The Role of Neurotransmitters in Anesthesia

Atabak Najafi[1], Farhad Etezadi[1], Reza Shariat Moharari[1], Pejman Pourfakhr[1], Mohammad Reza Khajavi[1]*

General anesthetic drugs produce extensive neuronal changes in the central nervous system by enhancing inhibitory and reducing excitatory neurotransmission. The major neurotransmitters, which are thought to play a role in anesthesia, are glutamate, serotonin, norepinephrine, dopamine, acetylcholine, and GABA. The knowledge of neurotransmitters and their receptors' function is very important in perception of anesthesia in routines practice.

The purpose of this review article is to give an overview of the different types of neurotransmitters in CNS, classification of neurotransmitters and mechanism of action of various types of neurotransmitters and their receptors.

keywords: neurotransmitters; receptors; anesthesia; central nervous system

Anesthestetic science has improved in recent years. General anesthetic drugs produce a widespread neurodepression in the central nervous system by enhancing inhibitory neurotransmission and reducing excitatory neurotransmission. They act on different parts of the brain and various molecular targets and cause different behavioral responses like amnesia, unconsciousness, analgesia, and immobility [1].

The association between the specific sites of CNS and the functions of general anesthetics has been recently discovered. The amnesic effect of general anesthetics is closely related with the hippocampus. Sedation is related to the neocortex and thalamus, and hypothalamus is presumably the hypnotic action part [2].

Each of these behavioral responses is mediated by different neurotransmitters, receptors and neuronal pathways. Generally routine anesthetic drugs act by either enhancing inhibitory signals or by blocking excitatory signals. None of these current clinical general anesthetics are selective for a single ion channel. At clinical concentrations, every anesthetic modulates the function of multiple types of receptors or channels in the central nervous system.

Thus, in this review, the physiologic action of some important neurotransmitters, receptors and the association between various behavioral responses such as consciousness and memory to general anesthetics are summarized from recent pieces of research.
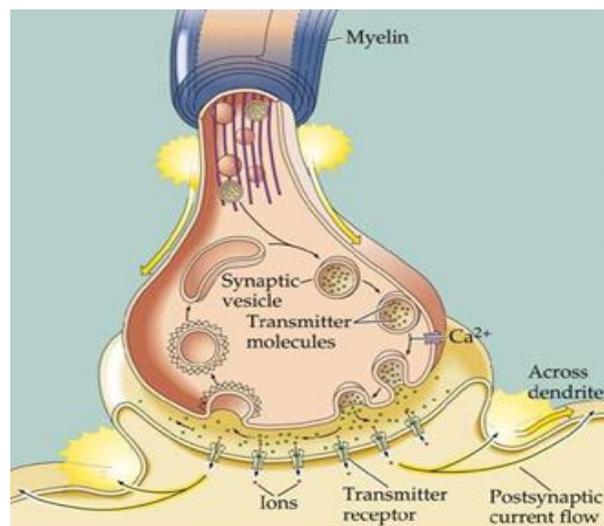
Definition and Classification of Neurotransmitters

Neurotransmitters are the chemicals responsible for signal transmission between the individual neurons and organs.

They are made at the terminal nerves, stored in a vesicle and released during stimulation to synaptic cleft. They transmit signals, from one neuron to another target neuron, muscle cell, or gland cell [3]. A released neurotransmitter in the synaptic cleft has a short time before it is metabolized by enzymes, pulled back into the pre-synaptic neuron through reuptake, or bound to a postsynaptic receptor and produce either excitation or inhibition of the target cell (Figure 1) [4].

From discovery of the first neurotransmitter, acetylcholine (ACh), until now, hundreds of chemicals substances were found that act as a neurotransmitter in the body. They can be classified based on function or structures [5].

Figure 1- Neurotransmitter circle

Structural classification of neurotransmitters

Major neurotransmitters can be classified chemically as:
1- Acetylcholine
2- Biogenic Amines: Dopamine, norepinephrine, epinephrine, Indolamines, Serotonin and histamine
3- Amino Acids: Glycine, GABA, Aspartate, Glutamate
4- Neuropeptides: Substance P, Endorphins, Enkephalins, Somatostatin, gastrin, cholecystokinin, oxytocin, vasopressin, Leutinizing hormone releasing hormone (LHRH)

5- Purines: Adenosine, ATP

6- Gases and Lipids: Nitric Oxide (NO), Carbonmonooxide (CO) Cannabinoids

According to function they can be classified as excitatory or inhibitory neurotransmitters. A neurotransmitter can influence the function of a target neuron through only one of two ways: excitatory or inhibitory. In excitatory synapses a neurotransmitter depolarizes the target nerve but inhibitory neurotransmitter hyperpolarizes the end nerve and stop the function of the end organ [6].

The appearance and shape of these synapses are different. In excitatory nerve synapses are typically located on the shafts or the spines of dendrites, whereas in inhibitory nerve synapses are typically located on cell body of nerve. Vesicles in excitatory nerve are round but in inhibitory nerve are flattened [7].

Neurotransmitter receptors

A neurotransmitter receptor is a specialized protein that is embedded in phospholipid bilayer of cell membrane and has a communication function with the internal organ of cells [8]. These receptors can be classified as postsynaptic or pre-synaptic. Neurotransmitters in postsynaptic receptors usually trigger an electrical signal into the cell that cause activation or inhibition but pre-synaptic receptor provide feedback and mediate regulatory action on neurotransmitter release from cells.

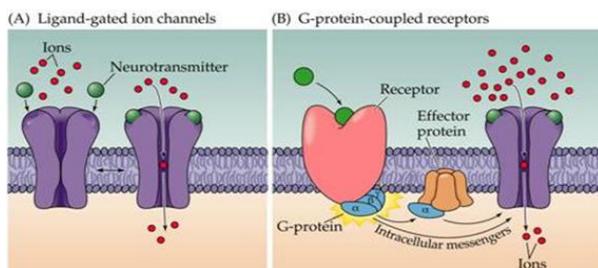There are two types of neurotransmitter receptors [9]:

1- ligand-gated receptors or ionotropic receptors

2- G protein-coupled receptors or metabotropic receptors.

Ligand-gated receptors

These receptors are a group of trans-membrane ion channel proteins that are opened or closed in response to the binding of a chemical messenger such as a neurotransmitter (ligand). These receptors according to type of neurotransmitter may have an excitatory or inhibitory function. These receptors typically have two different domains: a trans-membrane domain which act as a channel through the cell membrane, and an extracellular domain which includes the ligand binding location [10].

The action of this receptor is immediate and brief. In excitatory receptors there are channels for small cations, like Na+ Ca^{2+}, that influx into cells contributing to depolarization. Inhibitory receptors allow Cl– influx or K+ efflux that causes hyperpolarization (Figure 2). Ligand-gated ion channels are also different from voltage-gated ion channels which open and close depending on membrane potential, and stretch-activated ion channels which open and close depending on mechanical deformation of the cell membrane [11].

Figure 2- ligand-gated and G-protein-coupled receptors.

(A) Ligand-gated ion channels (B) G-protein-coupled receptors

Some type of Ligand-gated receptors:

5-HT$_3$ Receptors, Acetylcholine Nicotinic Receptors, GABA$_A$, and GABA$_A$-ρ Receptors, Glutamate (Ionotropic) Receptors, Glycine Receptors, Purinergic Receptors.

G Protein-Linked Receptors (Metabotropic receptors)

G protein coupled receptors constitute a large protein family of receptors, that detect molecules outside the cell and activate internal signal transduction pathways that cause cellular responses. They are also called seven-transmembrane receptors because they have seven subunits that pass through the cell membrane [12].

The ligands that bind and activate these receptors include, hormones, neurotransmitters, and vary in size from small peptides to large proteins.

There are two principal signal transduction pathways involving the G protein–coupled receptors:

The G protein–coupled receptor is activated by an external signal in the form of a ligand or other signal mediator. This creates a conformational change in the receptor, causing activation of a G protein. Further effect depends on the type of G protein. Activated G protein controls production of second messengers, like cyclic AMP, cyclic GMP, diacylglycerol or Ca^{2+}. These second messengers open or close ion channels, activate kinase enzymes, phosphorylate channel proteins, activate genes and induce protein synthesis. G proteins are subsequently inactivated by GTPase activating proteins and receptor activation terminated. Generally responses of this kind of receptors are indirect, slow, complex, and often prolonged and widespread [13].

Example of this class of receptors includes the metabotropic glutamate receptors, muscarinic acetylcholine receptors, GABA$_B$ receptors, and most serotonin receptors, as well as receptors for norepinephrine, epinephrine, histamine, dopamine, neuropeptides and endocannabinoids [14].

Ion channels

In addition to neurotransmitter receptors, there are some ion channels that are known to be other functional sites of general anesthetics as follow:

Potassium channels

Potassium channels, play an important role in forming the resting membrane potential membrane repolarization. Activation of this channel by volatile anesthetics increases the conductance of potassium ions, hyperpolarization of cell membrane and inhibition of the neuron activity [15].

Sodium channels

The voltage-gated sodium channel play an important role in axonal conduction, synaptic integration, and neuronal excitation. Some general anesthetics inhibit the pre-synaptic voltage-gated sodium channels in glutamatergic synapses, blocking the release of pre-synaptic neurotransmitters and inhibit the excitation of the neuron [16].

Important neurotransmitter in central nervous system

Acetylcholine (Ach)

It was the first neurotransmitter to be identified and the most abundant neurotransmitter in the brain. Acetylcholine is synthesized at the ending nerve by the enzyme choline acetyltransferase from the compounds choline and acetyl-

CoA. After release from nerve ending, the enzyme acetylcholinesterase converts acetylcholine into the inactive metabolites choline and acetate. This enzyme is abundant in the synaptic cleft, and its role in rapidly clearing free acetylcholine from the synapse is essential for proper muscle function [17]. It is a neurotransmitter at all autonomic ganglion, autonomically innervated organs, neuromuscular junction, and at many synapses in the CNS [18].

Autonomic Nervous System

Acetylcholine is the neurotransmitter in the preganglionic sympathetic and parasympathetic neurons. ACh is also the neurotransmitter at the adrenal medulla and serves as the neurotransmitter at all the parasympathetic ganglion, innervated organs at the sweat glands, and at the piloerector muscle of the sympathetic ANS.

Peripheral Nervous System

Acetylcholine is the neurotransmitter at the neuromuscular junction between the motor nerve and skeletal muscle.

Central Nervous System

In the CNS, acetylcholine as a neurotransmitter and a neuromodulator. It is found primarily in interneurons cholinergic projections from the basal forebrain to the cerebral cortex and hippocampus support the cognitive functions of those target areas (Figure 3). ACh has a variety of effects on plasticity, arousal, and reward. ACh has an important role in the enhancement of alertness when we wake up, in sustaining attention, wakefulness, learning and memory. It is also active during REM sleep during which the cortex is aroused [19].

Figure 3- The cholinergic diffuse modulatory system arising from the basal forebrian and brain stem
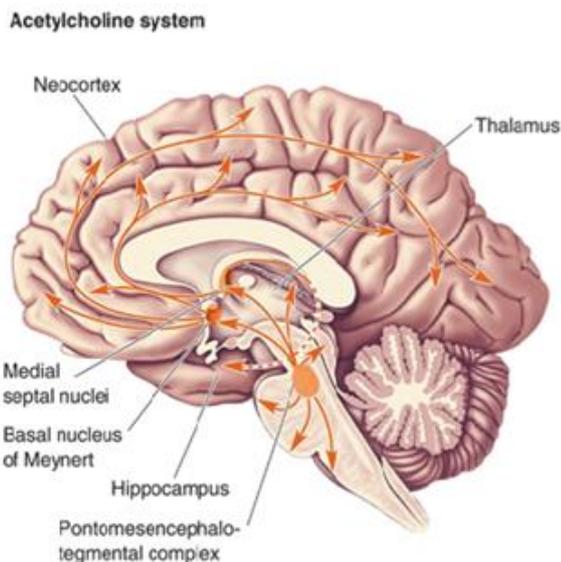
Acetylcholine receptor

There are two main classes of acetylcholine receptor, nicotinic and muscarinic (Figure 4-5) [20].

Nicotinic acetylcholine receptors are usually considered cholinergic receptors, they are ligand-gated ion channels permeable to sodium, potassium, and calcium ions. Nicotinic receptors come in two main types, known as muscle-type

and neuronal-type. The main location of muscle-type receptors is on muscle cells. Neuronal-type receptors are located in autonomic ganglia, both sympathetic and parasympathetic, and in the central nervous system [21].

Muscarinic acetylcholine receptors have a more complex mechanism, and affect target cells over a longer time frame. It has five types and all of them function as G protein-coupled receptors, meaning that they exert their effects via a second messenger system. These kinds of receptors are found in both the central nervous system and the peripheral nervous system of the heart, lungs, upper gastrointestinal tract, and sweat glands [22].
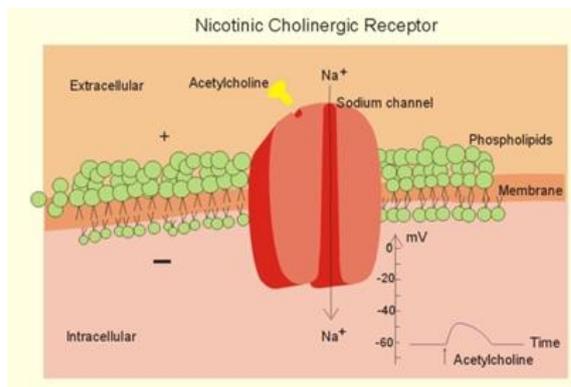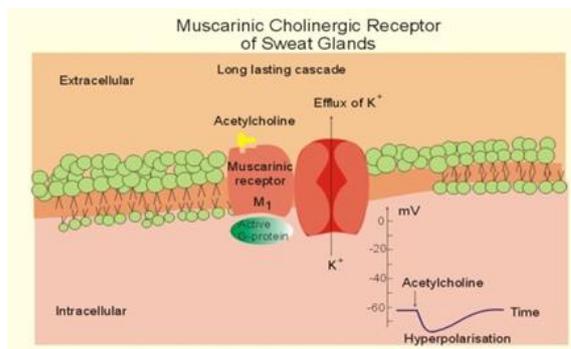
Figure 4- The nicotinic cholinergic receptor

Figure 5- The muscarinic cholinergic receptor

Anesthesia and Acetylcholine

Neuronal nicotinic acetylcholine receptors are more sensitive to anesthetics than their muscle counterparts. The main effect of anesthetic agents on nicotinic acetylcholine receptors is inhibitory. Volatile anesthetics and ketamine are the most potent inhibitors of nicotinic acetylcholine receptors; several intravenous anesthetics such as barbiturates, etomidate, and propofol exert also an inhibitory effect on the nicotinic acetylcholine receptors, but only at concentrations higher than those necessary for anesthesia [23].

The volatile anesthetic agents have no effects on nicotinic acetylcholine receptors at the level of the spinal cord to cause immobility [24].

Muscle-type nicotinic acetylcholine receptor is another site that muscle relaxant agents in general anesthesia block the receptors and cause immobility for surgery [25].

Gamma-Aminobutyric acid (GABA)

GABA is the chief inhibitory neurotransmitter in the central nervous system that plays an important role in

reducing neuronal excitability throughout the central nervous system. It was discovered as an integral part of the mammalian central nervous system in 1950 [26].

Exogenous GABA that is structurally an amino acid, does not penetrate the blood brain barrier therefore it is synthesized in the brain. It is synthesized from glutamate and pyridoxal phosphate [27]. The GABA system is the target of a wide range of drugs active on the CNS, including anxiolytics, sedative-hypnotics, general anesthetics, and anticonvulsants [28].

Neurons that produce GABA as their output are called GABAergic neurons, and have chiefly inhibitory action at GABA receptors. The actions of GABA in the pontine reticular formation in brain steam are associated with cortical arousal. The concentration of GABA increase in nonREM sleep and decrease in REM sleep.

There are two classes of GABA receptors [29]:

• $GABA_A$ in which the receptor is part of a ligand-gated ion channel complex

• $GABA_B$ metabotropic receptors, which are G protein-coupled receptors that open or close ion channels via G proteins.

Figure 6- Structure of the cys-loop superfamily GABAA receptor
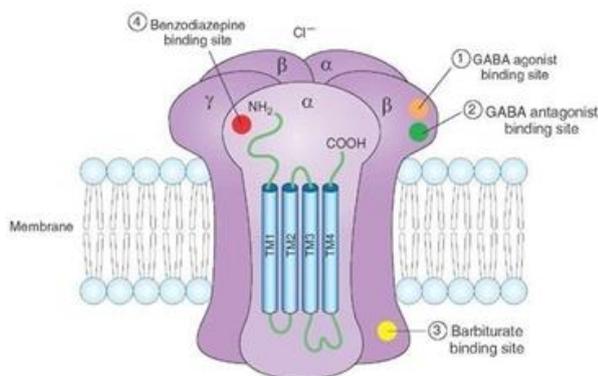
GABA$_A$ receptors are members of the Cys-loop superfamily of pentameric polypeptide ligand-activated chloride channels. The name of the superfamily comes from the characteristic "cys-loop" found in all subunits, defined by a disulfide bond between two cysteine residues separated by 13 amino acid residues (Figure 6). Neurotransmitter binding sites are located at two or more extracellular interfaces and in the case of GABA $_A$ Rs, the endogenous ligand binds between the α and β subunits. There are nine different receptor configurations distributed among different brain regions. Because each type of GABA $_A$R exhibits distinct biophysical and pharmacologic properties, these receptors are capable of diverse influences on regulating synaptic transmission and synaptic integration.

When GABA$_A$ receptors are activated by GABA, they allow the flow of chloride ions across the membrane of the cell. Whether this chloride flow is depolarizing (makes the voltage across the cell's membrane less negative), shunting (has no effect on the cell's membrane potential), or inhibitory/hyperpolarizing (makes the cell's membrane more negative) depends on the direction of the flow of chloride. When net chloride flows out of the cell, GABA is depolarizing; when chloride flows into the cell, GABA is inhibitory or hyperpolarizing. When the net flow of chloride is close to zero, the action of GABA is shunting. Shunting

inhibition has no direct effect on the membrane potential of the cell; however, it reduces the effect of any coincident synaptic input by reducing the electrical resistance of the cell's membrane. Shunting inhibition can "override" the excitatory effect of depolarizing GABA, resulting in overall inhibition even if the membrane potential becomes less negative [30].

Physiological and pharmacological effects of GABAergic drugs include: Anxiolysis; sedation; amnesia; anticonvulsive action and muscle relaxation.

GABA$_A$ receptors agonists: barbiturates, benzodiazepines, meprobamate, lorbamate, ethanol (alcohol), etomidate, neuroactive steroids [31].

GABA$_B$ receptors are metabotropic transmembrane receptors that are linked via G-proteins to potassium channels [32]. The changing potassium concentrations hyperpolarize the cell at the end of an action potential and reduce neurotransmitter release. Baclofen is a GABA analogue which acts as a selective agonist of GABAB receptors, and is used as a muscle relaxant [33].

Anesthetic actions of GABA$_A$ receptors

There is much strong evidence that GABA receptors are involved in mediating some of the classical components of general anesthesia: hypnosis, depression of spinal reflexes, and amnesia [34].

Each therapeutic drug have been linked to different GABA$_A$A receptors assemblies present in different brain regions; for example sedation produced by benzodiazepines has been associated with the α1 containing GABA Rs. Volatile anesthetics like: isoflurane, desflurane and sevoflurane all enhance the amplitude of responses to low concentrations of GABA and prolong the duration of GABA mediated synaptic inhibition [35]. The intravenous anesthetics (thiopental, etomidate and propofol) enhance the amplitude of responses to low concentrations of GABA at clinically relevant concentrations and prolong the duration of GABA mediated synaptic inhibition [36].

Glycine

Glycine is the simplest possible amino acid neurotransmitter in brain. It is an inhibitory neurotransmitter same as GABA that after release into a synapse, binds to a receptor which makes the post-synaptic membrane more permeable to Cl- ion. This hyperpolarizes the membrane, making it less likely to depolarize [37].

It is one of the major inhibitory neurotransmitters in posterior areas of the central nervous system, spinal cord, brainstem, and retina. In the spinal cord and brain stem, glycinergic interneurones provide an inhibitory feedback mechanism that controls the motor rhythm generation during movement and they also play an important role in the coordination of spinal reflex activity [38]. It is also an important neurotransmitter in the processing of auditive information through cochlear nuclei, the superior oliva complex and the inferior colliculus and in the processing of visual information in retinal ganglion cells [39]. Besides its inhibitory action, glycine exerts a positive modulation on excitatory glutamatergic neurotransmission through N-methyl-D-aspartate (NMDA) receptors [40].

Clinical usage

Recently it is used in sleep disorder, schizophrenia and

also serves as a buffering agent in antacids, analgesics, antiperspirants. It would be useful in the treatment of epilepsy and pain by interfering with strychnine-sensitive glycine receptor systems [41]. Glycine has a great potential to protect from ischaemia– reperfusion injury. For certain organs such as the liver and the small intestine, several reports demonstrating protection have been published, while for other organs, especially the heart, very limited information on protection by glycine is available [42].

Glycine receptor

Glycine receptor is an ionotropic receptor that produces its effects through chloride current (Figure 7). The glycine receptor is primarily found in the ventral spinal cord. It has an important role in a variety of physiological processes, especially in mediating inhibitory neurotransmission in the spinal cord and brainstem [43]. This receptor can be activated by a range of simple amino acids including glycine, β-alanine and taurine, and can be selectively blocked by the high-affinity competitive antagonist strychnine. The poison strychnine is a glycine antagonist which can bind to the glycine receptor and results in spinal hyperexcitability, tetanic convulsions in which the body is arched and the head bent backward. Caffeine is a competitive antagonist of Glycine receptor [44].

Figure 7- Glycine, receptor Br J Pharmacol. 2012; 165 (7): 2059–2072.
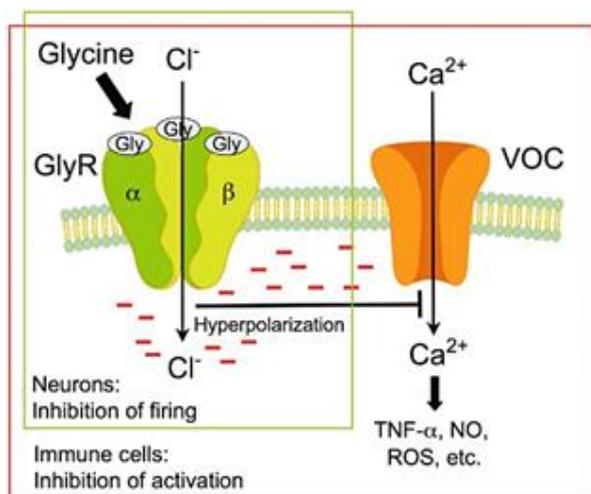
Glutamate

Glutamate is the most abundant free amino acid and the major excitatory transmitter in the brain. It is used in more than 90% of the synaptic connections in the human brain. Glutamate & GABA form an excitatory/inhibitory pair in the brain [45].

Glutamate cannot cross the blood brain barrier unassisted, and it is actively transported into the nervous system by a high affinity transport system, which maintains its concentration in brain fluids at a fairly constant level [46]. Glutamate is synthesized in the central nervous system from glutamine as part of the glutamate-glutamine cycle by the enzyme glutaminase. This can occur in the pre-synaptic neuron or in neighboring glial cells. Glutamate itself serves as metabolic precursor for the neurotransmitter GABA, via the action of the enzyme glutamate decarboxylase [47].

There are three families of ionotropic glutamate receptors

with intrinsic cation permeable channels (NMDA & non NMDA receptors). There are also three groups of metabotropic, G-protein-coupled glutamate receptors that can modify neuronal excitability. There are also two glial glutamate transporters and three neuronal transporters in the brain [48]. The function of glutamate as an excitatory neurotransmitter is memory creation, messaging for body movement and human thought process [49]. The nonNMDA receptors subdivided into AMPA and kainite receptors.

In brain injury or disease, they often work in reverse, and excess glutamate can accumulate outside cells. This process causes calcium ions to enter cells via NMDA receptor channels, leading to neuronal damage and eventual cell death, and is called excitotoxicity. The mechanisms of cell death include
• Damage to mitochondria from excessively high intracellular Ca^{2+}
• Glutamate/Ca^{2+}-mediated promotion of transcription factors for pro-apoptotic genes, or down regulation of transcription factors for anti-apoptotic genes [50].

Therefore, the rapid removal of extracellular glutamate must occur on a millisecond time scale to avoid cellular damage. The mechanisms which can maintain low extracellular concentrations of glutamate are essential for brain functioning. The only significant mechanism for removal of glutamate from the extracellular fluid is cellular uptake of glutamate. This uptake is mediated by a family of special transporter proteins which act as pumps. These proteins bind glutamate, one molecule at the time, and transfer them into the cells. In agreement with the abundance of glutamate and the ubiquity of glutamate receptors, brain tissue displays a very high glutamate uptake activity [51].

In general anesthesia inhaled anesthetics block excitatory neurotransmission by inhibiting not only postsynaptic glutamate receptors but also the glutamate release from pre-synapse. Glutamate release was most sensitive to inhibition compared with other neurotransmitters.

Neurochemical and electrophysiological evidence suggests that volatile anesthetics inhibit glutamate release by blocking presynaptic Na channels, thereby inhibiting nerve terminal depolarization [52].

N-methyl-D-aspartate receptor (NMDA)

The NMDA is a postsynaptic glutamate receptor and ion channel protein found in nerve cells. It is a specific type of ionotropic glutamate receptor that activates, when glutamate and glycine bind to it, and when activated it allows positively charged ions such as Ca^{2+} and Na^+ to flow into the cell and K^+ out of the cell. The NMDA receptor is very important for controlling synaptic plasticity and a cellular mechanism for learning and memory function [53].

NMDA receptors have been implicated in a number of studies to be strongly involved with excitotoxicity [54].

There is evidence to suggest that stimulation of synaptic NDMA receptors contributes to the health and longevity of the cell but stimulation of extrasynaptic NMDA receptors appear to contribute to cell death. Excitotoxicity has been thought to play a role in the degenerative properties of neurodegenerative conditions like Alzheimer's disease [55].

NMDA receptors Agonists

Activation of NMDA receptors requires binding of

glutamate or aspartate. In addition, NMDARs also require the binding of the co-agonist glycine for the efficient opening of the ion channel, which is a part of this receptor (Figure 8). Some other known NMDA receptor agonists include: D-Serine,L-Serine,D-Alanine, Quinolinate [56].

Figure 8- NMDARs require the binding of two molecules of glutamate or aspartate and two of glycine.
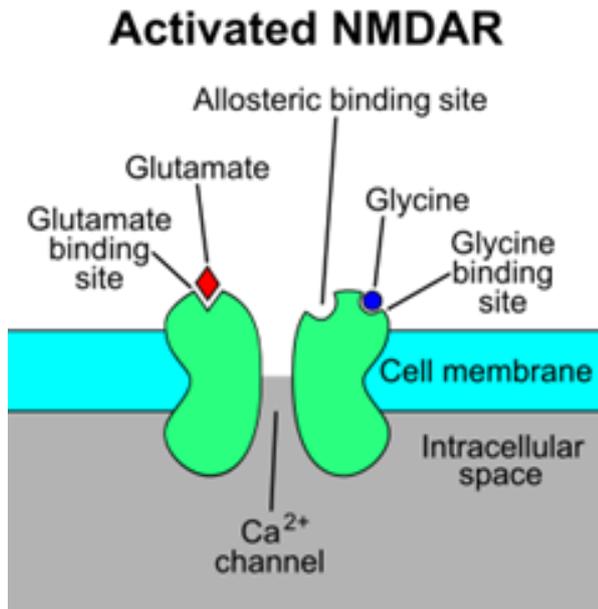
Partial agonists: N-Methyl-D-aspartic acid (NMDA)

Antagonists: Dexanabinol, Diethyl ether, Dizocilpine, Ketamine, Dextromethorphan, Nitrous oxide, xenon [57].

The role of NMDA receptors has been established in several neuropsychiatric disorders such as ischemia and traumatic brain injury, neurodegenerative disorders, pain syndromes, addiction, depression, affective disorders and neuro developmental disorders as autism or schizophrenia [58].

NMDA receptor antagonism is important for anesthetic-induced analgesia and control of central-sensitization component of postoperative pain. The contribution of NMDA receptor antagonism to the amnesic effect of ketamine is not completely clear. Inhalation anesthetics also have hypnotic effect by NMDA receptor antagonism [59].

Aspartate

Aspartate is released in the spinal cord. It is an excitatory neurotransmitter, which increases the likelihood of depolarization in the postsynaptic membrane. Aspartate & glycine form an excitatory/inhibitory pair in the ventral spinal cord.

Serotonin (5-hydroxytryptamine)

Serotonin is a monoamine neurotransmitter biochemically derived from tryptophan is primarily found in the gastrointestinal tract, blood platelets, and the central nervous system. Serotonin is a key mediator in the physiology of mood, vascular function and gastrointestinal motility. It is popularly thought to be a contributor to feelings of well-being and happiness [60].

Approximately 90% of the human body's total serotonin is located in the enterochromaffin cells in the GI tract, where it is used to regulate intestinal movements. The remainder is synthesized in serotonergic neurons of the CNS, where it has various functions. These include the regulation of mood, appetite, and sleep [61]. Serotonin secreted from the enterochromaffin cells eventually finds its way out of tissues into the blood. There, it is actively taken up by blood platelets, which store it. When the platelets bind to a clot, they release serotonin, where it serves as a vasoconstrictor and helps to regulate hemostasis and blood clotting. Serotonin also is a growth factor for some types of cells, which may give it a role in wound healing [62].

The neurons of the raphe nuclei are the principal sources of 5-HT release in the brain. There are nine raphe nuclei, designated B1-B9, which contain the majority of serotonin-containing neurons, all of which are located along the midline of the brainstem, and centered on the reticular formation. Axons from the neurons of the raphe nuclei form a neurotransmitter system reaching almost every part of the central nervous system (Figure 9). Axons of neurons in the lower raphe nuclei terminate in the cerebellum and spinal cord, while the axons of the higher nuclei spread out in the entire brain [63].

Figure 9- Serotonine and dopamine pathways and functions
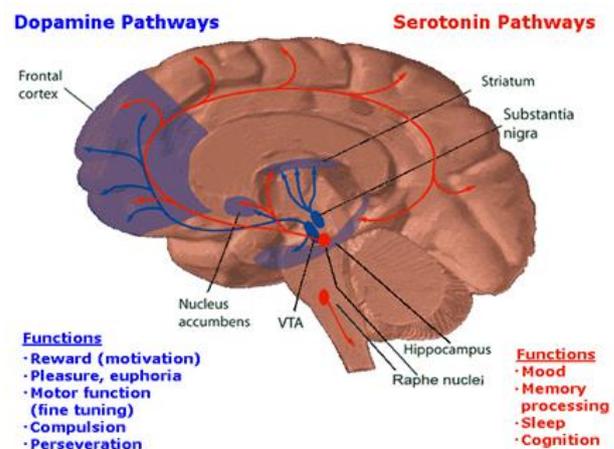
Serotonin-synthesizing neurons localized in the midline medulla, have widely distributed projections that influence homeostatic processes across the autonomic, motor, somatosensory, and limbic systems. Serotonergic ascending projections to the forebrain mediate arousal, cognition, anxiety, and cerebral blood flow and descending projections to the brainstem and spinal cord mediate respiratory, cardiovascular and motor control, thermoregulation, and nociception. Investigation has shown anesthetic, analgesic, hypnotic, and immobilizing actions of volatile anesthetics such as isoflurane on post-synaptic receptor types that are targets of serotonergic projections. Isoflurane also in presynaptc, inhibits 5-HT neuron discharge [64].

Serotonin (5-HT) receptors

Serotonin receptors are classified into seven main receptor subtypes, 5-HT1–7. Of major pharmacotherapeutic importance are those designated 5-HT1, 5-HT2, 5-HT4, and 5-HT7, all of which are G-protein-coupled, whereas the 5-HT3 subtype represents a ligand-gated ion channel. They are found in the central and peripheral nervous systems and mediate both excitatory and inhibitory neurotransmission [65].

Serotonergic action is terminated primarily via uptake of 5-

HT from the synapse. This is accomplished through the specific monoamine transporter for 5-HT, SERT, on the presynaptic neuron. Various agents can inhibit 5-HT reuptake, including cocaine, dextromethorphan, tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs).

Catecholamine

A catecholamine is a monoamine, an organic compound that has a catechol (benzene with two hydroxyl side groups at carbons) and a side-chain amine. Catecholamines are derived from the amino acid tyrosine. They are produced mainly by the chromaffin cells of the adrenal medulla and the postganglionic fibers of the sympathetic nervous system. The major neurotransmitters in brain are dopamine and norepinephrine [66].

Inside the brain, dopamine plays important roles in executive functions, motor control, motivation, arousal, reinforcement, and reward, as well as lower-level functions including lactation, sexual gratification, and nausea. The dopaminergic cell groups and pathways make up the dopamine system which is neuromodulatory [67]. It is largely produced in neuronal cell bodies in two areas of the brainstem: the ventral tegmental area and the substantia nigra, the latter of which contains neuromelanin-pigmented neurons [68].

There are two primary dopamine receptor-types, both of which act through G-proteins: D1 and D2. Upon depletion of striatal dopamine to 20% the original level, symptoms of Parkinson's disease appear, and treatment is L-DOPA. Schizophrenia is thought to be due to an overstimulation of D2 receptors in the mesolimbic and mesocortical systems. D2 antagonist drugs such as haloperidol alleviate the symptoms, whereas substances which increase D2 stimulation, such as amphetamines, can induce psychotic symptoms resembling schizophrenia. Dopamine also is the primary neuroendocrine inhibitor of the secretion of prolactin from the anterior pituitary gland [69].

Anesthesia and dopamine

Dopaminergic neurotransmission plays a critical role in processes such as learning, memory, motivation, reward, risk assessment and locomotion. The activation of the central dopaminergic D1 receptor decreases the emergence time and induces the recovery from isoflurane anesthesia [70]. Electrical stimulation of the ventral tegmental area (VTA), a major dopamine nuclei in the brain, also induces reanimation from general anesthesia [71]. In addition the depletion of brain dopaminergic can induce a state of immobility [72]. The inhaled anesthetic isoflurane presynapticaly inhibits dopamine and norepinephrine release [73].
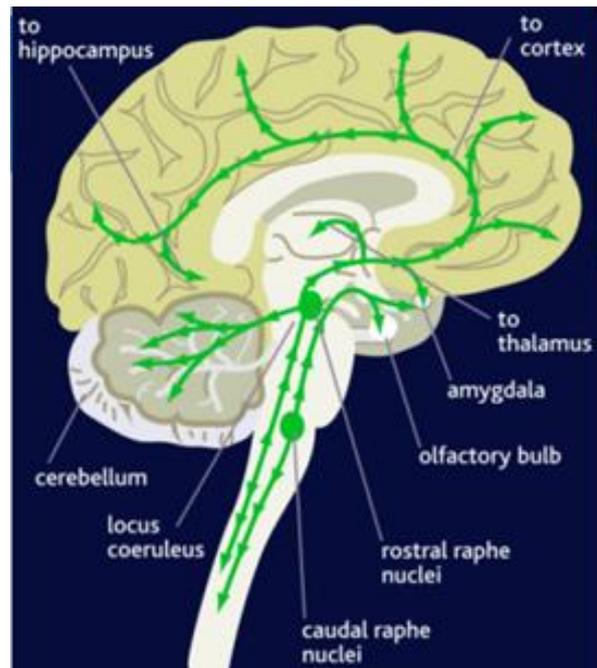
Norepinephrine

Norepinephrine is produced in neuromelanin-pigmented cell bodies of the locus ceruleus in the pons (Figure 10). It is the most prominent noradrenergic nucleus in the pons. Fibers from these nuclei innervate a large number of cortical, subcortical, and spinomedullary fields. The noradrenergic system seems to be very important for arousal, wakefulness and attention [74]. It is used as a neurotransmitter by sympathetic ganglia located near the spinal cord or in the abdomen, and it is also released directly into the

bloodstream by the adrenal glands.

It has two receptors, known as α and β, G protein-coupled receptors. Alpha receptors are divided into subtypes α1 and α2; beta receptors into subtypes β1, β2, and β3. α2 receptors are located pre-synaptically and usually have inhibitory effects [75].

Dexmedetomidine and other α2 adrenoceptor agonists are used to reduce the requirement of general anesthetic in humans. Lesion of locus ceruleus or NE depletion enhanced the effects of anesthetics drugs. Isoflurane inhibits release of norepinephrine in locus ceruleus aria [76].

**Figure 10- The site of Norepinephrine release in brain stem**

Epinephrine

The adrenal medulla produces over 90% of circulating epinephrine. In brain epinephrine is produced in small groups of neurons in the human brain which express its synthesizing enzyme, phenylethanolamine N-methyltransferase; these neurons project from a nucleus that is adjacent to the area postrema and from a nucleus in the dorsal region of the solitary tract. In brain endogenous epinephrine, can produce retrograde enhancement of long-term memory. It also modulates memory consolidation of the events, ensuring memory strength that is proportional to memory importance [77].

Histamine

Histamine origin is neuroepithelial and hematopoietic cells. It is synthesized from the amino

acid histidine and serves distinct functions: gastric acid secretion, immunomodulation, smooth muscle contraction (bronchial), vasodilatation (vascular), as well as epi- and endothelial barrier control [78]. In human brain, histaminergic system is located around the tuberomamillary nucleus (Figure11). Histamine like other brain monoamines (serotonin, norepinephrine, dopamine) plays an important role in emotions and cognition. It also stimulates serotonin, norepinephrine, and dopamine transmission in the brain.

Figure 11- The histaminergic system in the human brain. The histaminergic fibers emanating from the tuberomamillary nucleus project to and arborize in the whole central nervous system. (Modified from Haas and Panula)
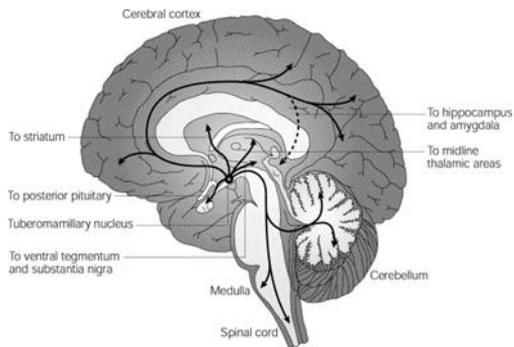
Histamine Receptors

A. Metabotropic Receptors: Four metabotropic histamine receptor types are found. H1-H3R is expressed in abundance in the brain and H4R occurs mainly in peripheral tissues. The cellular function of brain receptors are postsynaptic excitability and plasticity that lead to behavioral state like cognition, emotion, learning, memory and blood-brain barrier control. Pathologic state of these receptors cause sleep, mood, memory, eating, and addiction disorders.

The histamine H3 receptor is found mainly in the central nervous system, to act through presynaptic H3 receptor and regulates its own release as well as the release of other neurotransmitters such as noradrenaline, dopamine, serotonin, acetylcholine, and gammaamino-butyric acid.

B. Ionotropic Receptors: The ionotropic histamine receptor is likely a GABA receptor with a particular subunit composition and activates chloride conductance in hypothalamus and thalamus [79].

Brain histamine acts as a modulator of several neurotransmitters in the brain that it is crucial for wakefulness, motivation and goal-directed behaviors [80].

Histaminergic neurons that originate from the tuberomamillary nucleus (TMN) of the posterior hypothalamus have an established role in natural sleep and possible target site for the sedative effect of some general anesthetics. Histamine release in the anterior hypothalamus is depressed during sleep and halothane anesthesia [81]. In animal model tuberomamillary nucleus destruction enhances isoflurane-induced hypnosis [82]. A recent study demonstrated that histaminergic neurons are resistant to the effects of propofol [83]. The role of TMN and histaminergic transmission in the mechanism of anesthesia is still unclear.

Owing to their ability to cross the bloodebrain barrier, firstgeneration H1 antihistamines were used as sedative premedication vertigo, motion sickness (cinnarizine) and treatment/prevention of PONV (cyclizine) [84].

Summary

At the present time, it is widely accepted that general anesthesia is mediated by a direct interaction of the anesthetics on many neurotransmitter systems and receptor proteins in the CNS. The progression in understanding of functional mechanism of general anesthetics on CNS continues. Most of the general anesthetics act on various neurotransmitter-gated ion channels. Glutamate is the main excitatory neurotransmitter in the CNS and N-methyl-D-aspartate (NMDA) receptors are important in mediating excitatory neurotransmission in the nervous system. It appears, that NMDA receptor antagonism by ketamine, nitrous oxide and xenon may be important for maintenance of general anesthesia and control of the central-sensitization component of postoperative pain. GABA is the major inhibitory neurotransmitter in the brain, and most of the inhibition is mediated by GABA_A receptors. The target of the most general anesthetics is the GABA_A receptor histaminergic neurons have a role in modulating isoflurane anesthesia and hypnosis that may differ from intravenous drug anesthetics. In the coming years to understanding the molecular mechanisms of general anesthesia we should learn a great deal more about the molecular mechanisms of sleep, sensation, pain and consciousness.

References

1. Campagna JA, Miller KW, Forman SA. Mechanisms of actions of inhaled anesthetics. N Engl J Med. 2003; 348(21):2110-24.
2. Brown EN, Purdon PL, Van Dort CJ. General Anesthesia and Altered States of Arousal: A Systems. Annu Rev Neurosci. 2011; 34:601-628.
3. Whishaw, Bryan Kolb, Ian Q. An introduction to brain and behavior. 2014;4th ed. New York, NY: Worth Publishers. pp. 150–151
4. Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth. 2013 Principles of Neural Science. New York: McGraw Hill. p. 229
5. Patton KT. Anatomy and physiology. Elsevier Health Sciences; 2015 Feb 10.
6. M. Sheng, C. Hoogenraad; Hoogenraad. Annual Review of Biochemistry. 2006;76: 823–47.
7. Gitler D, Takagishi Y, Feng J, Ren Y, Rodriguiz RM, Wetsel WC, Greengard P, Augustine GJ. Different presynaptic roles of synapsins at excitatory and inhibitory synapses. Journal of Neuroscience. 2004 Dec 15;24 (50):11368-80.
8. Pocock JM, Kettenmann H. Neurotransmitter receptors on microglia. Trends in neurosciences. 2007. 31;30 (10):527-35.
9. Snyder SH. Drug and neurotransmitter receptors in the brain. Science. 1984 Apr 6;224:22-32.
10. Keramidas A, Moorhouse AJ, Schofield PR, Barry PH. Ligand-gated ion channels: mechanisms underlying ion selectivity. Progress in biophysics and molecular biology. 2004 Oct 31;86 (2):161-204.
11. Catterall WA. Structure and function of voltage-gated ion channels. Annual review of biochemistry. 1995 Jul;64 (1):493-531.
12. Trzaskowski B, Latek D, Yuan S, Ghoshdastider U, Debinski A, Filipek S. Action of molecular switches in GPCRs--theoretical and experimental studies. Current Medicinal Chemistry.2012; 19 (8): 1090–109.
13. De Vries L, Farquhar MG, Zheng B, Fischer T, Elenko E (2000). "The regulator of G protein signaling family". Annu. Rev. Pharmacol. Toxicol. 40: 235–271.
14. Gilman A.G. (1987). "G Proteins: Transducers of Receptor-Generated Signals". Annual Review of Biochemistry. 56: 615–649.
15. Son Y. Molecular mechanisms of general anesthesia. Korean Journal of Anesthesiology. 2010;59 (1):3-8.
16. Hemmings HC., Jr Sodium channels and the synaptic mechanisms of inhaled anaesthetics. Br J Anaesth. 2009;103:61–69
17. Tuček, S. "Choline acetyltransferase and the synthesis of acetylcholine." The Cholinergic Synapse. Springer Berlin Heidelberg, 1988. 125-165.
18. Kleinz MJ, Spence I. The pharmacology of the autonomic nervous system. Small animal clinical pharmacology. 2nd Ed. Philadelphia: Saunders Elsevier, USA. 2008:59-82.
19. Picciotto MR, Higley MJ, Mineur YS. Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. Neuron. 2012 Oct 4;76 (1):116-29.
20. Miyazawa A, Fujiyoshi Y, Unwin N. Structure and gating mechanism of the acetylcholine receptor pore. Nature. 2003. 26; 423 (6943):949-55.
21. Melroy-Greif, W. E., Stitzel, J. A., & Ehringer, M. A.Nicotinic acetylcholine receptors: upregulation, age-related effects and

associations with drug use. Genes, Brain, and Behavior.2016; 15 (1), 89–107.

22. Haga T. Molecular properties of muscarinic acetylcholine receptors. Proceedings of the Japan Academy, Series B. 2013;89 (6):226-56.

23. Tassonyi E, Charpantier E, Muller D, Dumont L, Bertrand D. The role of nicotinic acetylcholine receptors in the mechanisms of anesthesia. Brain research bulletin. 2002 Jan 15;57 (2):133-50.

24. Wong SM, Sonner JM, Kendig JJ. Acetylcholine receptors do not mediate isoflurane's actions on spinal cord in vitro. Anesthesia & Analgesia. 2002 Jun 1;94 (6):1495-9.

25. Liu L, Li W, Wei K, Cao J, Luo J, Wang B, Min S. Synergistic effect of sevoflurane and isoflurane on inhibition of the adult-type muscle nicotinic acetylcholine receptor by rocuronium. Journal of anesthesia. 2013 Jun 1;27 (3):351-8.

26. Li K, Xu E. The role and the mechanism of γ-aminobutyric acid during central nervous system development. Neuroscience bulletin. 2008 Jun 1;24 (3):195.

27. Petroff OA. Book review: GABA and glutamate in the human brain. The Neuroscientist. 2002 Dec;8 (6):562-73.

28. Macdonald RL, Olsen RW. GABA receptor channels. Annu Rev Neurosci 1994;17: 569–602.

29. Bormann J. The 'ABC'of GABA receptors. Trends in Pharmacological Sciences. 2000 Jan 1;21 (1):16-9.

30. Forman SA, Miller KW. Anesthetic Sites and Allosteric Mechanisms of Action on Cys-loop Ligand-gated Ion Channels. Canadian journal of anaesthesia 2011;58 (2):191-205.

31. Fritschy JM, Panzanelli P. GABAA receptors and plasticity of inhibitory neurotransmission in the central nervous system. European Journal of Neuroscience. 2014 Jun 1;39 (11):1845-65.

32. Olsen, R.W., Sieghart, W. GABA A receptors: subtypes provide diversity of function and pharmacology. Neuropharmacology.2009; 56, 141-148.

33. Chalifoux JR, Carter AG. GABAB receptor modulation of synaptic function. Current opinion in neurobiology. 2011;21 (2):339-344.

34. McGaugh, J.L., Izquierdo, I. The contribution of pharmacology to research on the mechanisms of memory formation. Trends Pharmacol. Sci.2000; 21, 208-210.

35. Garcia PS, Kolesky SE, Jenkins A. General Anesthetic Actions on GABAA Receptors. Current Neuropharmacology. 2010;8 (1):2-9.

36. Trudell JR, Bertaccini E, MacIver BM. Teaching an Old GABA Receptor New Tricks. Anesthesia and analgesia. 2012;115 (2):270-273.

37. Aragón C1, López-Corcuera B. Structure, function and regulation of glycine neurotransporters. Eur J Pharmacol. 2003 Oct 31;479 (1-3):249-62.

38. Sibilla S, Ballerini L. GABAergic and glycinergic interneuron expression during spinal cord development: dynamic interplay between inhibition and excitation in the control of ventral network outputs. Progress in neurobiology. 2009 Sep 30;89 (1):46-60.

39. Kramer F, Griesemer D, Bakker D, Brill S, Franke J, Frotscher E, Friauf E. Inhibitory glycinergic neurotransmission in the mammalian auditory brainstem upon prolonged stimulation: short-term plasticity and synaptic reliability. Inhibitory Function in Auditory Processing. 2015 Oct 28.

40. Cummings KA1, Popescu GK2. Glycine-dependent activation of NMDA receptors. J Gen Physiol. 2015 Jun;145 (6):513-27.

41. Harvey RJ, Yee BK. Glycine transporters as novel therapeutic targets in schizophrenia, alcohol dependence and pain. Nature reviews Drug discovery. 2013 Nov 1;12 (11):866-85.

42. Petrat F, Boengler K, Schulz R, de Groot H. Glycine, a simple physiological compound protecting by yet puzzling mechanism (s) against ischaemia–reperfusion injury: current knowledge. British Journal of Pharmacology. 2012;165 (7):2059-2072.

43. Breitinger HG. Glycine receptors. eLS. 2014.

44. Pérez-Torres I, María Zuniga-Munoz A, Guarner-Lans V. Beneficial Effects of the Amino Acid Glycine. Mini reviews in medicinal chemistry. 2017 Jan 1;17 (1):15-32.

45. Meldrum BS1.Glutamate as a neurotransmitter in the brain: review of physiology and pathology. J Nutr. 2000 Apr;130 (4S Suppl):1007S-15S.

46. Hawkins RA, Viña JR. How Glutamate Is Managed by the Blood–Brain Barrier. Cooper AJL, Jeitner TM, eds. Biology. 2016;5 (4):37. doi:10.3390/biology5040037.

47. Smith QR. "Transport of glutamate and other amino acids at the blood-brain barrier". J. Nutr. 2000;130 (4S Suppl): 1016S–22S.

48. Hawkins RA1, Viña JR2. How Glutamate Is Managed by the Blood-Brain Barrier. Biology (Basel). 2016 Oct 8;5 (4). pii: E37.

49. McEntee, William J., and Thomas H. Crook. "Glutamate: its role in learning, memory, and the aging brain." Psychopharmacology 111.4 (1993): 391-401.

50. Zhou, Y., and N. C. Danbolt. "Glutamate as a neurotransmitter in the healthy brain." Journal of neural transmission 121.8 (2014): 799-817.

51. Niciu MJ, Kelmendi B, Sanacora G. Overview of Glutamatergic Neurotransmission in the Nervous System. Pharmacology, Biochemistry, and Behavior. 2012;100 (4):656-664. doi:10.1016/j.pbb.2011.08.008.

52. Westphalen RI, Desai KM, Hemmings HC. Presynaptic inhibition of the release of multiple major central nervous system neurotransmitter types by the inhaled anaesthetic isoflurane. British journal of anaesthesia. 2012 Dec 4:aes448.

53. Wood PL. The NMDAR complex: a long and winding road to therapeutics. IDrugs. 2005;8:229.

54. Parsons MP, Raymond LA. Extrasynaptic NMDA receptor involvement in central nervous system disorders. Neuron. 2014 Apr 16;82 (2):279-93.

55. Hardingham GE, Bading H. Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. Nature Reviews Neuroscience. 2010 Oct 1;11 (10):682-96.

56. Vyklicky V, Korinek M, Smejkalova T, Balik A, Krausova B, Kaniakova M, Lichnerova K, Cerny J, Krusek J, Dittert I, Horak M. Structure, function, and pharmacology of NMDA receptor channels. Physiological Research. 2014 Jan 1;63:S191.

57. Ogden KK, Traynelis SF. New advances in NMDA receptor pharmacology. Trends in pharmacological sciences. 2011 Dec 31;32 (12):726-33.

58. Gonda X. Basic pharmacology of NMDA receptors. Curr Pharm Des. 2012;18 (12):1558-67.

59. Defining the role of NMDA receptors in anesthesia: Are we there yet? European Journal of Pharmacology 723 (2014) 29–37

60. Berger M, Gray JA, Roth BL; Gray; Roth. The expanded biology of serotonin. Annu. Rev. Med.2009; 60: 355–66.

61. Zhou M, Engel K, Wang J; Engel; Wang. Evidence for significant contribution of a newly identified monoamine transporter (PMAT) to serotonin uptake in the human brain.2007; Biochem. Pharmacol. 73 (1): 147–54.

62. Gershon MD. 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract. Current opinion in endocrinology, diabetes, and obesity. 2013;20 (1):14-21. doi:10.1097/MED.0b013e32835bc703.

63. Kim, D., & Camilleri, M. (2000). Serotonin: A mediator of the brain-gut connection. The American Journal of Gastroenterology, 95 (10), 2698-2709.

64. Johansen S, Iceman K, Iceman C, Taylor B, Harris M. Isoflurane causes concentration-dependent inhibition of medullary raphé 5-HT neurons in situ. Autonomic neuroscience : basic & clinical. 2015;193:51-56.

65. Wacker D, Wang C, Katritch V, et al. Structural Features for Functional Selectivity at Serotonin Receptors. Science (New York, NY). 2013;340 (6132):615-619.

66. Williams, Freddie M., and Timothy J. Turner. "Adrenergic pharmacology." Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy (2008): 129.

67. Björklund A, Dunnett SB. Dopamine neuron systems in the brain: an update". Trends in Neurosciences.2007; 30 (5): 194–202

68. Rice ME, Patel JC, Cragg SJ "Dopamine release in the basal ganglia". Neuroscience. 198: 112–37.

69. Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. Pharmacological reviews. 2011 Mar 1;63 (1):182-217.

70. aylor NE, Chemali JJ, Brown EN, Solt K. Activation of D1 dopamine receptors induces emergence from isoflurane general anesthesia. Anesthesiology. 2013; 118: 30–39.

71. Solt K, Van Dort CJ, Chemali JJ, Taylor NE, Kenny JD, Brown EN. Electrical stimulation of the ventral tegmental area induces reanimation from general anesthesia. Anesthesiology. 2014; 121: 311–319.

72. Carey RJ, Huston JP, Muller CP. Pharmacological € inhibition of dopamine and serotonin activity blocks spontaneous and cocaine-activated behavior. Prog Brain Res 2008;172:347–360.

73. Westphalen, R. I., K. M. Desai, and H. C. Hemmings. "Presynaptic inhibition of the release of multiple major central nervous system

neurotransmitter types by the inhaled anaesthetic isoflurane." British journal of anaesthesia.2012: aes448.

74. Sara SJ. Locus Coeruleus in time with the making of memories".2015; Curr. Opin. Neurobiol. 35: 87–94

75. Rang HP, Ritter JM, Flower R, Henderson G. Noradrenergic transmission.2014; Rang & Dale's Pharmacology. Elsevier Health Sciences. pp. 177–196

76. Leung LS, Luo T, Ma J, Herrick I. Brain areas that influence general anesthesia. Progress in neurobiology. 2014 Nov 30;122:24-44.

77. Cahill L, Alkire MT. Epinephrine enhancement of human memory consolidation: interaction with arousal at encoding". Neurobiology of Learning and Memory.2003; 79 (2): 194–8

78. Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. Physiological reviews. 2008 Jul 1;88 (3):1183-241.

79. Lee KH, Broberger C, Kim U, McCormick DA. Histamine modulates thalamocortical activity by activating a chloride conductance in ferret perigeniculate neurons. Proc Natl Acad Sci USA 101: 6716–6721, 2004.

80. Passani MB, Panula P, Lin JS. Histamine in the brain. Frontiers in systems neuroscience. 2014;8.

81. Saper CB, Scammell TE, Lu J: Hypothalamic regulation of sleep and circadian rhythms. Nature 2005; 437:1257– 63

82. Luo T, Leung LS. Involvement of tuberomamillary histaminergic neurons in isoflurane anesthesia. The Journal of the American Society of Anesthesiologists. 2011 Jul 1;115 (1):36-43.

83. Zecharia AY, Yu X, Gotz T, et al: GABAergic inhibition of histaminergic neurons regulates active waking but not the sleepwake

84. Mahdy AM, Webster NR. Histamine and antihistamines. Anaesthesia & Intensive Care Medicine. 2014 31;15 (5):250-5.