**Galanthamine** is an important drug with powerful effects upon the acetylcholine system in the brain. Originally derived from bulbs of the common snowdrop (*Galanthus spp.)* and now from several other plants in the family *Amaryllidaceae*, Galanthamine has long been used in anaesthetics to reverse neuromuscular paralysis induced by turbocurarine-like muscle relaxants. More recently it has been shown to attenuate drug-and lesion-induced cognitive deficits in animal models of learning and memory

More specifically, Galanthamine is a tertiary alkaloid acetylcholinesterase inhibitor (AChEI) acts by directly inhibiting that enzyme. Galanthamine also stimulates pre-and post-synaptic nicotinic receptors, although the clinical significance of this finding is yet unclear. Numerous variants and analogues of Galanthamine have also been developed, with varying potency in inhibiting AChE activity. When administered as its hydrobromide salt it is readily absorbed after oral administration, with a t(max) of 52 min and a plasma elimination t(1/2) of 5.7 h.

Now Galanthamine has been approved in several countries for the symptomatic treatment of senile dementia of the Alzheimer's type, after its efficacy when administered to Alzheimer's disease (AD) patients was well demonstrated by large-scale clinical trials. Typical of AChEIs, the most common adverse events associated with the drug are nausea and vomiting, but evidence to date suggests Galanthamine to be similar to other AChEIs in improving cognitive function in AD patients. More recently, has been shown to attenuate drug and lesion-induced cognitive deficits in animal models of learning and memory.

**Acetylcholinesterase Inhibitors**

AChEIs act on the enzyme that breaks down acetylcholine in the brain as part of the normal recycling/control mechanism for brain function. Alzheimer's Disease sufferers have reduced levels of acetylcholine due to death of acetylcholine-producing cells in the brain. In general, reducing the breakdown of acetylcholine relieves some of the symptoms and slows progression of the disease by several months and in some cases by a few years.

Galanthamine appears to have a dual action whereby it not only acts as an AChEI but also acts on the target brain cell to strengthen its response to available acetylcholine.

The enzyme Acetylcholinesterase is a serine hydrolase that belongs to the esterase family, all of which act on different types of carboxylic esters. AChE's biological role is the termination of impulse transmissions at cholinergic synapses within the nervous system by rapid hydrolysis of the neurotransmitter, acetylcholine (Schumacher et al, 1986)

AChE is an ellipsoidal molecule approximately 45 x 60 x 65 angstroms, which consists of a 12 stranded central mixed beta sheet surrounded by 14 alpha helices (Sussman et al, 1991). Studies have indicated several major domains within the protein: a catalytic active site composed of two sub-sites, the aromatic gorge in which the catalytic active site lies, and a peripheral anionic site, distinct from the catalytic active site, which plays a role in the confirmation of the residues within the aromatic gorge and active site.

The active site is composed of two sub-sites: the esteratic sub-site which contains the catalytic triad, and the anionic sub-site that accommodates the positive quaternary pole of acetylcholine. The esteratic sub-site contains the catalytic machinery of the enzyme: a catalytic triad of Ser 200, His 440, and Glu 327. This catalytic triad is similar to other serine proteases, except that this triad is the first to show Glu as the third member as opposed to Asp. In addition, the triad is of opposite handedness to that of the other proteases. The anionic sub-site is defined by Trp 84, Phe 330, and Phe 331. Its role is to orient the charged part of the substrate that enters the active centre. This role is the main function of the Trp residue (Sussman et al, 1991). This sub-site has another interesting characteristic; it is

involved in a "cross-talk" mechanism with the peripheral anionic site which will be discussed later.

The aromatic gorge in the protein is approximately 20 angstroms deep and penetrates halfway into the enzyme. The active site lies at the base of this gorge only 4 angstroms above the base, leading some to label this the active gorge. The aromatic gorge is a more appropriate term, though, because 40% of its lining is composed of 14 aromatic residues which are highly conserved from different species of AChE (Harel et al, 1993). The high aromatic content of the walls and floor may explain why studies have proposed hydrophobic and anionic binding sites independent of the active site. Only a few acidic residues are present within the gorge.

The most interesting aspect of this enzyme is the peripheral anionic site (PAS) on its surface. Site-directed labelling and mutagenesis studies place the location of the PAS at or near the rim of the aromatic gorge (Barak et al, 1994). This site has the ability to bind to many different types of ligands, and by doing so effects the conformation of the active centre. Six residues have established activity within this site: Trp 286, Tyr 72, Tyr 124, Glu 285, and Asp 74 and Tyr 341, which are located on the opposite side of the gorge entrance to the previous four. This array of residues exhibits flexibility which accommodates many distinct ligands, and also implies their conformational mobility (Ordentlich et al, 1993). The common feature of these conformations is a core comprised of Trp 286 and Asp 74.