

Neurotransmitters

- Neurotransmitters are endogenous chemical messengers that transmit signals from a neuron to a target cell across a synapse that enable neurotransmission.
- Neurotransmitter is unevenly distributed in the nervous system and its distribution parallels that of its receptors and synthesizing and catabolizing enzymes.

neurotransmitters

Cells of the **nervous system**, called **nerve cells** or neurons, are specialized to carry "messages" through an electrochemical process. The human **brain** has approximately 86 billion neurons.

Each neuron may be connected to up to 10,000 other **neurons**, passing signals to each other via as **many** as 1,000 trillion **synaptic** connections.

neurotransmitters

Neurotransmitters have half decay time of ~2 ms that roughly matched the time course of intracellularly recorded EPPs. Seven major neurotransmitters (acetylcholine, dopamine, gamma-aminobutyric acid (GABA), glutamate, histamine, norepinephrine, and serotonin) do the majority of the work

Neurotransmitters

Major neurotransmitters

I Acetyl Choline

**2 Biogenic Amines: a) Catecholamines
b) Serotonin *5HT)
c) Histamine**

**3. Amino acid neurotransmitters
a) Excitatory Amino acid- Glutamic acid, Aspartic acid**

Neurotransmitters

**b) Inhibitory Aminoacid- GABA
(Gamma amino butyricacid), Glycine**

**4. Polypeptide neurotransmitters-
Enkephalins, Endorphins Substance
P, Neuropeptide Y**

**5. Purinergic neurotransmitters-
Adenosine, ATP**

**6. Other neurotransmitters- Nitric
Oxide, Prostaglandins**

Muscarinic ACh receptor subtype	Location	Function	Diseases Associated
M ₁	Cerebral cortex, hippocampus, neostriatum, gastric glands, autonomic ganglia	Cognition, salivation	Alzheimer's Disease (AD), Cognitive dysfunction
M ₂	Heart and throughout the brain	Cardiac inhibition	Cardiac dysfunction, Pain
M ₃	Smooth muscles of viscera, eye, exocrine glands, blood vessels also expressed in low levels in cortex and hippocampus	Blood vessel contraction, regulation of movement of GIT, lachrymal secretion	Chronic obstructive pulmonary disorder, urinary incontinence, irritable bowel syndrome
M ₄	Striatum, cerebral cortex, hippocampus	Direct regulatory actions on K ⁺ and Ca ⁺² channels	Parkinson's disease, schizophrenia, neuropathic pain
M ₅	Substantia nigra	Regulate dopamine release at terminals	Drug dependence, Parkinson's disease,

Neurotransmitters

Neurotransmitter	Function	Other Facts
Acetylcholine (ACh)	Muscle action, Memory	Too little = Alzheimer's
Dopamine	Learning, pleasure emotion	Too much = hallucinations (Schizophrenia) Too little = Parkinson's
Serotonin	Mood Control, Aggression	Too Little = Depression
Epinephrine/Norepinephrine	Alertness and Arousal	Also a hormone Sometimes called adrenaline Also Depression
GABA "Get a Brake adjustment"	Inhibits/stops us from getting too aroused	Too Little = OCD thoughts, Seizures and Anxiety
Endorphins	Natural Painkillers	Example: Runner's High

Neuromodulators

- Some chemicals released by neurons have little or no direct effects on their own **but can modify the effects of neurotransmitters**. These chemicals are called neuromodulators.
- **Neurotransmitters and neuromodulators can be divided into two major categories: small-molecule transmitters and large-molecule transmitters.**

Neurotransmitters and Neuromodulators

- **Small-molecule transmitters:** Monoamines (eg, **acetylcholine, serotonin, histamine**), catecholamines (dopamine, norepinephrine, and epinephrine), and amino acids (eg, glutamate, GABA, glycine)
- **Large-molecule transmitters:** Large-molecule transmitters include a large number of (short chains of amino acids linked by peptide bonds) called **neuropeptides** including **substance P, enkephalin, vasopressin**, and a host of others. In general, neuropeptides are colocalized with one of the small-molecule neurotransmitters.

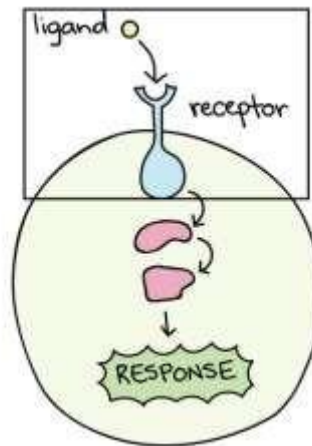
Neurotransmitters and Neuromodu

Examples of colocalization of small-molecule transmitters with neuropeptides

Small-Molecule Transmitter	Neuropeptide
Monoamines	
Acetylcholine	Enkephalin, calcitonin-gene-related peptide, galanin, gonadotropin-releasing hormone, neurotensin, somatostatin, substance P, vasoactive intestinal polypeptide
Serotonin	Cholecystokinin, enkephalin, neuropeptide Y, substance P, vasoactive intestinal polypeptide
Catecholamines	
Dopamine	Cholecystokinin, enkephalin, neurotensin
Norepinephrine	Enkephalin, neuropeptide Y, neurotensin, somatostatin, vasopressin
Epinephrine	Enkephalin, neuropeptide Y, neurotensin, substance P
Amino Acids	
Glutamate	Substance P
Glycine	Neurotensin
GABA	Cholecystokinin, enkephalin, somatostatin, substance P, thyrotropin-releasing hormone

Recepto

- Receptors are proteins and usually present on the cell surface
- Receptors are macromolecule or binding site located on the surface or inside the effector cell that serves to recognize the signal molecule/drug and initiate the response to it, but itself has no other



STRUCTURAL FAMILY	FUNCTIONAL FAMILY
GPCR	β Adrenergic receptors
	Muscarinic cholinergic receptors
	Eicosanoid receptors
	Thrombin receptors (PAR)
Ion channels	Ligand gated
	Voltage gated
Transmembrane enzymes	Receptor tyrosine kinases
	Membrane bound GC
	Tyrosine phosphatases
Transmembrane, nonenzymes	Cytokine receptors
	Toll-like receptors
Nuclear receptors	Steroid receptors
	Thyroid hormone receptors
	PPAR γ
Intracellular enzymes	Soluble GC

Criteria for Neurotransmitters

- The transmitter must be present in the presynaptic terminals of the synapse.
- Enough quantity transmitter must be released from the presynaptic nerve concomitantly with nerve activity to have an effect.
- The effects of experimental application of the transmitter should mimic the effects of stimulating the presynaptic pathway.
- If available, specific pharmacological agonists and antagonists should stimulate and block, respectively, the measured functions of the putative transmitter.
- There should be a mechanism present (either reuptake or enzymatic degradation) that terminates the actions of the transmitter.

Cell Signaling and Synaptic Transmission

- Cellular signaling links neurotransmitter receptor activation to downstream biological effects.
 - **Neurotransmitter synthesis:** Small-molecule neurotransmitters are synthesized in nerve terminals and peptides are synthesized in cell bodies and transported to nerve terminals.
 - **Neurotransmitter storage:** Synaptic vesicles store transmitters.
 - **Neurotransmitter release:** Release of stored transmitter from the storage vesicle into the synaptic cleft occurs by exocytosis. Depolarization of the presynaptic neuron initiates the release process. The release is based on Ca^{2+} -dependent release of vesicular contents.
 - **Neurotransmitter recognition:** Neurotransmitters diffuse from sites of release and bind selectively to receptor proteins to initiate intracellular signal transduction events within the postsynaptic cell.

Central Neurotransmitters

- Neurotransmitters can be classified by chemical structure into various categories, including **amino acids, acetylcholine (ACh), monoamines, neuropeptides, purines, lipids, and gases.**

Central Neurotransmitters - Amino Acids

- **Gamma-Aminobutyric Acid (GABA)**
(inhibitory neurotransmitter)
- **Glycine (inhibitory neurotransmitter)**
- **Glutamate and aspartate**
(excitatory neurotransmitter)
- All three compounds are present in high concentrations in the CNS and are extremely potent modifiers of neuronal excitability.

Central Neurotransmitters - Amino

• ~~Acids~~ Gamma-Aminobutyric Acid (GABA)

- GABA is the main inhibitory neurotransmitter in the CNS.
- GABA is synthesized in the brain from the Krebs cycle.
- GABA acts by binding to and activating specific ionotropic or metabotropic receptors on both pre- and postsynaptic membranes.
- It also mediates inhibition within the cerebral cortex and

GABA between the caudate nucleus and the substantia nigra.

receptors:

**GABA_A
receptors**

**GABA_B
receptors**

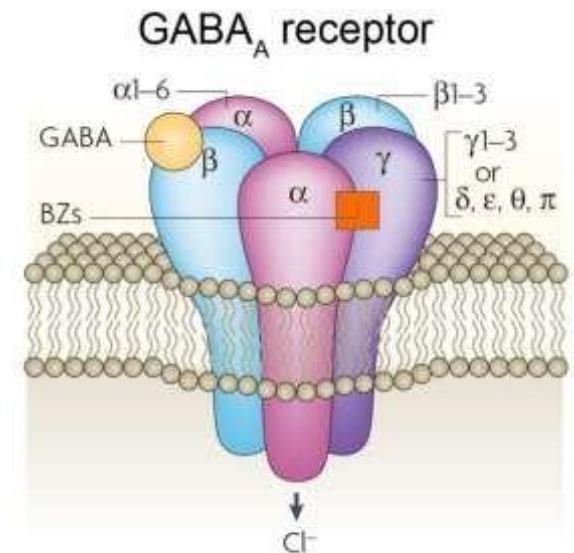
One subtype formerly known as

Central Neurotransmitters - Amino Acids

- **Gamma-Aminobutyric Acid (GABA)**

- **GABA_A receptors:**

- GABA_A receptors are the most prominent GABA receptor subtype.
- GABA_A are ionotropic, ligand-gated Cl⁻ channels.
- The GABA_A receptors have been extensively characterized as important **drug targets** and are the **site of action** of many neuroactive drugs including benzodiazepines, barbiturates, ethanol, anesthetic steroids, and volatile anesthetics.



Jacob et al., Nature Reviews Neuroscience, 2008

Central Neurotransmitters - Amino

Acids

- **Gamma-Aminobutyric Acid (GABA)**

- **GABA_B receptors:**

- The GABA_B receptors are metabotropic GPCRs.
- GABA_B receptors are widespread in the CNS and regulate both pre- and postsynaptic activity.
- Presynaptic GABA_B receptors function as autoreceptors, inhibiting GABA release, and may play the same role on neurons releasing other transmitters.
- **Drugs such as baclofen (skeletal muscle relaxant) and Gamma-hydroxybutyrate [GHB] (psychoactive drug; sometimes used to treat narcolepsy) are acting on GABA_B receptors .**
- Subtypes of GABA_B receptors : GABA_{B1}; GABA_{B2}

Central Neurotransmitters - Amino

• ~~Acids~~ Glycine

- Glycine is an amino acid normally incorporated into proteins that can also act as an inhibitory neurotransmitter, particularly in the spinal cord and brainstem.
- Glycine acts as a coagonist at NMDA receptors, such that both glutamate and glycine must be present for activation to occur.
- Agonist for glycine receptor: Taurine and β -alanine
- Antagonist for glycine receptor: Strychnine

Central Neurotransmitters - Amino Acids

- **Glutamate and aspartate**
- Glutamate and aspartate are dicarboxylate amino acid neurotransmitters with excitatory actions in the CNS.
- Both amino acids are found in high concentrations in the brain and have powerful excitatory effects on neurons.
- **Glutamate is the most abundant and the principal fast excitatory neurotransmitter**
- Glutamate acts through either ligandgated ion channels (ionotropic) or metabotropic GPCRs receptors.
- Types of ligandgated ion channels: NMDA receptors, AMPA receptors, and KA receptors.

Central Neurotransmitters -

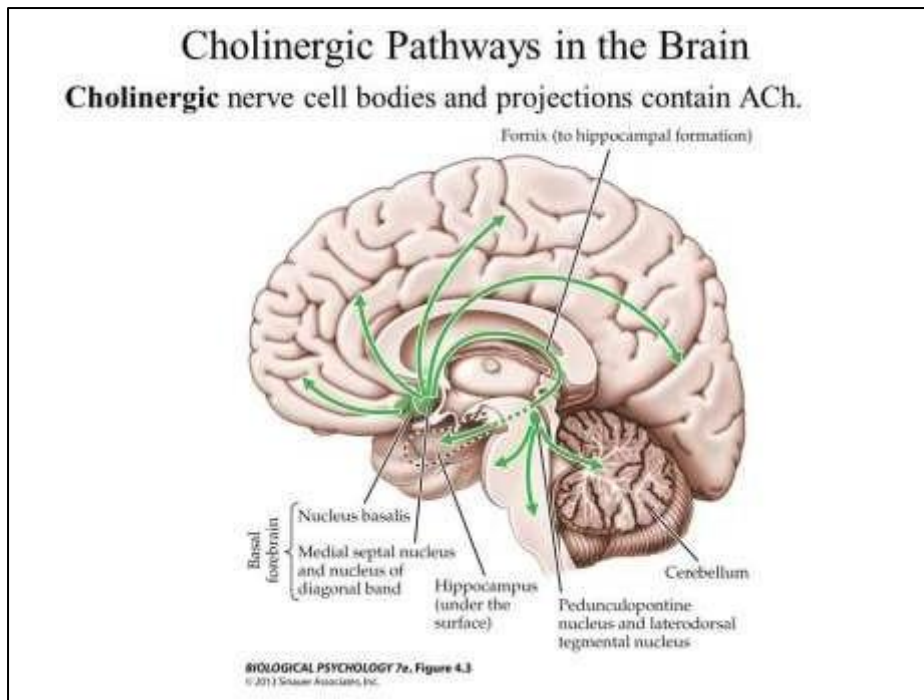
Acetylcholine

- Acetylcholine is present throughout the nervous system and functions as a neurotransmitter. It was **the first neurotransmitter discovered** and plays a primary role in the autonomic nervous system in ganglionic transmission as well as the peripheral nervous system.
- **The effects of ACh** result from interaction with **nicotinic receptors** (ionotropic ligand-gated ion channels) and **muscarinic receptors** (metabotropic GPCRs).

Central Neurotransmitters -

Acetylcholine

- Activation by ACh results in a rapid increase in Na^+ and Ca^{2+} influx and subsequent depolarization.
- Nicotinic cholinergic receptors appear to desensitize rapidly.



- The degeneration of particular cholinergic pathways is a hallmark of Alzheimer disease.

Central Neurotransmitters -

Monoamines

- **Dopamine**
- **Norepinephrine**
- **Epinephrine**
- **Histamine**
- **Serotonin**

Each system is anatomically distinct and serves separate, but similar, functional roles within its field of innervations.

Central Neurotransmitters -

Monoamines

- **Dopamine (DA):**

- DA is the precursor norepinephrine and it is the predominant catecholamine in the CNS.
- **DA play a role in motivation and reward** (most drugs of abuse increase DA signaling), motor control, and the release of various hormones.

Central Neurotransmitters -

• **Monoamines** **Dopamine (DA):**

- There are four major DA-containing pathways in the CNS

The nigrostriatal pathway: neural pathway between substantia nigra and corpus striatum

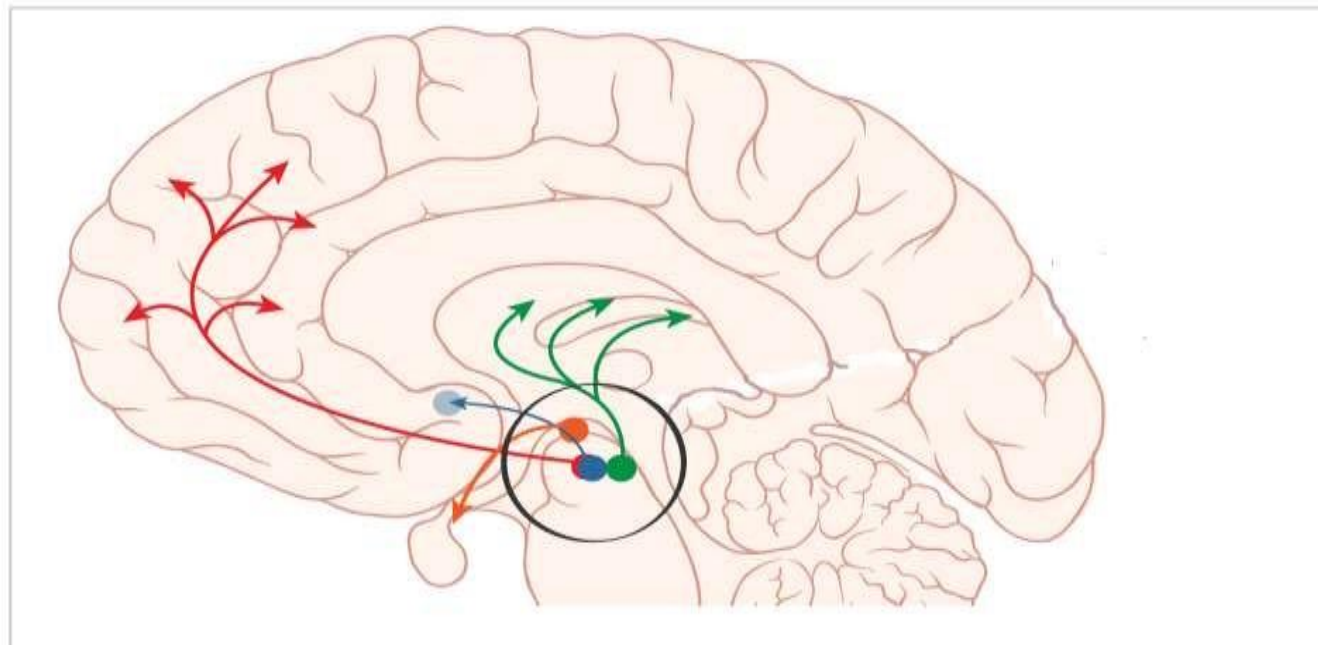
The mesocortical pathway: neurons in the ventral tegmental nucleus project to a variety of midbrain structures and to the frontal cortex

Mesolimbic pathway: this pathway is made up of projections from the ventral tegmental area that innervate many forebrain areas, the most important is the nucleus accumbens.

The tuberoinfundibular pathway: delivers DA to cells in the anterior pituitary

Central Neurotransmitters - Monoamines

- Dopamine (DA)



- MESOCORTICAL**
Cognition, Memory, Attention, Emotional Behavior, & Learning
- NIGROSTRIATAL**
Movement & Sensory Stimuli
- MESOLIMBIC**
Pleasure & Reward Seeking Behaviors; Addiction, Emotion, Perception

- Mesocortical Pathway
- Mesolimbic Pathway
- Nigrostriatal Pathway
- Tuberoinfundibular Pathway

DA-containing pathways and receptors have been implicated in the pathophysiology of schizophrenia and Parkinson disease and in the side effects seen following pharmacotherapy of these disorders

Central Neurotransmitters -

• ~~Monoamines~~ Norepinephrine (NE):

- Large amounts of NE present within the hypothalamus and in certain zones of the limbic system (e.g., the central nucleus of the amygdala, the dentate gyrus of the hippocampus).
- NE also is present in lower amounts in most brain regions.
- NE is an endogenous neurotransmitter for the α and β adrenergic receptor subtypes that are present in the CNS

Central Neurotransmitters -

Monoamines • **Epinephrine (EPI):**

- NE is converted into EPI by enzyme phenylethanolamine-N-methyltransferase.
- EPI-containing neurons are found in the medullary reticular formation and diencephalic nuclei.
- Their physiological properties have not been unequivocally identified.

Central Neurotransmitters -

Monoamines

- **Histamine.**

- Histamine is a monoamine neurotransmitter in the CNS in addition to its well-known physiological function in immune and digestive responses in the periphery.
- Histaminergic neurons are located in the ventral posterior hypothalamus.
- Histamine signals through four GPCR subtypes (H_1 – H_4) that regulate either adenylyl cyclase or Phospholipase C.

Central Neurotransmitters -

Monoamines

Histamine (Receptor subtypes):

- The H_1 receptors are widely distributed in the brain, where high densities are found in regions linked to neuroendocrine, behavioral, and nutritional state control.
- The H_2 receptors activate adenylyl cyclase and are primarily involved in gastric acid secretion and smooth muscle relaxation.
- The H_3 receptors are also present in the CNS and can act as **autoreceptors** on histaminergic neurons to inhibit histamine synthesis and release.
- The H_4 receptors are expressed on cells of hematopoietic origin (eosinophils, T cells, mast cells, basophils, and dendritic cells) and are involved in eosinophil shape and mast cell chemotaxis.

Central Neurotransmitters -

Monoamines

- **Serotonin (5-**

- Hydroxytryptamine):**

- Neurons containing 5-HT are found in nine nuclei lying in or adjacent to the midline (raphe) regions of the pons and upper brainstem.

Central Neurotransmitters - Trace Amines

- As the name implies, they are detected at trace levels (they have very short half-lives due to rapid metabolism by monoamine oxidase [MAO]).
- Some trace amines act as neurotransmitters at neuromodulators/speakers (TAAR1, TAAR2, TAAR5, TAAR6, TAAR8, TAAR9). receptors
- Examples: tyramine, β -phenylephrine, and octopamine

Central Neurotransmitters -

Peptides

- Neuropeptides typically behave as modulators in the CNS rather than causing direct excitation or inhibition.
- Peptides are involved in a wide array of brain functions, ranging from analgesia to social behaviors, learning, and memory.
- Some CNS peptides function independently, most are thought to act in concert with coexisting neurotransmitters. Their action is not terminated by rapid reuptake into the presynaptic cell; rather, they are enzymatically inactivated by extracellular peptidases.

Central Neurotransmitters -

TABLE 14-5 ■ EXAMPLES OF NEUROPEPTIDES

Calcitonin Family

Calcitonin

Calcitonin gene-related peptide (CGRP)

Hypothalamic Hormones

Oxytocin, vasopressin

Hypothalamic Releasing and Inhibitory Hormones

Corticotropin-releasing factor (CRF or CRH)

Gonadotropin-releasing hormone (GnRH)

Growth hormone-releasing hormone (GHRH)

Somatostatin (SST)

Thyrotropin-releasing hormone (TRH)

Neuropeptide Y Family

Neuropeptide Y (NPY)

Neuropeptide YY (PYY)

Pancreatic polypeptide (PP)

Opioid Peptides

β -Endorphin (also pituitary hormone)

Dynorphin peptides

Leu-enkephalin

Met-enkephalin

Pituitary Hormones

Corticotropin (formerly adrenocorticotrophic hormone; ACTH)

α -Melanocyte-stimulating hormone (α -MSH)

Growth hormone (GH)

Follicle-stimulating hormone (FSH)

β -Lipotropin (β -LPH), luteinizing hormone (LH)

Tachykinins

Neurokinins A and B

Neuropeptide K, substance P

VIP-Glucagon Family

Glucagon, glucagon-like peptide (GLP-1)

Pituitary adenylyl cyclase-activating peptide (PACAP)

Vasoactive intestinal polypeptide (VIP)

Other Peptides

Agouti-related peptide (ARP)

Bombesin, bradykinin (BK)

Cholecystokinin (CCK)

Cocaine/amphetamine-regulated transcript (CART)

Galanin, ghrelin

Melanin-concentrating hormone (MCH)

Neurotensin, nerve growth factor (NGF)

Orexins, orphanin FQ (nociceptin)

Hemopressin (CB₁ inverse agonist)

Source: Modified with permission from Nestler EJ, et al., eds. *Molecular Neuropharmacology*. 2nd ed. McGraw-Hill, New York, 2009.

Central Neurotransmitters -

Purines

- **Adenosine, ATP, Uridine diphosphate (UDP), and uridine triphosphate (UTP)** have roles as extracellular signaling molecules.
- ATP is also a component of many neurotransmitter storage vesicles and is released along with transmitters.
- Extracellular nucleotides and adenosine can act on a family of diverse **purinergic receptors**, which have been implicated in a variety of functions, including **memory and learning, locomotor behavior, and feeding.**

Central Neurotransmitters -

Neuromodulatory

Lipids

- Cannabinoids:

- **Cannabinoids identified as a psychoactive substance in marijuana.**
- Delta-9-tetrahydrocannabinol (THC) is one of several active substances in marijuana
- It has dramatic short-term effects, including causing feelings of euphoria and altered sensory perception. After chronic or long-term use, withdrawal symptoms include irritability and sleep disturbances.
- The primary pharmacologic effects of THC follow its interaction with CB₁ receptors in the CNS and CB₂ receptors in the periphery.
- **CB₁ receptors are found primarily in the basal ganglia, hippocampus, cerebellum, and cerebral cortex.**
- They are also expressed in some non-neuronal cells and tissues, including leukocytes and testis.

Central Neurotransmitters -

Neuromodulatory

- Other Lipid Mediators **Lipids**

- **Arachidonic acid**, normally stored within the cell membrane as a glycerol ester, can be liberated during phospholipid hydrolysis.
- Arachidonic acid can be converted to reactive intermediates highly by three major enzymes (cyclooxygenase, lipoxygenase and peroxidase) and these intermediates are involved in the synthesis of eicosanoids (prostaglandins, thromboxane, and leukotrienes) which act as mediators of inflammation and pain.

Central Neurotransmitters -

Gases

- **Nitric Oxide and Carbon Monoxide**
 - Important regulator of vascular and inflammatory mediation.
 - Both constitutive and inducible forms of NOS are expressed in the brain.

Regulatory Substances

- **Neurotrophins**
 - **Neurosteroids**
 - **Cytokines**
- **Neurotrophins:** Neurotrophins regulate neuronal proliferation, differentiation, survival, migration, dendritic arborization, synaptogenesis, and activity-dependent forms of synaptic plasticity in the CNS. Biological effects of neurotrophins and pro-NTs are mediated by the **Trk family of tyrosine kinase receptors and the p75 neurotrophins receptor.**

Regulatory Substances

Neurosteroids:

- Neuroactive steroids that are in synthesized in the brain are known as neurosteroids. Based on structural features, the neurosteroids can be categorized.
- Neurosteroids can allosterically modulate GABAA receptor complexes; glutamate receptors, including NMDA, AMPA, and KA; nicotinic and muscarinic ACh receptors; as well as sigma and glycine receptors.
- Involved in cognition, stress, sleep, and arousal

Regulatory Substances

Cytokines:

- Cytokines are low-molecular-weight proteins that are secreted by many different cell types to modulate key cellular functions.
- The primary immune effector cells in the CNS are glia, microglia, and astrocytes.
- These cells can express and release a variety of cytokines, including the IL-1 β and IL-6, TNF- α , and IFN- γ .