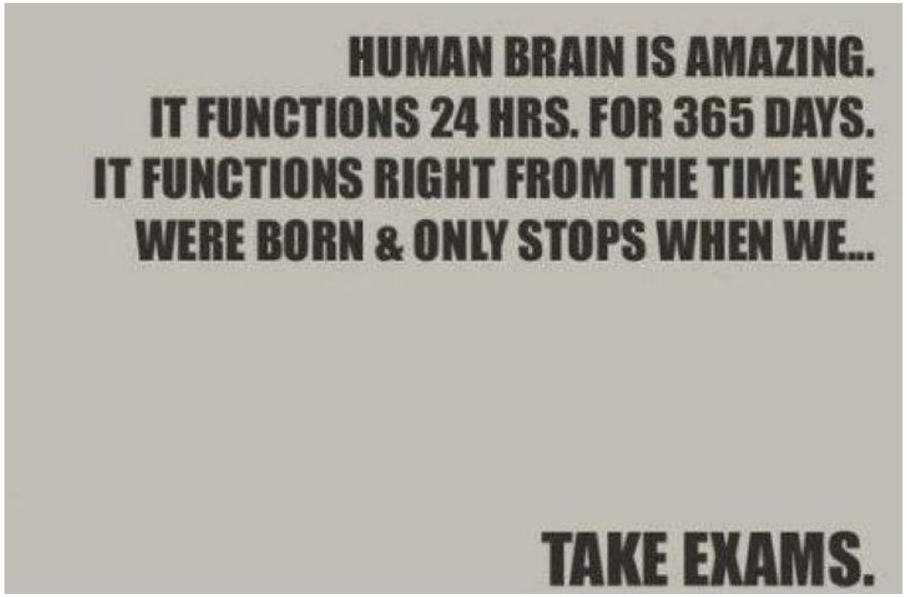
Exam

Written exam will take place on Monday, June 15, 2020, at 16-17.

Oral exam will take place on June 16-17, 2020.

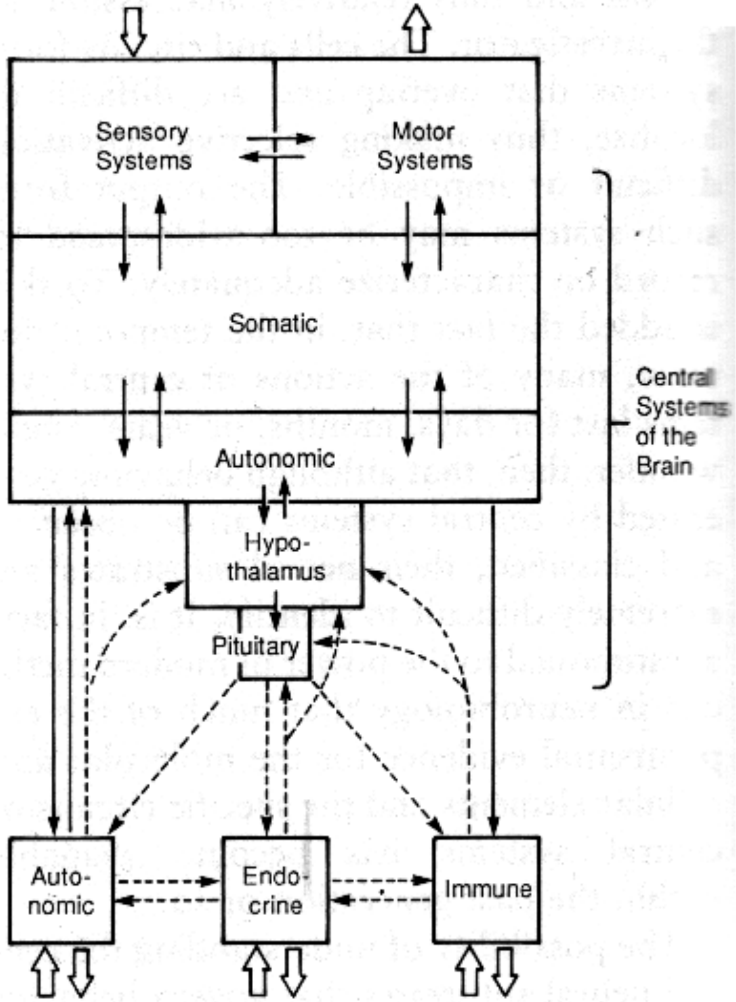


Central systems

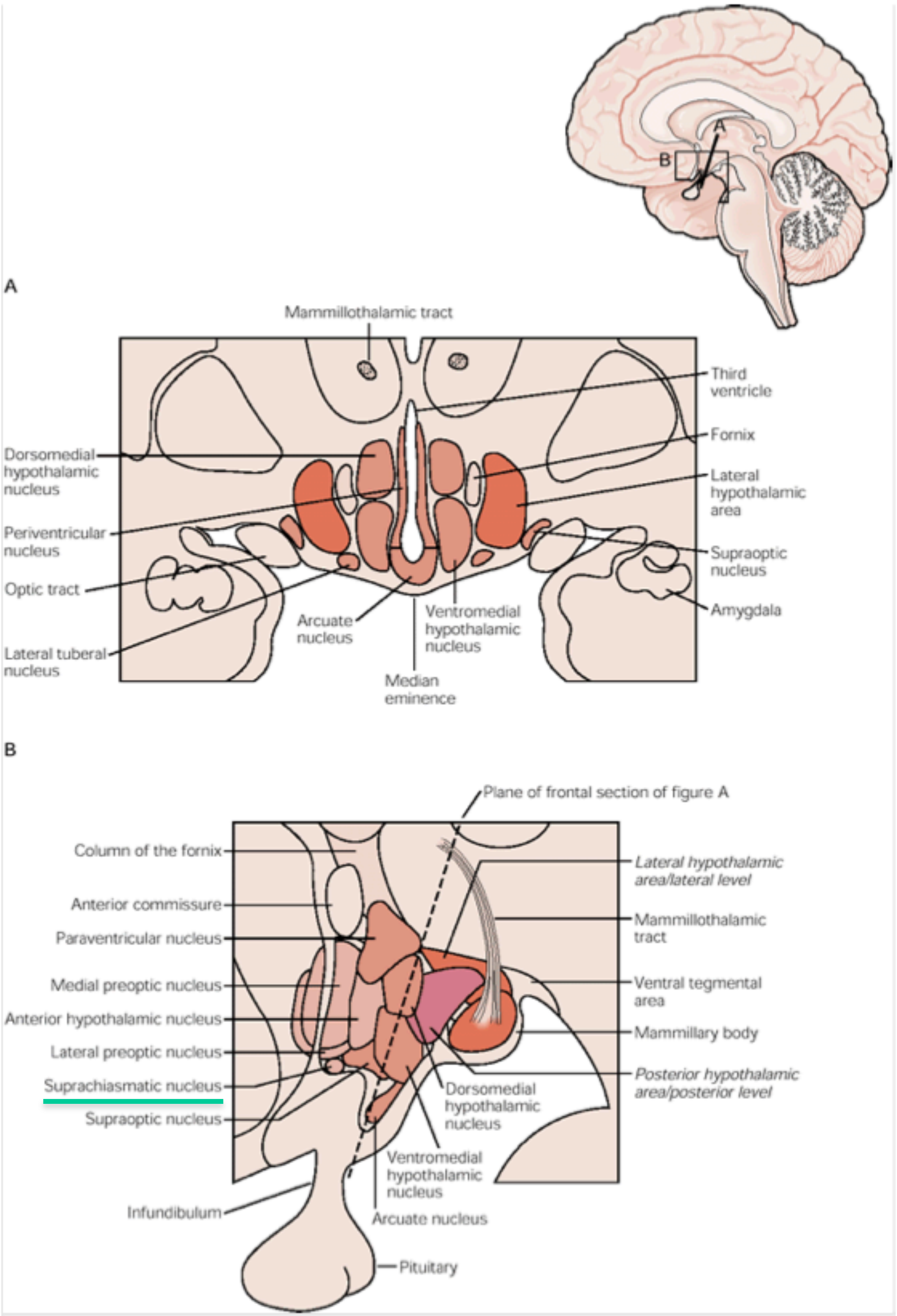
Central systems – cells and circuits that mediate functions necessary for the coordinated behavior of the whole organism

Table 24.1 Summary of central systems

Systems relating brain and body
Autonomic nervous system
Neuroendocrine system
Neuroimmune system
Systems within the brain
Specific transmitter systems
Diffuse transmitter systems
Distributed systems



The hypothalamus

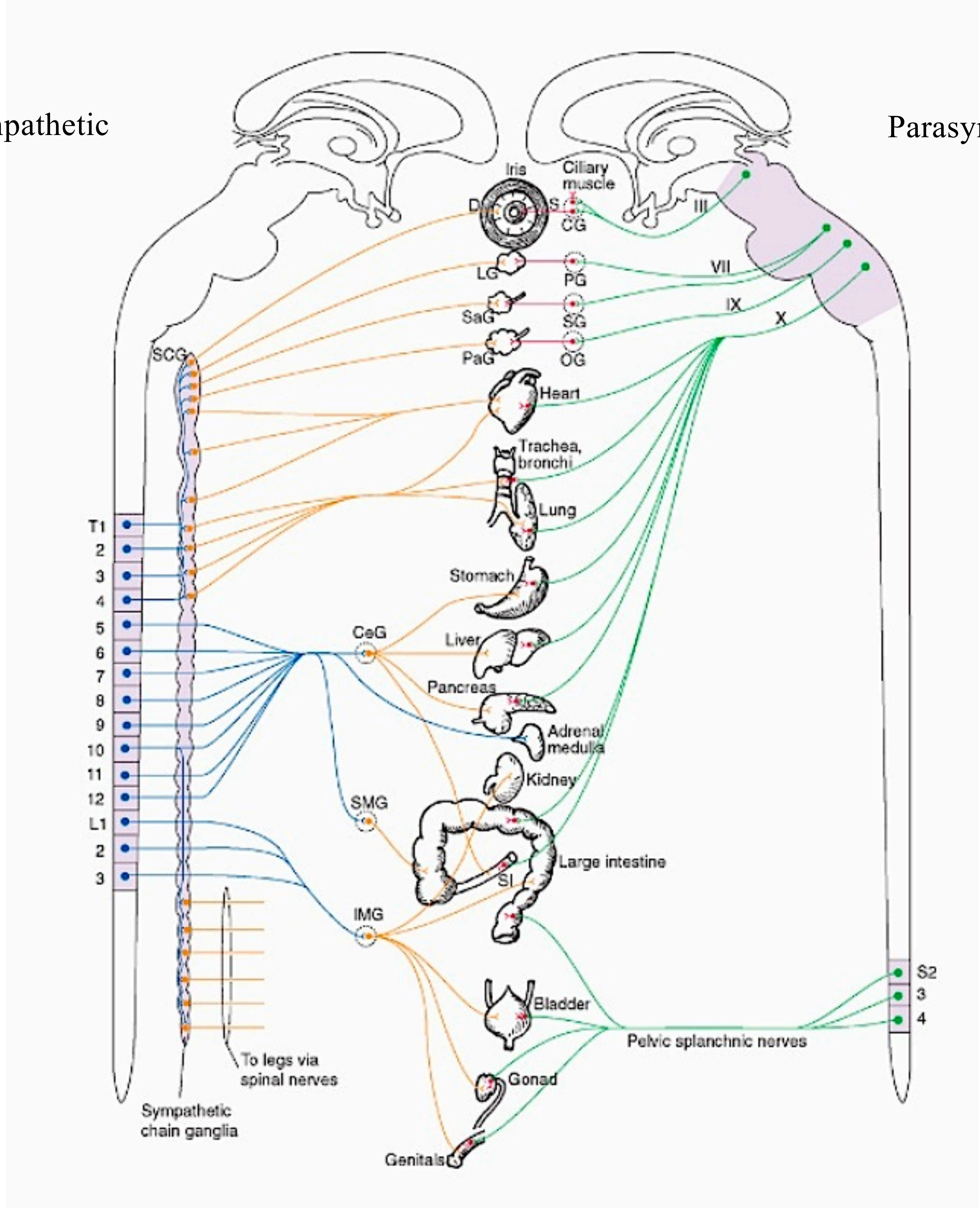


The hypothalamus is important nodal point in pathways concerned with autonomic, endocrine, emotional, and somatic functions. Its main role is to maintain our internal environment in a physiological range (i.e. maintain homeostasis). It is involved in drives (e.g. eating, drinking, sexual behavior) and emotions (e.g., rage). It also synchronizes internal clock to day-night cycle (suprachiasmic nucleus). It controls the the most important gland - pituitary gland.

Autonomic nervous system

Sympathetic

Parasympathetic



Origin and distribution of sympathetic (left) and parasympathetic (right) connections with their target organs. Most organs (but not all) receive inputs from both systems, which have mainly opposite effects. Parasympathetic neurons release acetylcholine onto their targets. Sympathetic neurons, in contrast, release norepinephrine. CeG, celiac ganglion; CG, ciliary ganglion; D, pupillary dilator; IMG, inferior mesenteric ganglion; LG, lacrimal gland; OG, optic ganglion; PaG, parotid gland; PG, pterygopalatine ganglion; S, pupillary sphincter; SaG, submandibular and sublingual salivary glands; SCG, superior cervical ganglion; SG, submandibular ganglion; SMG, superior mesenteric ganglion.

Structure or System	PSN	Sympathetic Effect	PPN*	Parasympathetic Effect
Head				
Pupillary sphincter			E-W	Contract (miosis)
Pupillary dilator	T1-T3	Contract (mydriasis)		
Superior tarsal muscle	T1-T3	Contract (lid elevation)		
Ciliary muscle			E-W	Contract (accommodation)
Lacrimal gland	T1-T3	Slightly ↑secretion	SSN	↑ Secretion
Salivary glands	T1-T3	Slightly ↑ secretion, ↑ viscosity	ISN, SSN	↑ Secretion, ↓ viscosity
Pineal gland	T1-T3	↑ Melatonin synthesis		
Respiratory System				
Bronchial muscles	T1-T5	Relax	DMNX	Contract
Cardiovascular System				
Heart rate and output	T1-T5	↑	NA	↓
Arteries (skeletal muscle)	T1-L3	Constrict or dilate†		
Arteries (skin)	T1-L3	Constrict		
Arteries (viscera)	T1-L3	Constrict	DMNX	Dilate
Gastrointestinal System				
Motility	T6-L3	↓	DMNX‡	↑
Sphincters	T6-L3	Contract	DMNX‡	Relax
Secretion	T6-L3	↓	DMNX‡	↑
Gallbladder	T6-T9	Relax	DMNX	Contract
Urogenital System				
Bladder detrusor	T12-L2	Relax	S2-S4	Contract
Bladder sphincter (internal)	T12-L2	Contract	S2-S4	Relax
Seminal vesicles, vas deferens	T10-L1	Contract (during ejaculation)		
Penile/clitoral arteries	T10-L1	Dilate or constrict§	S2-S4	Dilate (erection)
Skin				
Sweat glands	T1-L3	↑ Secretion‖		
Piloerector muscles	T1-L3	Contract (goose bumps)		
Adrenal Medulla	T8-L1	↑ Secretion		

Physiological Effects of Autonomic Activity

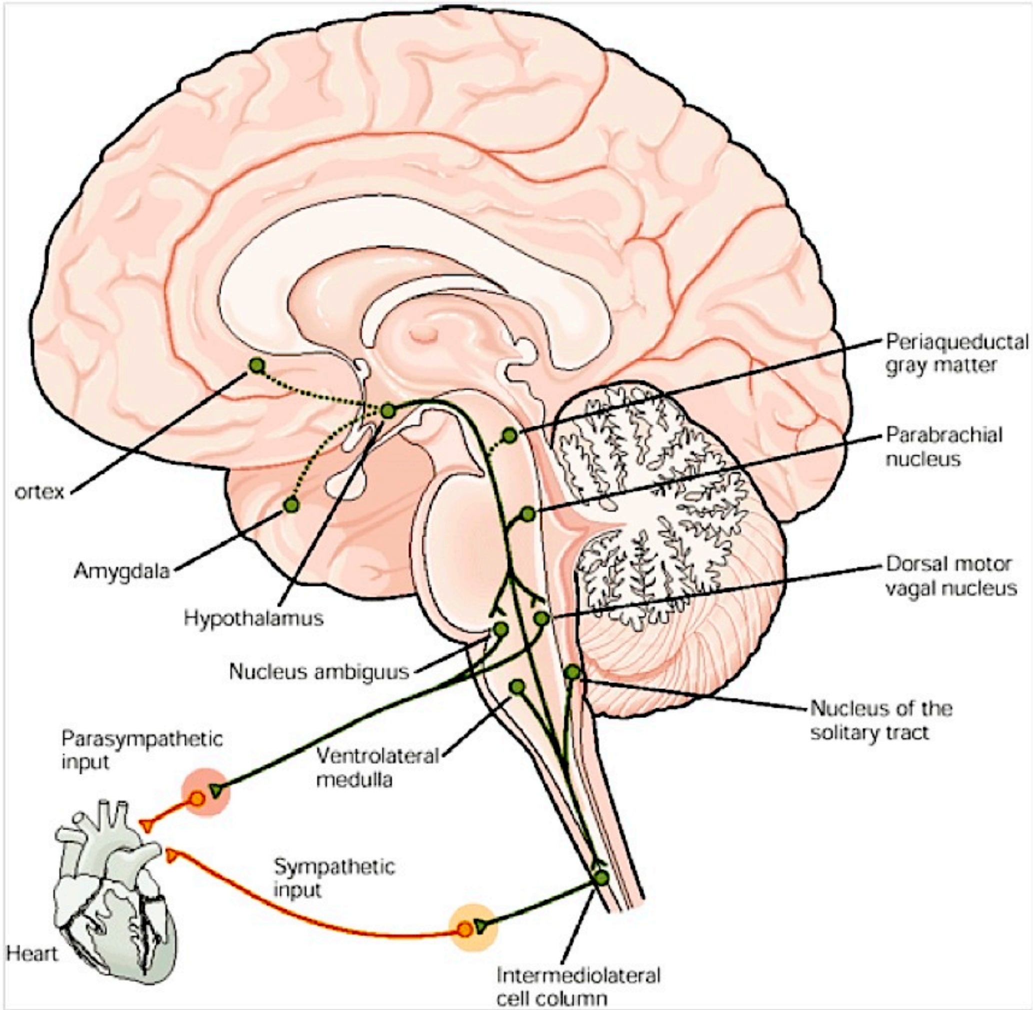
The sympathetic system prepares us for situations in which energy needs to be expended (‘fight or flight’). Activation of sympathetic fibers increases heart rate, decreases peristalsis, and diverts blood from the gut to skeletal muscles.
The parasympathetic system enhances energy storage (‘rest and digest’). Activation of parasympathetic nerves causes decreased cardiac output and blood pressure, increased peristalsis in the gut, and salivation, as well as pupillary constriction.

The two systems cooperate in male sexual function, with erection mediated by parasympathetic fibers and ejaculation by sympathetic fibers.

DMNX, dorsal motor nucleus of the vagus (in the medulla); E-W, Edinger-Westphal nucleus (in the midbrain); ISN, inferior salivary nucleus (in the medulla); NA, nucleus ambiguus (in the medulla); PPN, location of preganglionic parasympathetic neurons; PSN, location of preganglionic sympathetic neurons; SSN, superior salivary nucleus (in the pons).

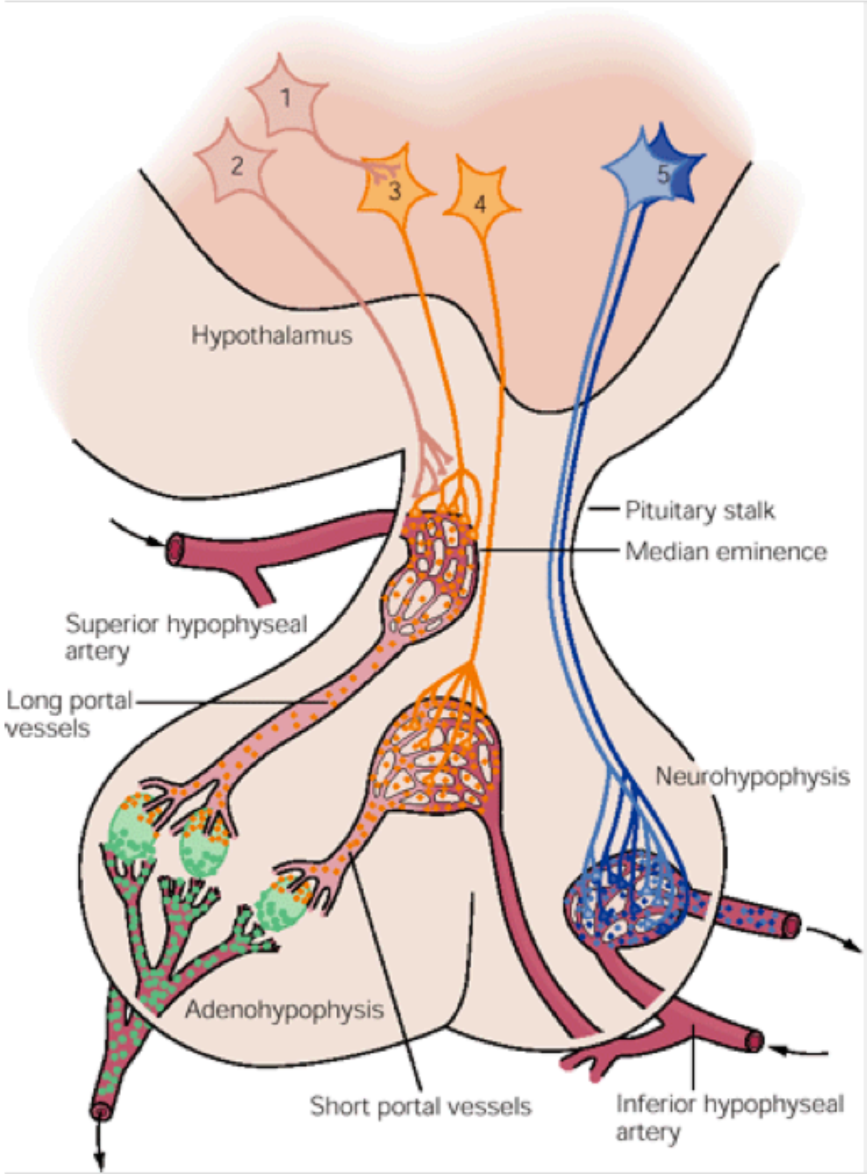
Brain control of autonomic activity

The main control center for autonomic system is the hypothalamus. Other important inputs come from amygdala and cortex.



Pituitary gland

Pituitary gland releases hormones and controls many other glands in the body. Therefore it is considered a master gland.



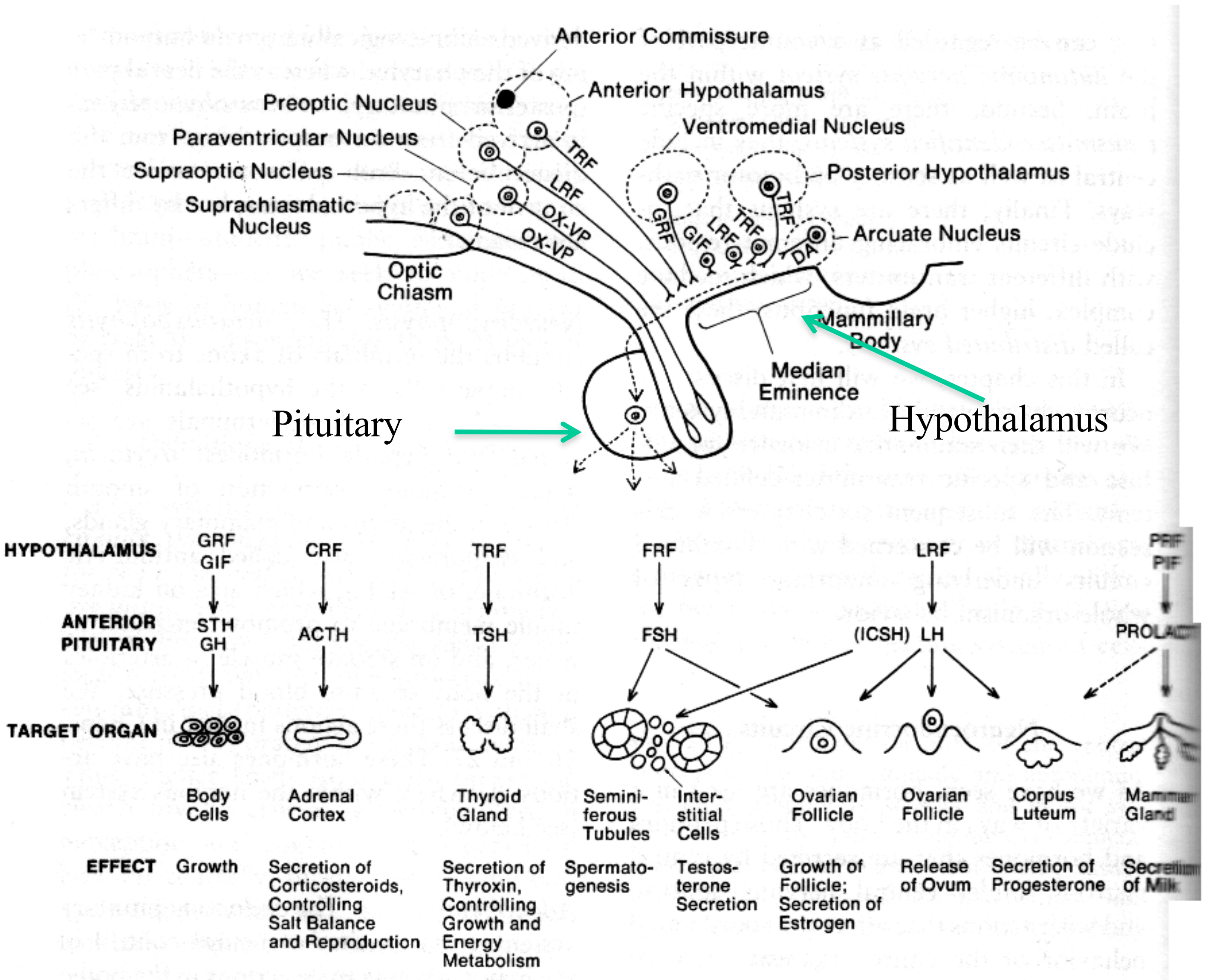
The hypothalamus controls the endocrine system through the pituitary directly and indirectly.

The pituitary consists of an endocrine and a neural part.

Direct control:
Neural part contains axons terminals (5) releasing two peptide hormones: oxytocin and vasopressin. They are important for labor (giving birth), lactation and social functions (pair bonding, male aggression, parental behavior).

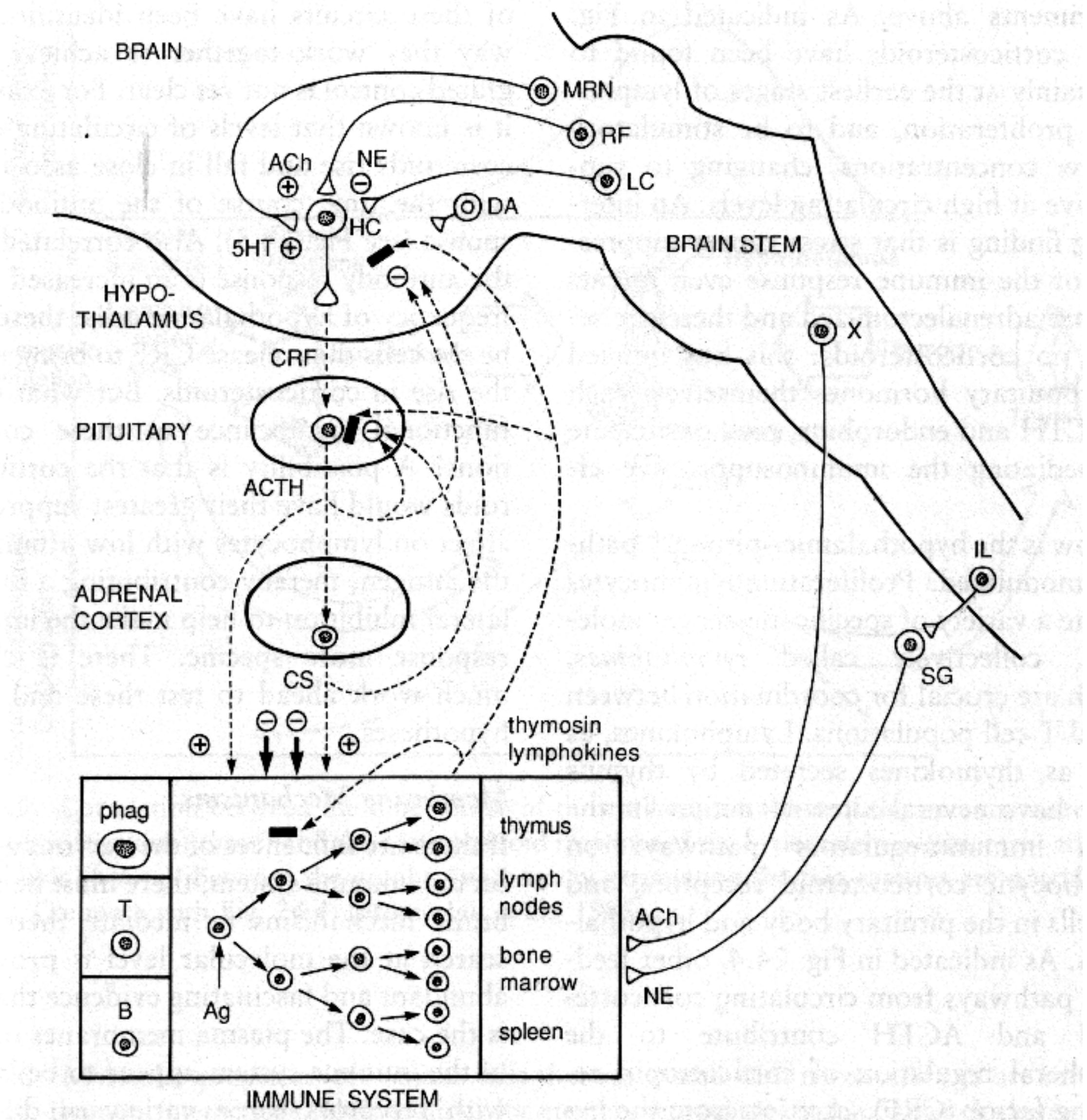
Indirect control:
Hypothalamic axons terminals (1-4) secrete regulatory hormones into the bloodstream. They travel to pituitary gland and control the synthesis and release of pituitary hormones into the general circulation.

Hypothalamic – pituitary system



Cells in different regions (hypothalamus and other sites) all send axons to the median eminence. Discharge of these neurons release so called releasing factors (RF). Their action on pituitary cells are to stimulate immediate release as well as to induce long term synthesis of hormones.

Neuroimmune circuits



The main route of neural immunoregulation is the hypothalamic-pituitary-adrenal cortical axis (HPA) (oś podwzgórze – przysadka – kora nadnerczy).

Within the immune system organs phagocytic (phag) and B and T lymphocytes proliferate in response to antigenic (Ag) stimulus.

Pituitary gland releases adrenocorticotropic hormone (ACTH), which release stress hormons from adrenal cortex.

Adrenal cortex releases stress hormons corticosteroids (CS, cortisol) and adrenaline.

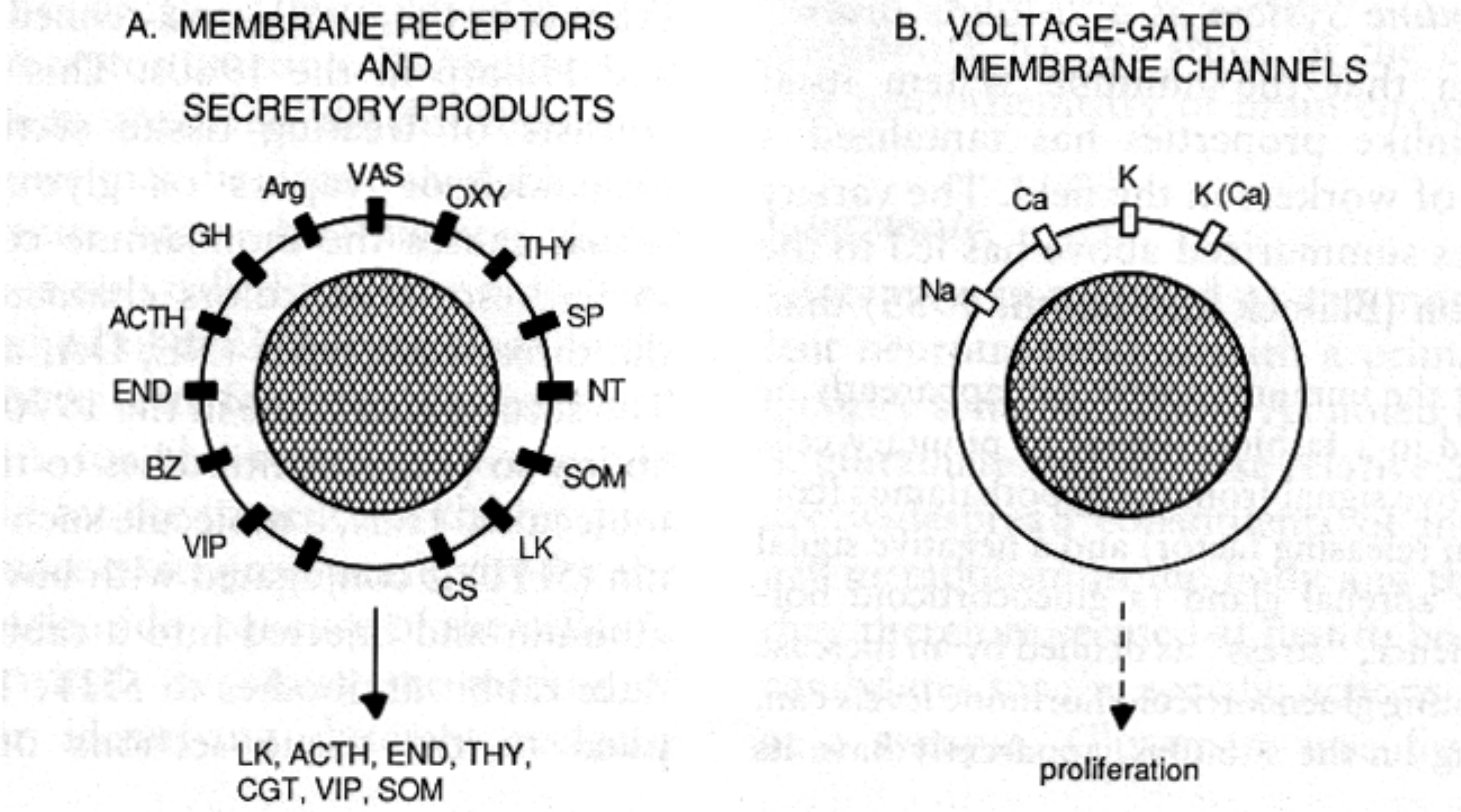
Low concentrations of CS and ACTH stimulate immunological response (+). High concentrations of CS and ACTH (thick arrows) suppresses immunological response (-).

The substances of the immune system regulate the immune response but also act to block the actions of other substances at different levels of the HPA axis (black bars).

The immunosupression in people suffering depression or stress is related to suppression of the immune response by CS and ACTH.

Immune system – membrane properties

A variety of substances can affect the immune response implying the presence of appropriate membrane receptors.



Immune cells have a number of receptors which are involved in neural – immune interactions. A. Ligand-gated channels. B. Voltage-gated channels. Because of the many receptors present, some researchers suggested that the certain cells of immune system may serve as „free-floating nerve cells”, and collectively may represent a mobile brain. It could serve as a sensory organ („sixth sense”) for stimuli such as bacteria, viruses and tumor cells.

Central systems

Central systems – cells and circuits that mediate functions necessary for the coordinated behavior of the whole organism

Table 24.1 Summary of central systems

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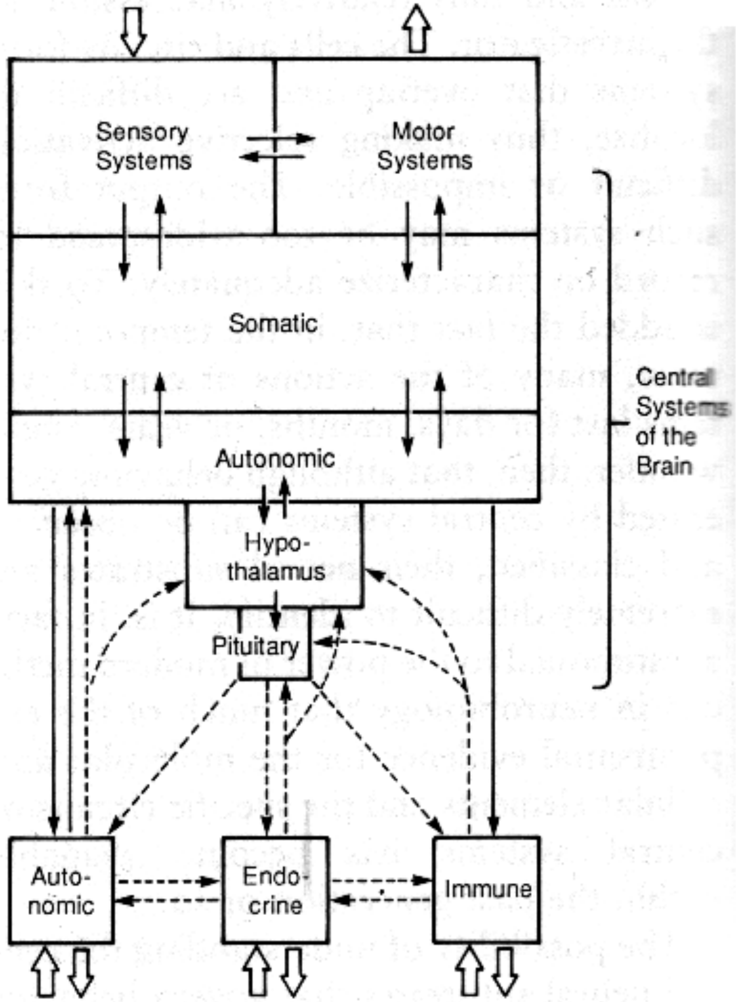
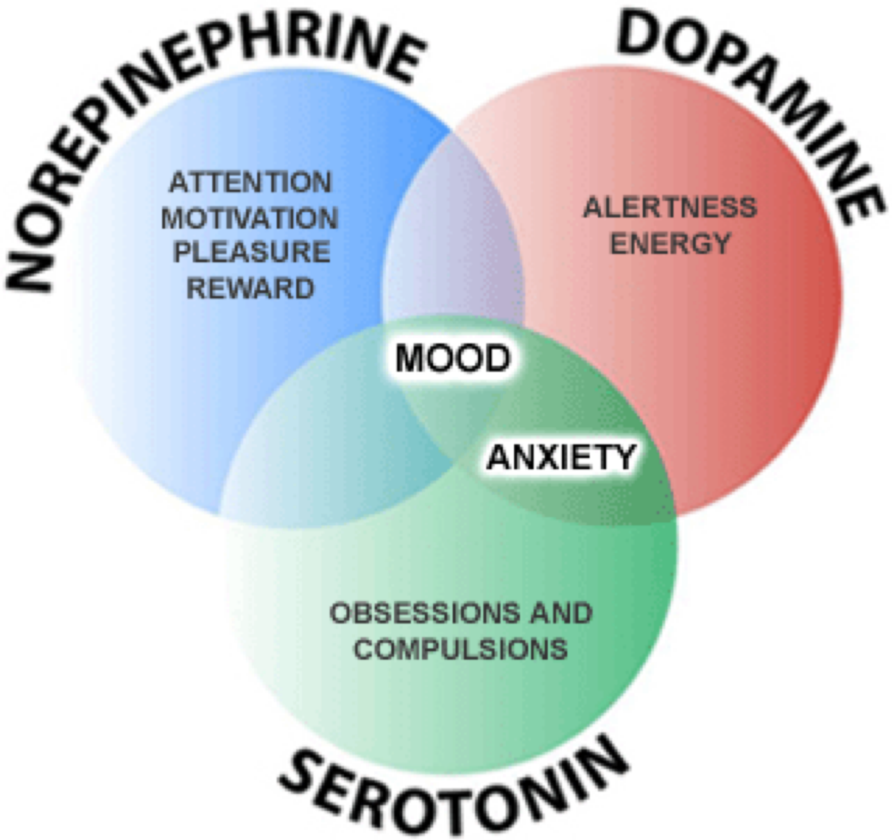
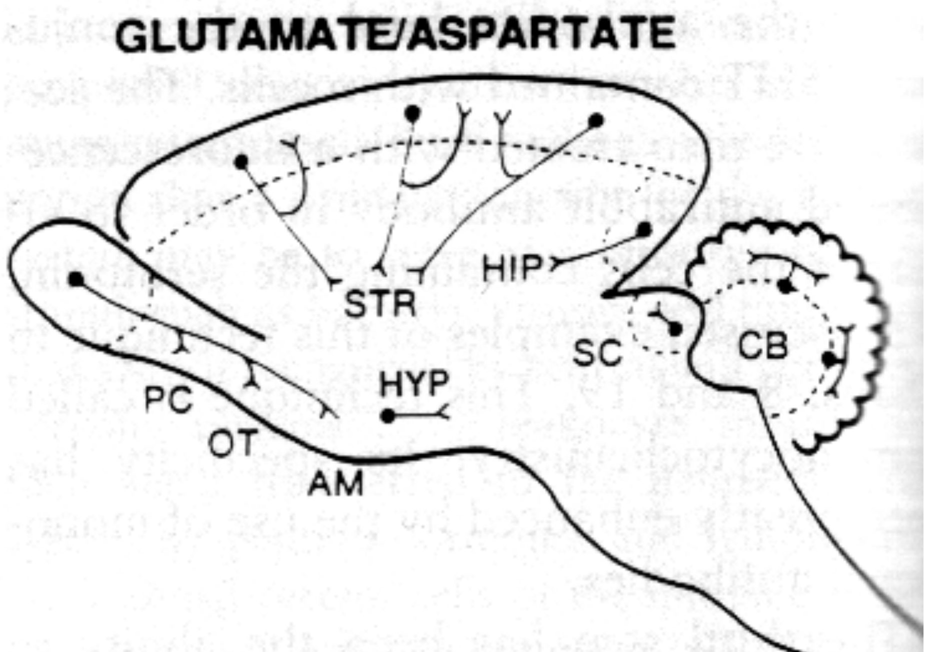


Specific and diffuse transmitter-defined systems



There are about a dozen known transmitters (nine of which are most common). Besides there are more than 100 neuroactive peptides.

Glutamate

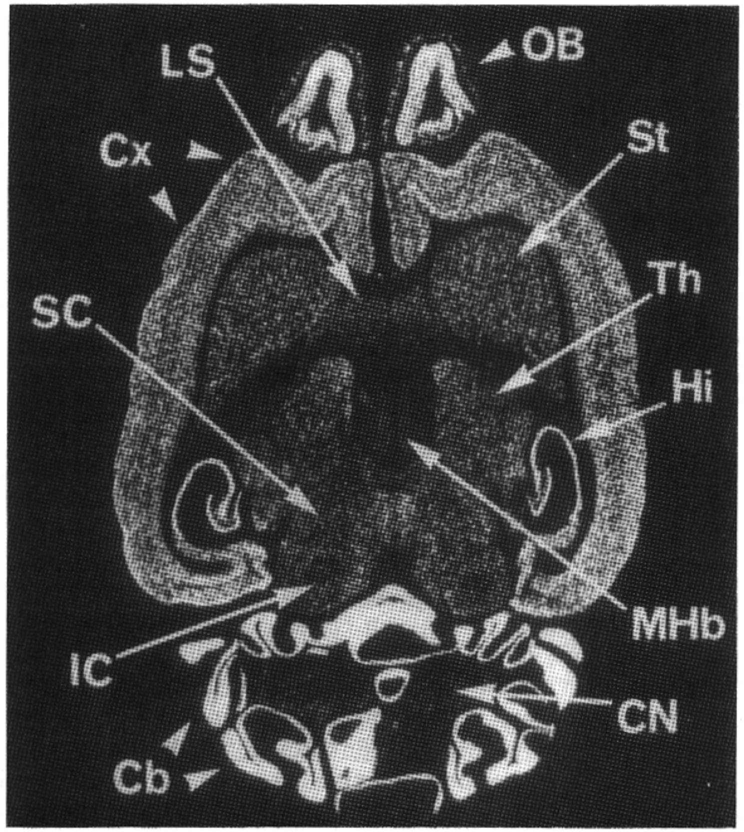


Distribution of neurons using glutamate as a neurotransmitter in the rat brain.

Most prevalent neurotransmitter with a primarly excitatory action.

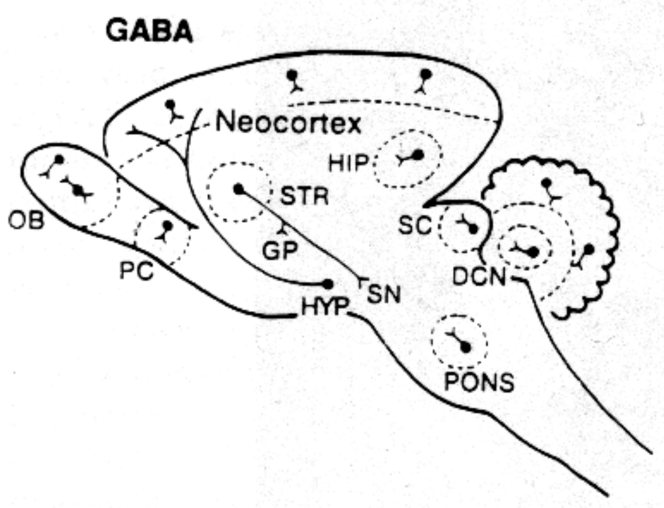
Low and moderate glutamate levels, activate AMPA receptors

High glutamate concentrations activate NMDA receptors



Distribution of NMDA receptors in the rat brain. Highest receptor concentration include the olfactory bulb (OB), hippocampus (Hi), cerebellum (Cb). Intermediate receptor densities are seen in the cerebral cortex (Cx), striatum (St), thalamus (Th).

γ-Aminobutyric Acid (GABA)



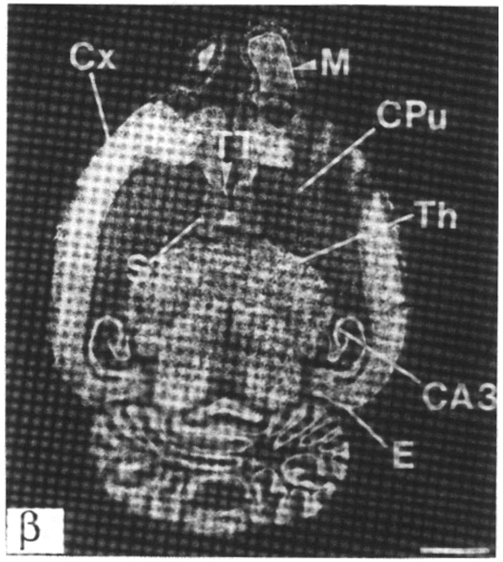
Distribution of GABAergic neurons. There are short tracts from striatum to substantia nigra and in cerebellum. The long pathway projects form hypothalamus to cerebral cortex. Most GABAergic neurons are local interneurons in cortex, olfactory bulb, hippocampus, cerebellum and retina.

Most prevalent neurotransmitter with a primarily inhibitory action. There are two classes of GABA receptors: $GABA_A$ and $GABA_B$. There are numerous subunit isoforms for the $GABA_A$ receptor. The subunit composition determines which ligands may bind and modulate the receptors besides GABA itself. Ligand examples: Barbiturates (hypnotics e.g. phenobarbital), Benzodiazepines (relaxants e.g. Valium), Ethanol (alcohol).

Brain Region	α1	α2	α3	α5	α6	β1	β2	β3	γ1	γ2	δ
Olfactory bulb											
mitral cells	★★★	O	☆	O	O	★★	★★★	★	O	★★	O
granular layer	O	★	☆	☆	O	O	O	★★	☆	★	★
glomerular layer	★	☆	☆	O	O	O	★	★	☆	★	☆
accessory olf. bulb	★★	★	O	O	O	★★★	★★	★★	★	★	O
Caudate putamen	O	★	☆	O	O	☆	☆	★★	O	★	★
Cerebral cortex											
lamina I	O	O	O	O	O	O	O	O	O	O	O
lamina II + III	★★	★	★	O	O	☆	★★	★	☆	★	★
lamina IV +V	★★	☆	★	☆	O	☆	★★	★	☆	★	☆
lamina VI	★★	O	★	★	O	★	★★	★	☆	★	O
Pallidum											
ventral pallidum	★★	☆	☆	O	O	O	★	O	★	★	O
globus pallidum	★★	☆	O	O	O	O	★	O	–	★	O
insula Calleja	★★★	☆	O	O	O	O	★	O	★	☆	O
Hippocampal formation											
cells in stratum oriens	★	O	O	O	O	O	★	O	☆	☆	O
CA1	★	★	O	★	O	★	★	★★	☆	★★	☆
CA2	★	★★	☆	★	O	★★	★	★★	☆	★★	O
CA3	★	★★	☆	★	O	★	★	★★	☆	★★	O
hilus cells	★	★	O	O	O	★	☆	★★	☆	★★	O
dentate gyrus	★	★★	☆	★	O	★	★	★★	☆	★★	★
subiculum	★	☆	☆	★	O	O	☆	★	O	★	★
Thalamus	★★	O	★	O	O	O	★★★	O	☆	★	★★
Substantia nigra											
zona compacta	O	O	★	O	O	O	O	O	O	☆	O
zona reticularis	★★★	O	O	O	O	☆	★★	O	★	★	O
Cerebellum											
Bgl layer	O	☆	O	O	O	☆	O	O	☆	O	O
molecular layer	★	O	O	O	O	O	☆	O	O	☆	O
PC	★★★	O	O	O	O	O	★★	O	O	★★	O
granular layer	★★	O	O	☆	★★★	☆	★★★	★	O	★	★★★
white matter	O	O	O	O	O	O	O	O	O	O	O
Colliculus inferior	★★	O	☆	O	O	☆	★★	☆	O	★	O
Colliculus superior											
optic nerve layer	★	☆	★	★	O	★	★	★	SuG ☆	★	☆
Nucleus interpositus	★★★	O	O	O	O	O	★★	O	O	★	O
Vestibular nucleus	★	★	☆	☆	O	O	★	★	O	★★	☆
Facial nucleus	★★	★★	☆	O	O	☆	★	★	O	☆	O
Motor trigeminal nucl.	O	★	☆	☆	O	O	★	★	O	★★	O
Pontine nuclei	☆	★	O	☆	O	O	☆	☆	★	★★	O
Spinal cord											
spinal cord layers 2-3	O	O	★	☆	O	O	O	★	O	★	O
spinal cord layers 4-5	★	O	★	☆	O	O	★	★	O	★	O
spinal cord layers 6-9	★	★★	☆	☆	O	O	★	★	☆	★★	O

Isoforms of $GABA_A$ receptors in different brain areas. Each region, subregion and layer has its unique combination of subunits.

Glycine



Distribution of the β subunits of the glycine. High density of receptor is visible in the olfactory bulb (OB), hippocampus (CA3), cerebellum (Cb), cerebral cortex (Cx), striatum (St) and thalamus (Th).

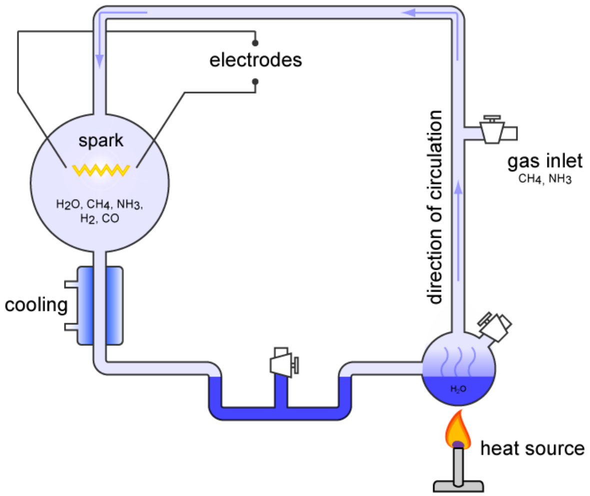
Traditionally, glycine has been localized mainly to the brainstem and spinal cord. Recent years have brough the evidence of a widespread distribution of glycine in the brain. Glycine is an inhibitory neurotransmitter.

Glycine was discovered in the interstellar medium, in the samples from comets:
Comet Wild 2 (2004)
Comet 67P/Churyumov-Gerasimenko (2016)

In 2008, the glycine-like molecule aminoacetonitrile was discovered in a giant gas cloud near the galactic center in the constellation Sagittarius by the Max Planck Institute for Radio Astronomy.

Glycine is an amino acid, which are building blocks of proteins. Reserchers speculte that if amino acids exsist in outer space than there might be proteins and life as well.

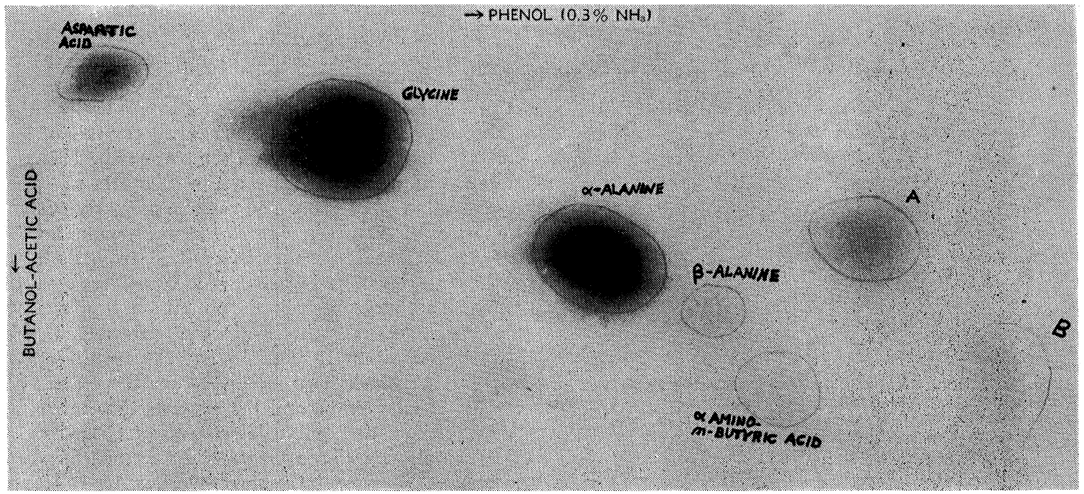
Miller-Urey experiment (1953)



Simulations of the conditions of the early Earth's atmosphere: water (H_20), methane (CH_4), ammonia (NH_3), hydrogen (H_2), carbon monoxide (CO).

Experimental setup of Miller-Urey experiment - replication at NASA.

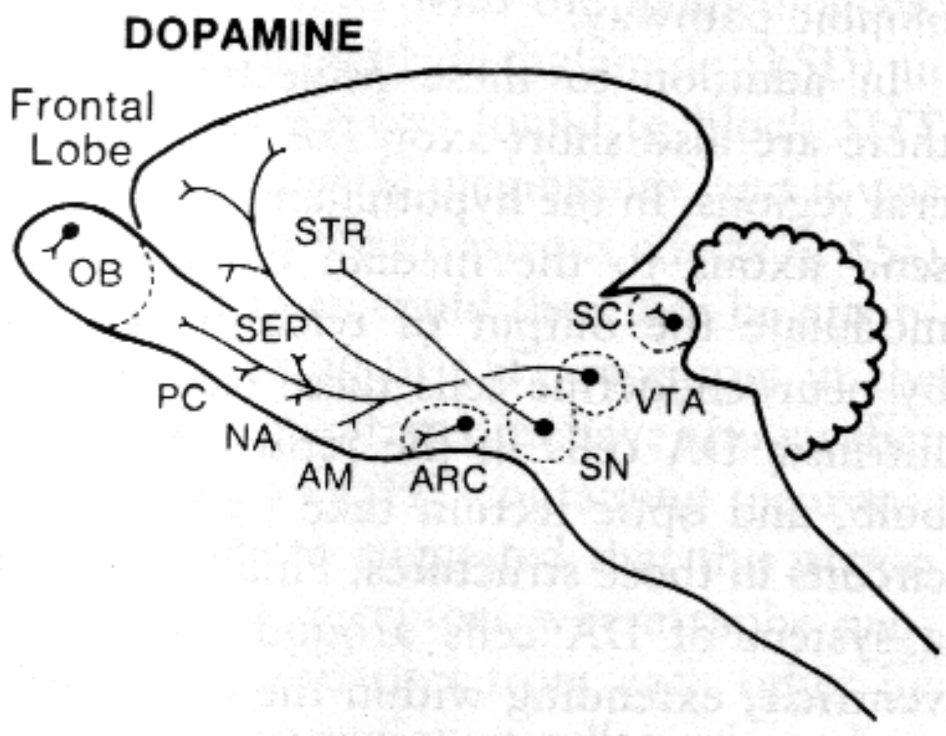
Jupiter's atmosphere – methane (CH_4), ammonia (NH_3), hydrogen (H_2), helium (He).



Glycine detected by paper chromatography method. From: Miller S. L. (1953). "Production of Amino Acids Under Possible Primitive Earth Conditions". *Science* **117**: 528.

At the end of two weeks of continuous operation 10–15% of the carbon within the system was in the form of organic compounds. Two percent of the carbon had formed amino acids that are used to make proteins in living cells, with glycine as the most abundant.

Dopamine



•Loss of DA synapses in the striatum (of basal ganglia) is primary cause of movement disorders (e.g. Parkinson's disease).

• In hypothalamus DA influences the release of the hormones, mainly prolactin that enables mammal females to produce milk.

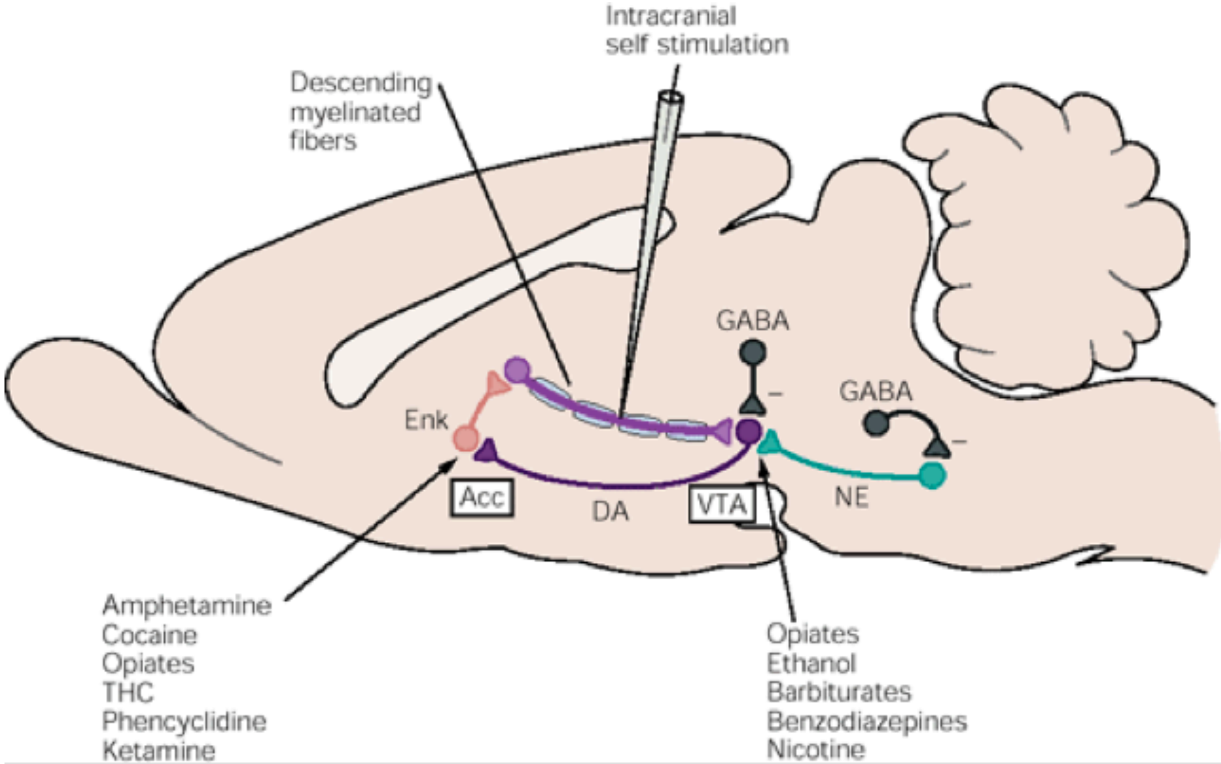
•In the limbic system DA is implicated in the reward system responsible for biological drives (feeding, drinking, sex) and motivation. Dopamine is important for immediate pleasant rewards and for arousal effects that are predictive of impending rewards.

Distribution of dopamine-containing neurons.

The two main projection neuron groups are located in substantia nigra (SN) and ventral tegmental area (VTA). Besides there are short axon DA cells in olfacory bulb, hypothalamus, retina.

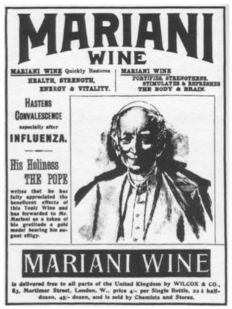
Main projections reach the limbic structures (septum, amygdala, prefrontal cortex) and are implicated in emotion and control of agression.

Dopamine

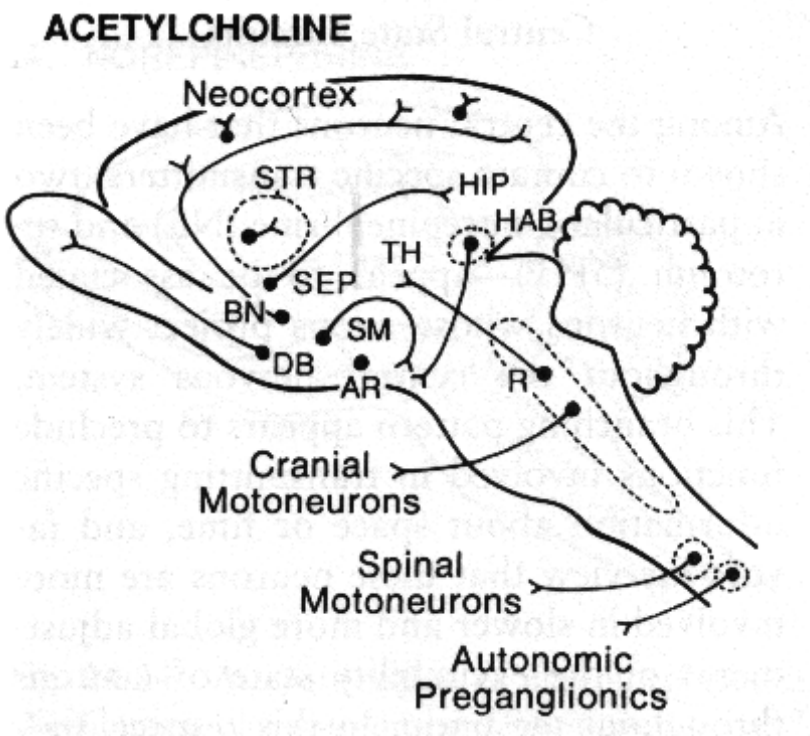


Brain-reward circuitry in the rat

- Almost all addictive substances eg. cocaine, opiates (morphine, heroin), nicotine or alcohol increase the DA level in NA (Acc).
- Addiction involves positive reinforcement related to increase of DA release and negative visceral side-effects related to drug withdrawal.
- In people in the state of romantic love there is strong activation of dopaminergic pathways of the VTA, hence some argue that love is rather a motivation system than an emotion.
- The original Coke formula had a significant amount of cocaine in it, it was removed by 1903. At present ingredients from the coca leaf are still used, but there is no cocaine in it.



Acetylocholine



Distribution of cholinergic cell groups and their projections in the rat brain. Main projections are from habenula (HAB), septum (SEP), striatum (STR), basal nucleus (BN).

ACh acts on either nicotinic receptors (producing brief synaptic potentials) or muscarinic receptors (producing slow synaptic potentials).

It is the only neurotransmitter used as an excitatory neurotransmitter at neuromuscular junctions in skeletal muscles.

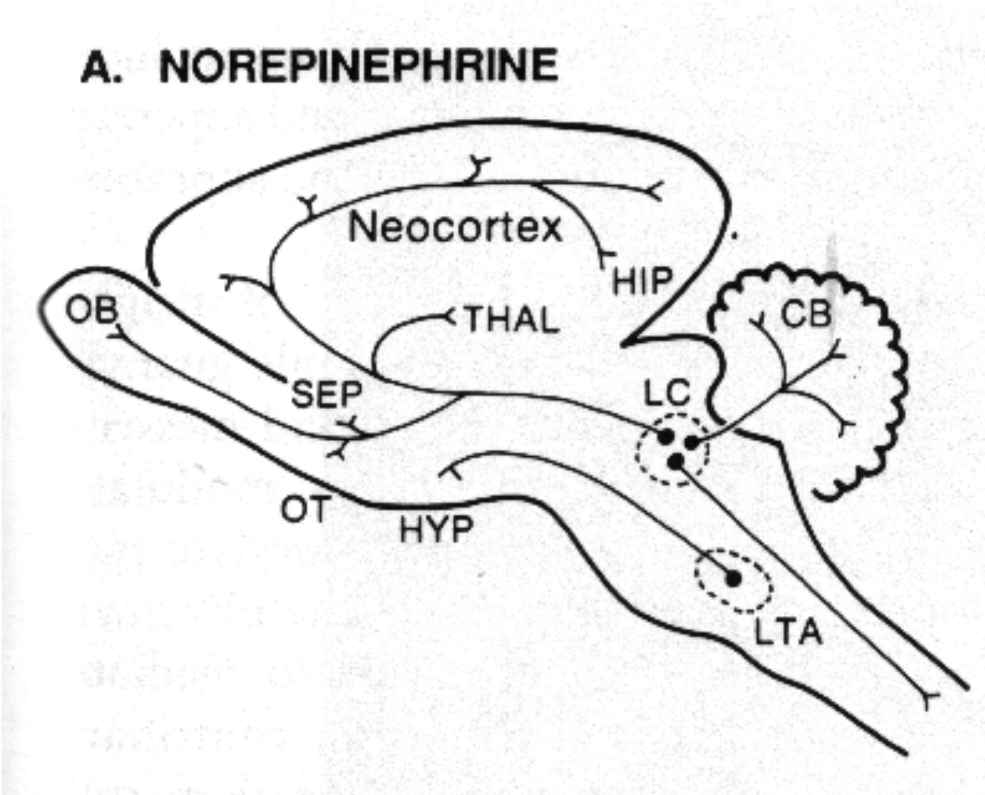
Acetylcholine is one of many neurotransmitters in the autonomic nervous system. In cardiac tissue acetylcholine has an inhibitory effect, which lowers heart rate.

It produces both excitatory and inhibitory responses in the brain.

ACh has an important role in the enhancement of sensory perceptions when we wake up and in sustaining attention.

Damage to the cholinergic (acetylcholine-producing) system in the brain has been shown to be associated with dementia (Alzheimer's disease).

Norepinephrine



Distribution of norepinephrine containing neurons. The widespread patterns of projections suggest that these neurons are involved in adjustments of global neuronal excitability.

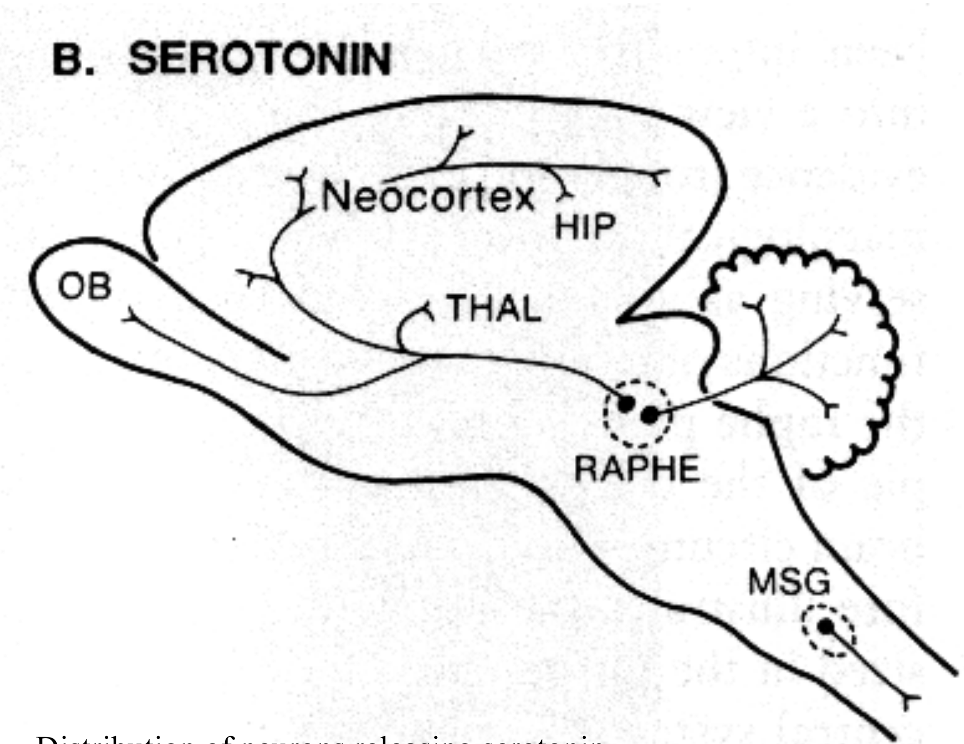
The terms noradrenaline (from the Latin) and norepinephrine (from the Greek) are interchangeable.

Norepinephrine (NE) has neuromodulatory action and its function is to mobilize the brain and body for action. In the brain, norepinephrine increases arousal and alertness, promotes vigilance, enhances formation and retrieval of memory, and focuses attention.

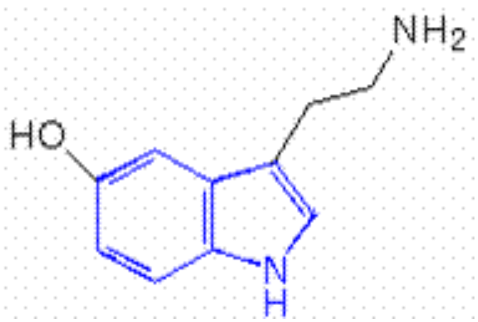
It is released by Locus Coeruleus (LC) neurons to almost every regions of the CNS.

NE neurons act like a central autonomic nervous system, to complement the peripheral autonomic system and its release of epinephrine (andrenaline) into the bloodstream.

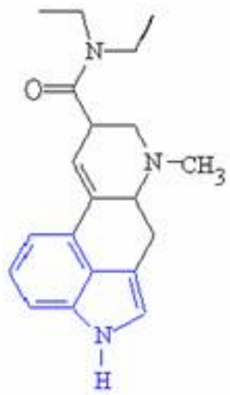
Serotonin



Distribution of neurons releasing serotonin.



serotonin



lysergic acid
diethylamide

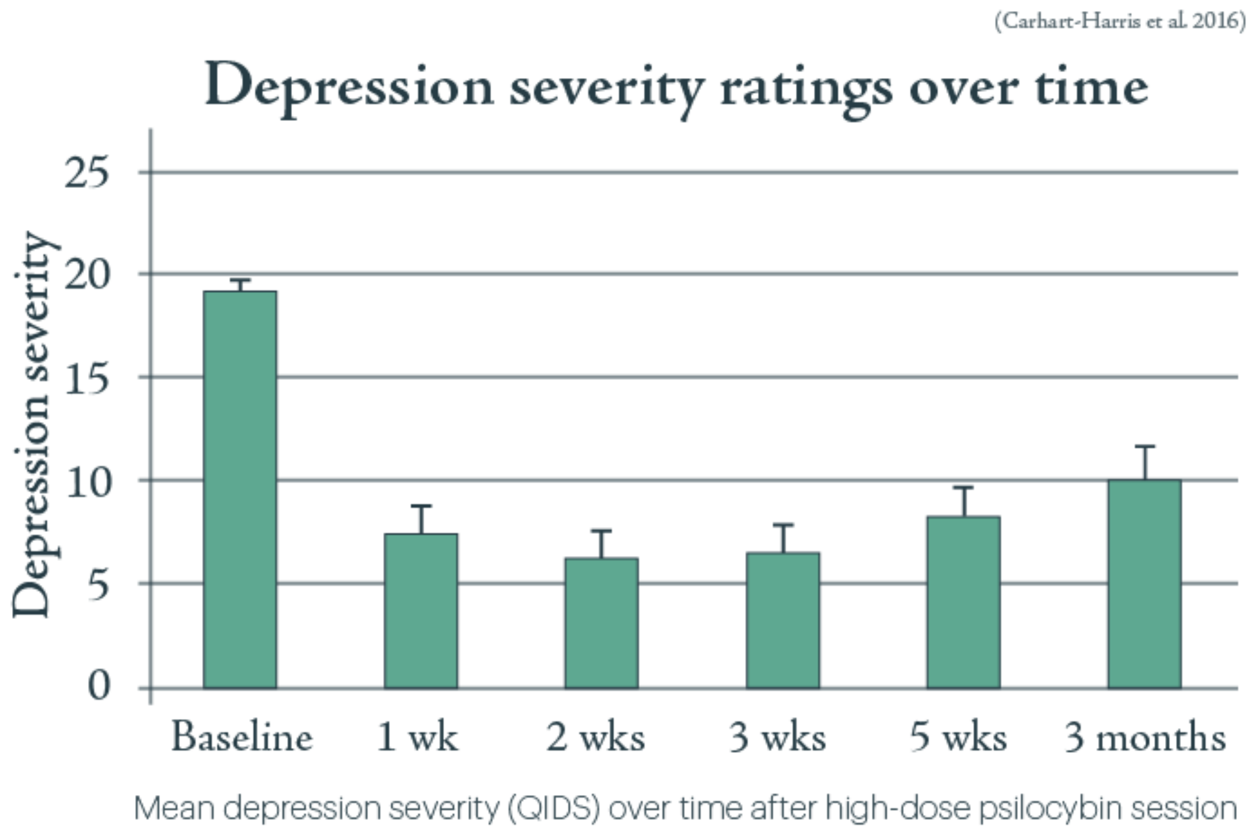
Serotonin (5HT) is released by neurons in Raphe Nuclei, which project widely to many brain regions, alike the NE neurons. Like the NE system, the 5HT system exerts widespread influence over arousal, sleep, sensory perception, emotion and higher cognitive functions (memory and learning), libido.

Serotonin is thought to be a contributor to feelings of well-being and happiness. Serotonin deficiency has been thought to play a role in depression. Recent results however don’t confirm low serotonin as a cause of depression.
Several antidepressive drugs inhibit the reuptake of serotonin, making it stay in the synaptic cleft longer.

The psychedelic drugs psilocin/psilocybin, dimethyltryptamine (DMT), mescaline, and LSD act as serotonin receptors agonists. They affect activities in various brain areas causing e.g. increase of connectivity in the visual areas and reduced activity in the default-mode network involved in internally directed thoughts.

Psilocybin treatment for depression

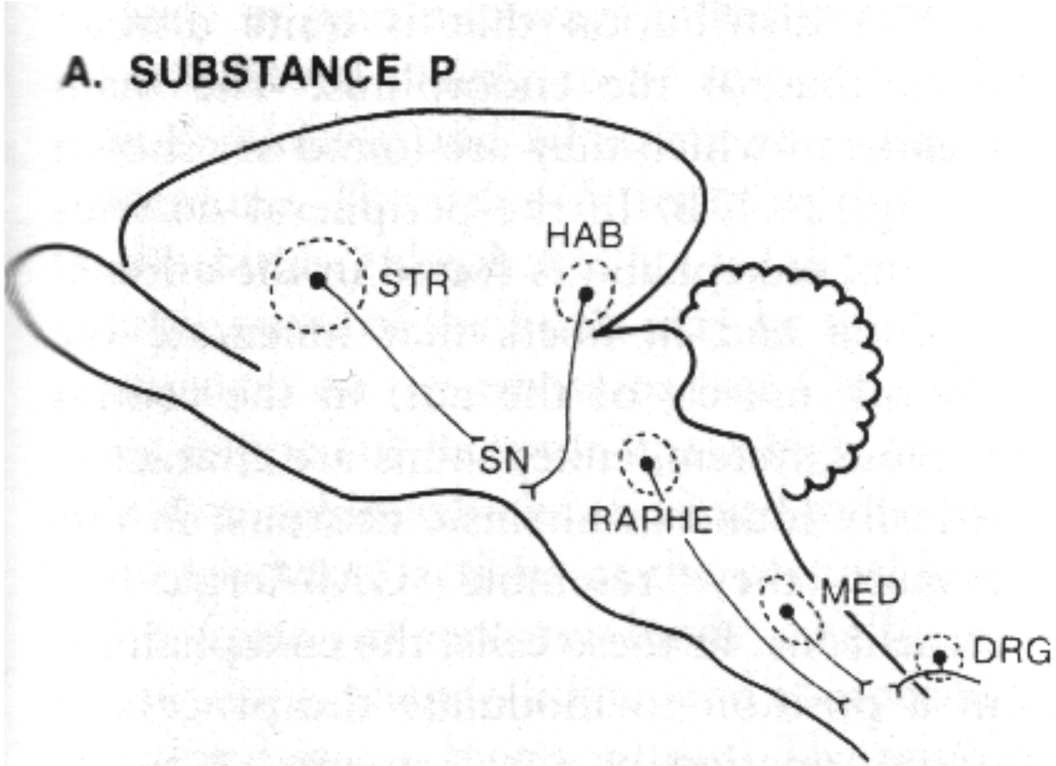
Depressive symptoms were markedly reduced after psylocybin treatment (2 doses, 1 week apart) and remained reduced for up to 3 months.



From: Carhart-Harris et al., Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry, 2016.

Peptides - substance P

Peptides are short chains of amino acid monomers linked by peptide bonds. Polypeptides are long, continuous peptide chains. Proteins consist of one or more polypeptides arranged in a biologically functional way.



Distribution of substance P containing neurons.

Substance P is a key first responder to most noxious/extreme stimuli (stressors). It is an important element in pain perception. The sensory function of substance P is thought to be related to the transmission of pain information into the CNS.

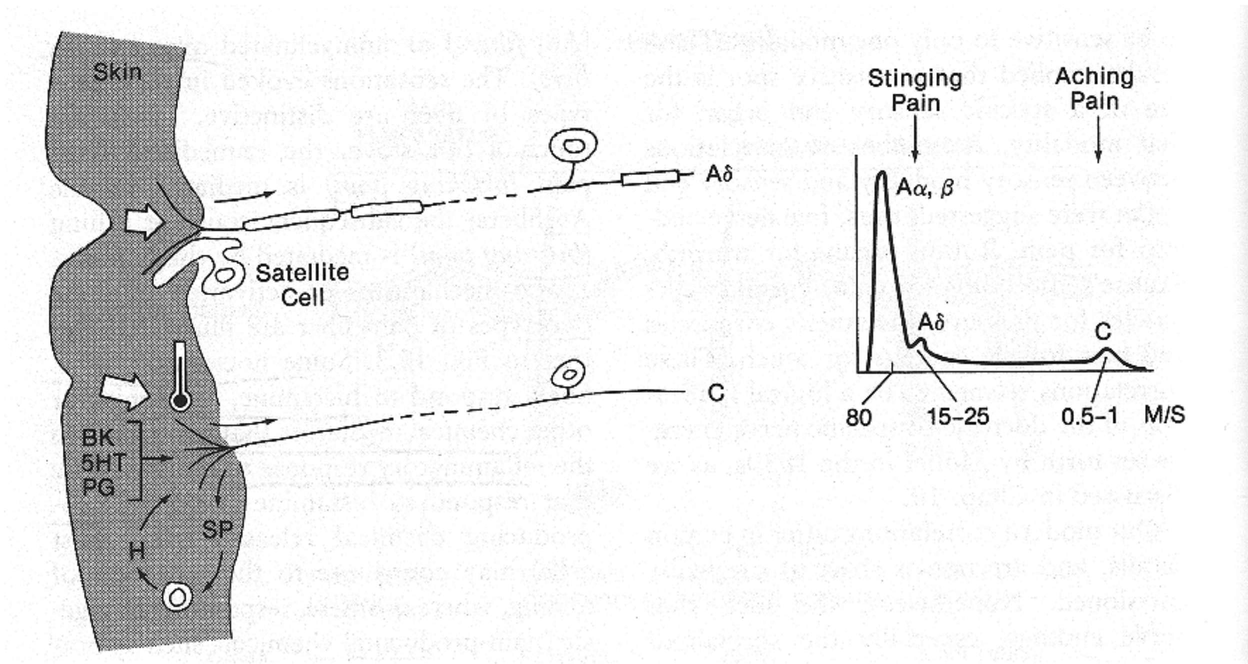
Substance P has been associated with the regulation of mood disorders, anxiety, stress, reinforcement, neurogenesis, respiratory rhythm, neurotoxicity, nausea/vomiting.

Can be thought of as immediate 'defense, stress, repair, survival system'.

Free nerve endings

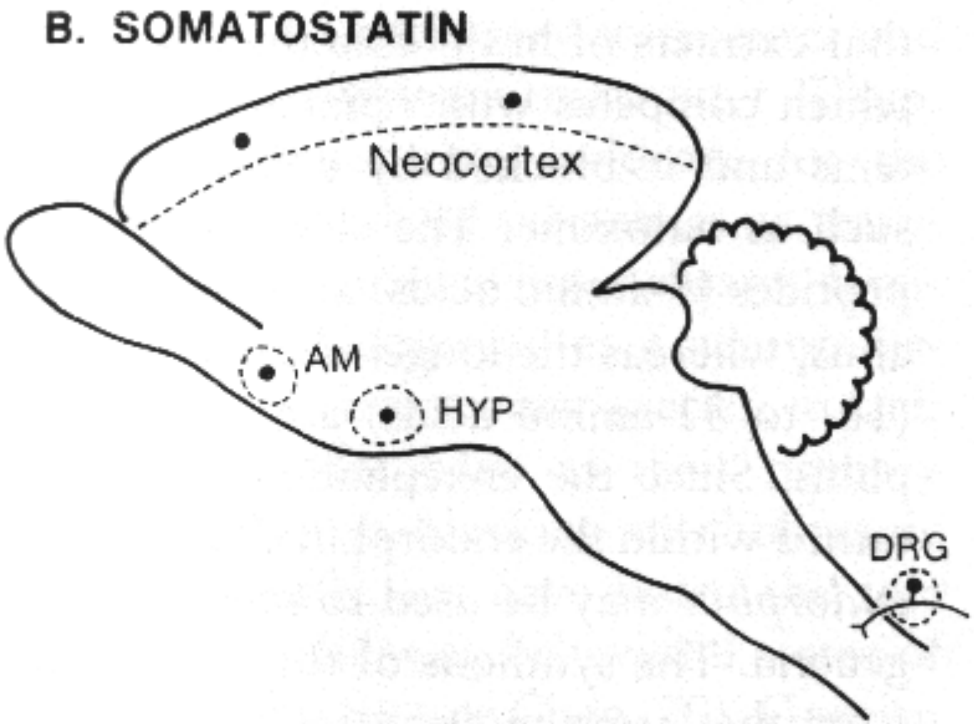
The simplest type of sensory receptor in the skin is the free nerve ending. They respond to:

- mechanical stimuli (mechanoreceptors)
- heating and cooling (thermal receptors)
- noxious stimuli (nociceptors – pain receptors)



Activation of receptors mediating pain. Recording of the compound action potential from a peripheral nerve in response to a single electric shock, showing different components of fast conducting (Aα, β), medium conducting (Aδ) and slow conducting (C) fibers. The immediate sharp pain is mediated by Aδ fibers, the subsequent constant aching is mediated by the C fibres.

Peptides - somatostatin



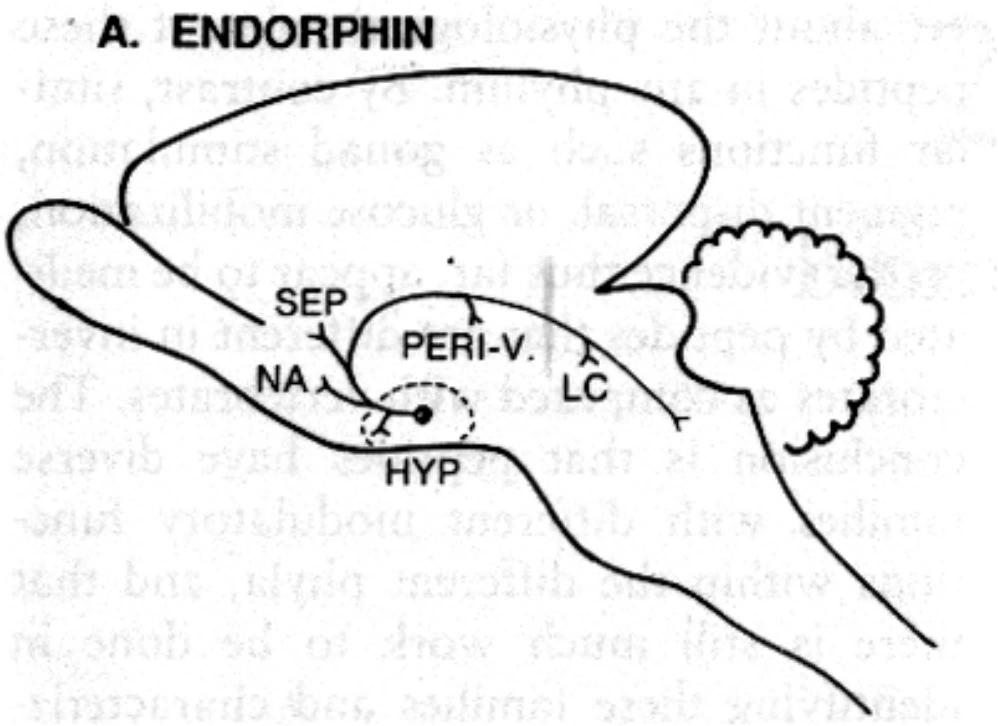
Distribution of somatostatin containing neurons.

Somatostatin regulates (inhibits) the secretion of growth hormone in anterior pituitary gland. The pattern of secretion of growth hormone is sexually dimorphic, and this is one reason why adult males are larger than females.

Somatostatin is also secreted in several locations in the digestive system: stomach, intestine and pancreas.

Somatostatin analogues are used to treat acromegaly.

Endorphin and enkephalin



Distribution of endorphin containing neurons.

Capsaicin is the chemical which gives rise to the heat of chillies.
When eaten, it stimulates body's production of endorphins.

The short chain penta-peptides are called enkephalins whereas the longer chain compounds are called endorphins. The term endorphins may be used to refer to both.

Endorphins ("endogenous morphine”) are produced by the pituitary gland and the hypothalamus during exercise, excitement, pain, consumption of spicy food, love and sex. They produce analgesia and a feeling of well-being.

Endorphins act on the μ_1 opioid receptors, which are are presynaptic, and inhibit neurotransmitter release; through this mechanism, they inhibit the release of the inhibitory neurotransmitter GABA, and disinhibit the dopamine pathways, causing more dopamine to be released.

Opioids are among the world's oldest known drugs (opium).

Morphine is refined from raw opium and is used for pain relief.

Interactions between neurotransmitter systems

In a state of romantic love:

-high dopamine level

-high norepinephrine level

-low serotonin level

Effects:

Heightened energy

Focused attention

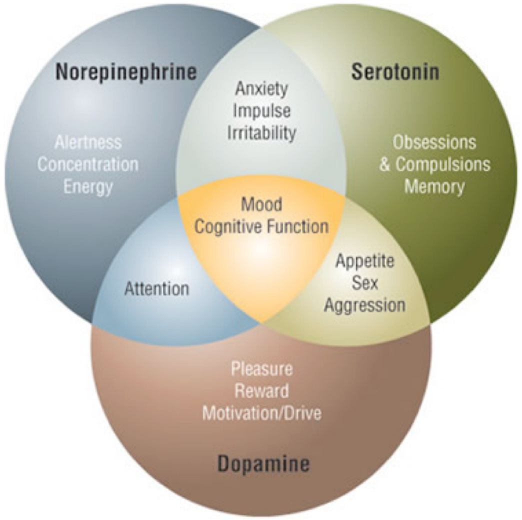
Obsessive thinking

Motivation

Elation (mood swings)

Increased testosterone level

(both males and females)



Serotonin-Enhancing Antidepressants:

-enhance serotonin level

-reduce dopamine level

-reduce norepinephrine level

Effects:

Diminished libido

Shallow emotions (including euphoria of romantic love)

Suppression of obsessive thinking (a central component of romance)

Conclusion: SSRI may reduce depression but they can also inhibit evolutionary mechanisms to attract and fall in love. They should be used with awareness.

H. Fisher, Anatomia miłości - nowe spojrzenie, Rebis, 2017