Neurotransmitter

Each neurotransmitter has its own NT system: a collection of proteins responsible for synthesis, release, response, and termination of action.

Ach

Ach is synthesis by CoA and choline. Free choline within the nerve terminal is acetylated by a cytosolic enzyme, choline acetyltransferase (CAT), which transfers the acetyl group from acetyl coenzyme A. The rate-limiting process in ACh synthesis appears to be choline transport, which is determined by the extracellular choline concentration and hence is linked to the rate at which ACh is being released. The **acetylcholinesterase(AChE)** hydrolysis of the Ach release in the cleft, forms the free choline and acetic acid. The choline reuptake into presynapse by **co-transport of Na**. In 1914, Dale classified two types of Ach receptors, the **muscarinic and nicotinic** because they mimicked the effects of muscarine and nicotine.

The n**icotinic ACh receptors (nAChRs) fall into three main classes**- the muscle, ganglionic, and CNS types. The CNS-type receptors are widespread in the brain most of them are located presynaptically and serve to facilitate or inhibit the release of other mediators, such as glutamate and dopamine. All **nAChRs are ligand-gated ion channels**, it is an excitatory receptors by increasing mainly **Na, Ca permeability.**

The muscarinic receptors are typical G protein-coupled receptors, The odd-numbered members of the **group (M1, M3, M5) couple with G q** to activate the inositol phosphate pathway, while the even-numbered receptors **(M2, M4) act through Gi** to open **potassium channels** causing membrane hyperpolarisation; they also **inhibit adenylyl cyclase** but intracellular cAMP is usually low. **M 1 receptors** ('neural') are found mainly on CNS and peripheral neurons and on gastric parietal cells. **They mediate excitatory effect**s, for example, the slow muscarinic excitation mediated by ACh in sympathetic ganglia. **M2 receptors ('cardiac')** occur in the heart, They exert **inhibitory effect**s, mainly by increasing K+ conductance and by inhibiting calcium channels. M2 —-receptor activation is responsible for **cholinergic inhibition of the heart**, as well as presynaptic inhibition in the CNS and periphery

Glutamate (major excitatory NT)

Glutamate is widely and fairly **uniformly distributed in the CNS**, where its concentration is much higher than in other tissues. Glutamate is produced through general metabolism and released in vesicles. Glutamate is taken up by **astrocytes via GLT-1 and GLAS**T transporter, glutamate is converted to **glutamine in astrocytes**, and recycled back to neurons, which convert the glutamine back to glutamate by **glutaminase.**

Glutamate has five classes of recetors, the ionotropic receptors are AMPA, NMDA, and kainate. The AMPA and NMDA receptors are generally co-localised from LTP. The **AMPA receptors lack GluA2** subunits so are not permeable to Ca. **while NMDA allow the Ca, Na influx and K outflux**. NMDAs contain an Mg block and need to be bound with both glutamate and glycine. Glutamate first binds with AMPA and then triggers an action potential. The depolarization removes the Mg block on NMDA, and then glutamate and glycine bind with NMDA, allowing the channel to open to induce a Ca influx. Increasing level of Ca in cell. This leads to more AMPA receptors present in the membrane. which increases the synaptic plasticity**. Plasticity can strengthen** synapses to form a long-term potentiation.

The metabotropic glutamate receptors are mGLuRs. **Group one is Gq** coupling and is an excitatory modulation. A**nd group 2 and 3 are Gi/o coupling** which is inhibitory modulation.

GABA

The synthesis of **GABA is from glutamate by GAD** then packaged into vesicles. The release of GABA can be taken up by GATs by **co-transport with 2 Na ions**. In astrocytes, GABA is metabolised by GABA-T. GABA acts on two distinct types of receptors: GABAA receptors are **ligand-gated ion** channels whereas GABAB receptors ar**e G protein-coupled.**

GABA A receptors are primarily **located postsynaptically and mediate both fast** and tonic postsynaptic inhibition. The GABA A channel is primarily located postsynaptically and selectively **permeable to Cl −** and because the equilibrium membrane potential for Cl − is usually negative to the resting potential, increasing Cl − permeability hyperpolarises the cell as Cl − ions enter, thereby reducing its excitability**. GABAa medaite both fast and tonic postsynaptic inhibition.**

GABA B receptors (see Bettler et al., 2004) are located pre- and postsynaptically. They are class C G protein-coupled receptors that couple through **Gi /G o to inhibit voltage-gated Ca 2 +** channels (thus reducing transmitter release), to **open potassium channels** (thus reducing postsynaptic excitability) and to **inhibit adenylyl cyclase.**

Several different sites in GABAa receptors can be acted with drugs. These include the GABA-binding site, several modulatory sites, and the ion channel. **The bicuculline can bind with GABA binding** sites to **prevent** the binding of GABA. **Benzodiazepine** site, binds with **high affinity** to accessory **allosteric site on GABAa receptor**, such as diazepam, in such a way that the binding of GABA is facilitated and **its agonist is enhanced**. This has a powerful **anti-anxious effect**. Conversely, inverse agonists at the benzodiazepine site like Ro15-4513s reduce GABA binding. The **barbiturate site also enhances the binding of GABA but is less effective.**

Dopamine

Most dopamine is produced in the substantia nigra (SN) and ventral tegmental area (VTA). The SN is involved in motor function. The VTA gives rise to the mesocortical and mesostriatal pathways and is involved in reward and addiction. DA is synthesized from tyrosine by tyrosine hydroxylase and dopa decarboxylase. After release, DA is taken up by DAT. DA that is not recycled is broken down by MAO and COMT. The dopamine function in motor control through the nigrostriatal pathway, learning and wanting through the mesocorticolimbic pathway, and regulation of hormone release through the tuberoinfundibular pathway.

Dopamine has two types of receptors, D1 and D2. They all belong to the family of GPRC. D1-like receptors which are D1 and D5 link through Gs to stimulate adenylyl cyclase and PKA. PKA mediates many effectors by phosphorylating a wide array of proteins, including voltage-gated Na, K, and Ca channels, as well as ionotropic glutamate and GABA receptors. D2-like receptors like D2 D3 D4 link through Gi/Go and active K channels as well as inhibiting Ca channels and adenylyl cyclase, and can also affect other cellular second messenger cascades.

Noradrenaline

Noradrenaline goes through the central pathway to control learning and memory, and control autonomic effects through sympathetic NS and the endocrine effects through adrenal glands

Noradrenaline interacts with several receptors, each initiating specific GPCR pathways with distinct physiological impacts. Alpha-1 receptors postsynaptic throughout the brain, engage the Gq pathway, activating phospholipase C, which leads to an increase in intracellular calcium, resulting in effects like vasoconstriction and pupil dilation. Alpha-2 receptors operate through the Gi pathway, inhibiting adenylate cyclase to reduce cAMP levels, which reduce neurotransmitter release and promotes sedation and analgesia. Beta-1 receptors, mainly expressed in the heart and the kidney connected to the Gs pathway, stimulate adenylate cyclase, raising cAMP levels that enhance cardiac contractility and heart rate, as well as stimulate renin release from the kidneys. Beta-2 receptors also use the Gs pathway, leading to the relaxation of smooth muscles in the airways and vasculature, and facilitating glucose metabolism in the liver and muscles. Finally, Beta-3 receptors, which are also linked to the Gs pathway, primarily function in adipose tissue to induce lipolysis and contribute to energy expenditure and thermogenesis. Postsynaptic noradrenergic receptors are generally excitatory (β1, β2, β3, and α1) while the presynaptic α2 autoreceptor is inhibitory.

Serotonin

Most serotonin (5-HT) is produced in the Raphe nuclei. Serotonergic projections are ubiquitous in the CNS. Most of the 5-HT receptors are G protein-coupled receptors except for 5-HT3, which is a ligand-gated cation channel. 5-HT 1receptors (5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F) 3 are predominantly inhibitory in their effects. 5-HT1A-F/5 operates with the Gi pathway to inhibit the activity of adenylyl cyclase. The 5HT4/6/7 couple with the Gs pathway to increase the activity of adenylyl. 5HT-2A-C couples with the Gq pathway, which active PIC first and convert PIP2 to IP3 and DAG. DAG is a hydrophobic lipid and transports in membrane and active PKC. IP3 could increase the concentration of Ca inside the cell. Also, IP3 links to active 5-HT3, which is a Ca channel, and this channel also induces a Na influx. 5-HT3 is a target point to treat nausea and vomiting.