are located in one dorsal and one ventral column.
- The ventral column contains neurons associated with the nucleus ambiguus. The dorsal column contains neurons from the dorsal motor vagal nucleus and the solitary tract nucleus. Both project to the hypothalamus and control cardiovascular and endocrine functions.
- The locus ceruleus in the periacqueductal gray matter provides major ascending output to the cortex as well as descending projections to the brain stem, cerebellum, and spinal cord.

Adrenergic cell groups

- Neurons located more ventrolaterally in the periacqueductal gray as well as those along the ventrolateral margin of the pontine tegmentum mainly innervate the brain stem and spinal cord. Modulate pain perception.
- Adrenergic projections arise in the ventrolateral medulla near the nucleus ambiguus and project to the spinal cord (sympathetic preganglionic column providing tonic excitatory input to vasomotor neurons) as well as to the hypothalamus, modulating cardiovascular and endocrine responses;

Adrenergic cell groups

- those arising in the nucleus of the solitary tract project to the parabrachial nucleus (gastrointestinal).
- Neuropeptide Y, somatostatin, enkephalins are also neurotransmitters found in adrenergic ganglia.

Dopaminergic cell groups

- Dopaminergic neurons in the substantia nigra, the adjacent retrorubral field, and ventral tegmental area provide a major ascending pathway that terminates in the striatum, the frontal temporal cortex, and the limbic system (including the amygdala and lateral septum).
- Dopaminergic neurons from the locus ceruleus project to the ventral tegmental area; ventral tegmental area to habenula as well as parabrachial nucleus (adjacent to locus ceruleus)

Dopaminergic cell groups

- Hypothalamic dopaminergic neurons in zona incerta provide long descending pathways to the autonomic areas of the lower brain stem and the spinal cord. Also project to thalamus. Those located along the wall of the 3rd ventricle are involved with endocrine control.
- Dopaminergic neurons also found in retina and olfactory bulb

Serotonergic cell groups

- Most serotonergic neurons are located along the midline of the brain stem in the raphe nuclei.
- Neurons from the raphe magnus, pallidus, and obscuris nuclei in the caudal medulla project to the motor and autonomic systems in the spinal cord.
- Neurons from the raphe magnus nucleus at the level of the rostral medulla project to the spinal dorsal horn and is thought to modulate the perception of pain.
- Neurons in the raphe nucleus in the pons and midbrain project to nearly all of the forebrain.

Cholinergic cell groups

- Cholinergic cell groups in the basal forebrain include the medial septum, diagonal band, and the nuecleus basalis of Meynert. These topographicaly innervate the entire cerebral cortex and hippocampus and amygdala.
- Pontine cholnergic cellgroups innervate the brain stem reticular formation as well as the thalamus.
- The pedunculopointine nucleus is located ventrolaterally near the superior cerebellar peduncle (and controls firing of glycinergic neurons in the lateral reticulospinal pathway).

Cholinergic cell groups

- The laterodorsal tegmental nucleus is a component of the periacqueductal gray matter just rostral to the locus ceruleus.
- VIP, substance P are neurotransmitters also found in cholinergic ganglia.

Histaminergic cell groups

- All of the histaminergic cells in the brain are clustered in the tuberomammillary nucleus in the posterior lateral hypothalamus. One cluster is located ventrolaterally along the edge of the brain; the other is located dorsomedially along the edge of the mammillary recess of the third ventricle.
- Histaminergic neurons innervate the entire neuraxia.

Dopamine

- The nigrostriatal pathway that runs from the substantia nigra to the basal ganglia (striatum) and modulates motor movement.
- The mesolimbic pathway that runs from the ventral tegmentum to the nucleus accumbens. Associated with pleasure and reward, delusions.

Dopamine

- The mesocortical pathway projects from the ventral tegmentum to the prefrontal cortex and modulates cognitive function (dorsolateral prefrontal cortex) and affective symptoms (ventromedial prefrontal cortex).
- The tuberoinfundibular pathway projects from the hypothalamus to the pituitary and controls prolactin secretion.
- Projections from the peri-acqueductal gray, the ventral meso-encephalon, hypothalamus, and lateral parabrachial nucleus project to the thalamus. They may be associated with arousal and sleep.

Norepinephrine

- Ascending adrenergic projections originate principally in the locus ceruleus and project to the cerebellum, hypothalamus, amygdala, hippocampus, basal forebrain, and the pre-frontal cortex.
- Descending projections in the spinal cord regulate pain pathways.
- Postganglionic terminations of the sympathetic system on blood vessels utilize norepinephrine.
- Norepinephrine regulates mood, arousal, and cognition, among other functions.

Serotonin

- Ascending serotonin projections originate in the ventral tegmentum and project to the cerebellum, hypothalamus, amygdala, hippocampus, striatum, nucleus accumbens, basal forebrain, and the pre-frontal cortex.
- Descending projections in the spinal cord regulate pain pathways.
- Serotonin regulates mood, anxiety, and arousal, among other functions.

Serotonin system

- The $5HT_{1A}$ autoreceptor is found in somatodendritic neurons. Its activation inhibits adenyl cyclase and activates receptor operated K^+ ion channels while inhibiting voltage gated Ca^{2+} channels. This hyperpolarization serves to decrease firing in the raphe cells.
- The $5HT^{1D}$ autoreceptor is found on presynaptic axon terminals and inhibits the release of 5HT. Vasoconstrictive. This autoreceptor is widely distributed in substantia nigra and basal ganglia and is thought to regulate firing of dopaminergic neurons.

Serotonin system

- Activation of the $5HT_{2A}$ receptor activates PLC, activating PKC and IP_3. K+ conductance diminishes, permitting slow depolarization. Excitatory to neurons.
- The $5HT_3$ receptor is mediated through the ligand gated mixed cation channel. Activation leads to rapid depolarization and neuronal excitation. The area postrema, the solitary tract nucleus, and postsynaptic axon terminals of the parasympathetic system are rich in these receptors.

Serotonin system

- The $5HT_4$ receptor is found in the superior and inferior colliculi, hippocampus and presynaptic axon terminals in the myenteric plexus (releasing acetylcholine). Its activation leads to diminished K^+ conductance, resulting in slow depolarization.

Acetylcholine

- Acetylcholine projections originate principally in the ventral tegmentum and project to the hypothalamus, thalamus, amygdala, hippocampus, basal forebrain, and the pre-frontal cortex.
- Regulate arousal, cognition, and memory, among other functions.

Acetylcholine

- Nicotinic receptors of the N type are the main receptors found on sympathetic as well as parasympathetic ganglion cells. These receptors are activated by acetylcholine released by preganglionic fibers. Nicotinic receptors of the M type are found on skeletal muscle and are activated by acetylcholine released by the motor nerve onto the end plate of the muscle.
- Muscarinic receptors are found at parasympathetic postganglionic terminations as well as in sympathetic postganglion terminations in sweat glands. Acetylcholine is the neurotransmitter.

Myasthenia gravis

- With unimpaired cholinergic signaling, the presynaptic neuron depolarizes. Ca^{2+} enters cell. Ca^{2+} dependent release of acetylcholine into the synaptic cleft follows.
- Acetylcholine transiently binds to receptors on postsynaptic cell. Acetylcholine comes off receptor and either binds another receptor or is degraded by the membrane bound enzyme, acetyl cholinesterase.
- Drugs that inactivate the enzyme lead to prolongation of acetylcholine.activity at the nerve ending.

Myasthenia gravis

- Myasthenia gravis is an autoimmune disorder where the nicotinic type 1 (N1) acetylcholine receptors are attacked and destroyed. The number of N1 receptors decreases causing a decrease in the muscle response to the released acetylcholine.
- Myasthenia gravis is a disruption of the cholinergic signaling at the neuromuscular junction.

Myasthenia gravis

- Typically begins with ptosis.
- Weakness of extra-ocular muscles may be intermittent and does not correspond to any specific brainstem syndrome.
- Pupils are not affected.
- Limb weakness is more marked proximally.
- Sensation and reflexes are preserved.
- May worsen with concurrent infection.
- Associated with thymoma.

Myasthenia gravis

- Tensilon (edrophonium chloride) is an anticholinesterase inhibitor preventing degradation. Intravenous administration decreases symptoms of weakness.
- Treat underlying disorder first.
- Treat with anticholinesterase durgs (pyridostigmine, neostigmine). High doses may lead to cholinergic crisis of weakness and respiratory failure.

Lambert-Eaton

- Myasthenic syndrome.
- Autoimmune disorder. Presynaptic calcium channels are destroyed, impairing acetylcholine release. May find circulating anti-calcium channel antibodies.
- Supramaximal stimulation does not show a decrease in response with successive stimuli (on EMG). Tetanic stimulation overcomes blockade and is associated with symptom improvement.
- Proximal limb weakness and autonomic symptoms.
- Often related to small cell lung cancer.

Receptor responses

Tissue		Parasympathetic	Sympathetic
Eye (Iris)	Radial muscle Circular muscle Ciliary muscle	 Contracts (M_3) Contracts (M_3)	Contracts (α_1) Relaxes (β)
Heart	SA node Atria Ventricle	Decreased rate (M_2) Decreased force, rate (M_2)	Increased rate (β_1) Increased force (β_1) Increased rate (β_1)
Lungs	Bronchi Bronchial glands	Contracts (M_3) Stimulated (M_3)	Relaxes (β_2)
GI Skin	Walls (motility, tone) Sphincters Pilomotor smooth muscle Sweat gland secretion	Contracts (M_3) Relax (M_3) Increases (M)	Relax (α_2,* β_2) Contract (α_1) Contracts (α) Increases (α)

* The sympathetic system acts on GI walls via presynaptic inhibition at cholinergic nerve endings.

Receptor responses

Tissue		Parasympathetic	Sympathetic
GU	Bladder wall Sphincter Uterus pregnancy Penis	Contracts (M_3) Relaxes (M_3) Contracts (M_3) Erection (M)	Relaxes (β_2) Contracts (α_1) Contracts (α_1) Relaxes (β_2) Ejaculation (α)
Metabolic	Liver Fat cells Pancreas		Glycogenolysis (α, β_2) Lipolysis (α, β_1, β_3) Insulin secretion (β)

Anesthetics

- Inhaled anesthetics inhibit two domain channels (K+), affect resting potential, and hyperpolarize. Particularly depress thalamic transmissions. Anesthetic effects (skin incision) related to glycine inhibition (at a spinal level).
- Halothane is used for induction because of it lacks odor; isoflurane has pungent odor but is often used to maintain anesthesia.
- Sevoflurane has a sweet odor. It is converted to an ether as it passes over CO_2. It inhibits NMDA receptors and may increase GABA response.
- Cyclopropane and nitrous oxide affect NMDA receptors. No effect on glycine.

Anesthetics

- Nitrous oxide does not dissolve readily in blood. Used for induction because rapid absorption/ release leads to relative concentration of halogenated anesthetic. When anesthetic discontinued, if Oxygen is not supplied, the same mechanism lowers the relative concentration of Oxygen in alveoli.
- The minimal alveolar concentration of an anesthetic (potency) is equal to the patients'' response to a skin incision.

Anesthetics

- Both inhaled and intravenous anesthetics depress hippocampal transmissions (memory).
- Pentobarbital and propofol affect GABA neurotransmitters (chloride gated channels). Both work at the tubero-mamillary nucleus. Additionally potentiates glycine activity. Thus, may see excitatory phase. Lesser effect on CNS evoked potentials than inhaled anesthetics.
- Propofol is the most commonly used intravenous anesthetic today. May exacerbate hypotension.

Anesthetics

- Ketamine inhibits NMDA receptors, induces a dissociative state. It does not potentiate glycine. Used for induction in those at high risk for hypotension, bronchospasm.
- Etomidate is used for induction for those at high risk of hypotension.
- Dexmedetomidane is an α_2 adrenergic agonist that works in the locus ceruleus.