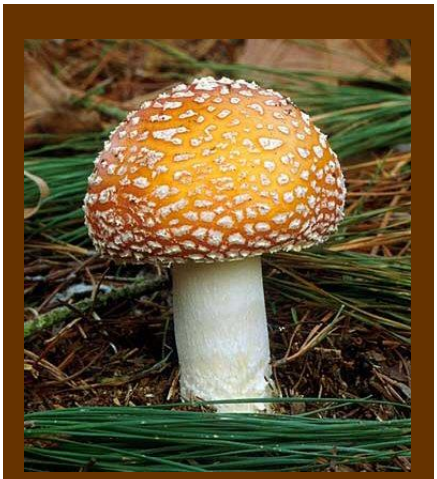
**Acetylcholine Receptors**

**Two Types of Receptors**

There are two types of acetylcholine receptors (AChR) that bind acetylcholine and transmit its signal: muscarinic AChRs and nicotinic AChRs, which are named after the agonists muscarine and nicotine, respectively. These receptors are functionally different, the muscarinic type being G-protein coupled receptors (GPCRs) that mediate a slow metabolic response via second messenger cascades, while the nicotinic type are ligand-gated ion channels that mediate a fast synaptic transmission of the neurotransmitter.

**Muscarinic Cholinergic Receptors**



***Amanita muscaria***

Muscarinic receptors are characterised through their interaction with muscarine, a water-soluble toxin derived from the mushroom *Amanita muscaria* that causes substantial activation of the peripheral sympathetic nervous system through its binding to muscarinic AChRs, resulting in convulsions and even death. The muscarinic AChRs occur primarily in the CNS, and are part of a large family of G-protein-coupled receptors ('G proteins'), which use an intracellular secondary messenger system involving an increase of intracellular calcium to transmit signals inside cells. Binding of acetylcholine to a muscarinic AChR causes a conformational change in the receptor that is responsible for its association with and activation of an intracellular G protein, the latter converting GTP to GDP in order to become activated and dissociate from the receptor. The activated G protein can then act as an enzyme to catalyse downstream intracellular events.

Muscarinic receptors are involved in a large number of physiological functions including heart rate and force, contraction of smooth muscles and the release of neurotransmitters. There are five subtypes of muscarinic AChRs based on pharmacological activity: M1-M5. All five are found in the CNS, while M1-M4 are also found in various tissues: M1 AChRs are common in secretory glands; M2 AChRs are found in cardiac tissue; M3 AChRs are found in smooth muscles and in secretion glands. M1, M3 and M5 receptors cause the activation of phospholipase C, generating two secondary messengers (IP3 and DAG) eventually leading to an intracellular increase of calcium, while M2 and M4 inhibit adenylate cyclase, thereby decreasing the production of the second messenger cAMP. The activation of the M2 receptor in the heart is important for closing calcium channels in order to reduce the force and rate of contraction.

**Nicotinic cholinergic receptors**

Nicotinic receptors are characterised through their interaction with nicotine in tobacco. The nicotinic AChRs are ligand-gated ion channels that form pores in cells' plasma membranes, mediating fast signal transmission at synapses. Nicotinic AChRs are involved in a wide range of physiological processes, and can be either neuronal or muscle-type. Muscle-type nicotinic AChRs are localised at neuromuscular junctions, where an electrical impulse from a neuron to a muscle cell signals contraction and is responsible for muscle tone; as such, these receptors are targets for muscle relaxants. The many types of neuronal nicotinic AChRs are located at synapses between neurons, such as in the CNS where they are involved in cognitive function, learning and memory, arousal, reward, motor control and analgesia.

The binding of acetylcholine to nicotinic AChRs brings about their activation. When two molecules of acetylcholine bind a nicotinic AchR, a conformational change occurs in the receptor, resulting in the formation of an ion pore. At the neuromuscular junction, the opening of a pore produces a rapid increase in the cellular permeability of sodium and calcium ions, resulting in the depolarisation and excitation of the muscle cell, thereby producing a muscular contraction.

The activation of neuronal nicotinic AChRs also causes the movement of cations through the opening of an ion channel, with the influx of calcium ions affecting the release of neurotransmitters. Nicotinic AChRs on a postganglionic neuron are responsible for the initial fast depolarisation of that neuron. However, the subsequent hyperpolarisation and slow depolarisation, which represent the recovery of the postganglionic neuron from stimulation, are mediated by muscarinic AChR types M2 and M1, respectively. The binding of nicotine can activate nicotinic AChRs, modifying the neurons in two

ways: the depolarisation of the membrane through the movement of cations results in an excitation of the neuron, while the influx of calcium acts through intracellular cascades affect the regulation of certain genes and the release of neurotransmitters.

Nicotinic AChRs are composed of five types of subunits: alpha (a1-a10), beta (b2-b5), delta, epsilon and gamma. These subunits are found in different combinations in different types of nicotinic AChRs:

- Muscle nicotinic AChRs (adult neuromuscular junction): a1-e-a1-b1-d
- Muscle nicotinic AChRs (foetal extrajunctional): a1-g-a1-b1-d
- Neuronal nicotinic AChRs (CNS, PNS and developing muscle): (a7)5
- Neuronal and autonomic nicotinic AChRs (ganglion): a3-b4-a3-b4-b4 and a3-b2-a3-b4-a5
- Neuronal and autonomic nicotinic AChRs (brain): a4-b2-a4-b2-b2
- Epithelial and neuronal nicotinic AChRs (cochlea hair cells): (a9)5

Theses receptors span the membrane, containing extracellular, transmembrane and cytoplasmic domains, the latter being the most variable. Nicotinic receptors are always pentamers, with the subunits arranged symmetrically around a central receptor channel. The receptors always contain two or more alpha subunits, which are critical in acetylcholine binding. The acetylcholine-binding site is comprised of a dimer formed by the alpha subunits (principal component) plus an adjacent subunit (complementary component), where binding to both sites is required for the channel to open. Neurotoxins frequently target the acetylcholine-binding site, reversibly blocking the opening of the ion channel and formation of a pore, thereby preventing cations from passing through. Neuronal nicotinic AChRs have been divided into two main groups based on their sensitivity to the snake venom toxin a-bungarotoxin (‘Snake Venom: Bungarotoxins’). The a-bungarotoxin-sensitive receptors are homomeric, containing a7 or a9, and are found primarily in pre- and post-synaptic neurons and in developing muscle. The a-bungarotoxin-insensitive receptors are heteromeric, containing combinations of a2-a6 and b2-b4, and which often modulate the release of other transmitters.