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REVIEW ARTICLE
ACETYLCHOLINESTERASE INHIBITORS: A MILESTONE TO TREAT NEUROLOGICAL DISORDERS

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Abstract

The Autonomic Nervous system possesses one of most potential neurotransmitter-Acetylcholine (ACh). Acetylcholine (ACh) interacts with mainly two types of receptors–Muscarinic and Nicotinic. These receptors are present in various parts of the body and impart highly efficient actions directly on various systems of the human body such as cardiovascular system, respiratory system, urinary system, nervous system, ocular system and many more. The hydrolysis of the neurotransmitter acetylcholine is involved as the principal mechanism of cholinergic signalling. The hydrolytic enzyme involved is acetylcholinesterase (AChE) which catalyzes acetylcholine (ACh) into choline and acetic acid. By inhibiting acetylcholinesterases, the amount of acetylcholine increases and possesses greater neuromuscular and other blocking effects. The basic mechanism behind the functioning of Acetylcholinesterase inhibitors is to slower the hydrolysis rate of the Acetylcholine. The effects produced are similar to the excessive stimulation of the cholinergic system. Anticholinesterase inhibitors have wide range of utilization and large diversity of drugs involved. The newer acetylcholinesterase inhibitors have greater and potential effects than the classical ones. Because of the greater diversity for the anticholinesterase compounds there has been complexity in understanding the various interactions as well as health consequences involved. Thus, the newer techniques have helped in determining the effects of the acetylcholine inhibitors in various diseases such as Myasthenia Gravis, Alzheimer's etc. This article explicate the drugs which help in the prolonging the effect of Acetylcholine by the inhibition of Acetylcholinesterase enzyme. Furthermore, the effect on human body, its sub types, interaction, mechanism, pharmacological properties has been well explained in this review text.

***Keywords*:** Alzheimer's disease, Myasthenia Gravis, Acetylcholinesterase, Neurological Disorders

Introduction

The difference between the working of autonomic nervous system (ANS) and somatic system lies in the voluntary action shown by latter system and the involuntary action shown by former. The efferent and afferent fibres of autonomic system enter and exit the CNS via cranial and spinal nerves. It adjoins to the medulla spinalis and intermediate neurons, which intervene reflexes of autonomic system in the brain component (Snell, 2002; Lantsova *et al.,* 2011). The foremost neurotransmitters comprising the autonomic nervous system are noradrenaline (NA) and Acetylcholine (Ach). The preganglionic sympathetic and parasympathetic neurons, adrenal medulla and all parasympathetic innervated organs contain Ach which serves as the neurotransmitter. The piloerector muscle and sweat glands also contains Ach which serves as neurotransmitter. Alongside, Ach also exhibits the property of neurotransmitter at the eeuromuscular interface between skeletal muscle and the motor nerve of the peripheral nervous system while in central nervous system, interneurons contains high amount of Ach and is even present in some amount in few long axon cholinergic pathways (Perrr *et al.,*1999; Voet *et al.,* 1995). Synthesizing Ach is a single step biochemical reaction where choline acetyltransferase catalyzes this reaction and serves as a "marker" representing presence of cholinergic reaction. The storage vesicles (100nm in number) of nerve endings contain the larger amount of Ach and minute amount is also found in cytosol. The storage vesicles are acidified by an energy-dependent pump that results in the uptake of Ach into the vesicles (Voet *et al.,* 1995). At the time of neurotransmission, nerve releases the Ach into the synaptic cleft which then binds to muscarinic and nicotinic receptors, present on the postsynaptic membrane. The inhibition of signal transmission is exerted by AChE , present on the post-synaptic membrane, by causing the degradation of Ach into choline and acetate. The choline liberated from the Ach hydrolysis is uptaken by the pre-synaptic nerve (Katzung, 2001; Bamard *et al.,* 1974).

Acetylcholine and cholinergic receptors

Acetylcholine is found to be considerably in almost whole of the autonomic preganglionic fibers which consists of the enite postganglionic fibers along with the peripheral parts of the ANS (Autonomic nervous system. In addition it also comprises of the cholinergic fibers which are the sympathetic post ganglionic nerve fibres (Goodman *et al.,* 2001). The biochemical synthesis of the Acetylcholine occurs in the cytoplasm of the the above fibres which is then carried to vesicles of the nerve fibres. The storage of the effective neurotransmitters occurs in these synaptic vesicles. It is estimated that about 10,000 molecules in an individual vesicle. Desirable action potential at nerve endings lead to the opening of the voltage gated- calcium (Ca^{2+}) channels which are present in substantial amount. Thus at the nerve endings, there is intensification of the calcium by a multi form number. This rise in concentration (Ca^{2+}) cause the embodiment of the Ach into the membrane of the nerve ending. This leads to rupture of the vesicle i.e. the exocytosis of the neurotransmitter in to the synaptic cleft. 125 vesicle undergo the exocytosis process in relation to the onset of a action potential. The integration of presynaptic membrane to the synaptic cleft involves various proteins for instance Synaptotagmin, Syntaxin, Synap, and Vamp. These proteins are responsible of the adjoining of the vesicles and the membrane through the formation of complexes through the calcium entry. This leads to the release of acetylcholine at the

interface. And attachment of it to the receptor (on post synaptic membrane) imparting desirable effect. Breakdown of Acetyl choline takes by the enzyme Acetyl cholinesterase into choline and acetate. The choline returns back to the nerve ending and can be used for the synthesis again for Acetylcholine (Guyton *et al.,* 2000).

The synaptic membrane depolarisation leads to the transmission of the synaptic membrane. Cholinergic receptors are mainly of two types-Muscarinic and nicotinic receptors. Cholinergic receptors are mainly transmembrane protein comprising of five subunits that makes an aqueous channel surrounded by the lipid bilayer, Receptors of muscarine are positioned at nerve synapses of muscles of heat and leading to the activation of transduction signals while the receptors of nicotine are presnt at the linkage synapse of two neurons as well as the skeletal muscle . These on induction unswervingly results in depolarization of the neuron. The proteins undergo conformational change, as Ach attaches to the receptor in the post synaptic terminal and opens the Na^+-K^+ channel in the receptor allowing the Na^+ ions to enter the post synaptic vesicles, construction of a positive charge within the membrane called as excitatory postsynaptic potential (EPSP). As soon as the EPSP attains a threshold, there is a generation of action potential in the neuron. The Ach in the post synaptic receptor is broken down BY AchE and BuCE thus inhibiting the synaptic activity. Regain of Ach for the subsequent chemical transmission is the last step in the neurotransmission. The choline is returned back to pre-synaptic neurons which reacts with acetyl co-enzyme A for the synthesis of Aceytl choline (Ach) in th attendance of the enzyme choline acetyltransferase (Guyton *et al.,* 2000; Dowling, 2006; Francis *et al.,* 1999; Nataranjan *et al.,* 2009).

Cholinesterases

The neurotransmitter acetylcholine (ACh) hydrolysis into choline and acetic acid is catalyzed by a family of enzymes known as Cholinestrases. After activation, the cholinergic neuron is required to re-attain its state of rest which is carried out by this reaction It consists of following two types:

1. Acetylcholinesterase (AChE, acetylcholine acetylhydrolase)

Following conducting tissue consists of Acetylcholinestrase - peripheral and central tissues, muscle and nerve, noncholinergic and cholinergic fibres and motor and sensory fibres, The efficacy of AChE is lower in sensory neurons than in motor neurons (Massoulie *et al.,* 1993; Chacho *et al.,* 1960; Koelle, 1954). The Yt blood group antigen of the RBC- red blood cell membrane is constituted by the AChE. AChE exhibits polymorphism having identical catalytic properties and different mode of attachment to the cell surface and their oligomeric assembly. AChE majorly exists as tetrameric form in the mammalian brain known as G4 form (10) and the monomeric form G1 (4S) is present in smaller amounts (Wang *et al.,* 2005). A single molecule of AChE is made up of a peripheral anionic site and a central esteratic site, constitutively forming six active sites. The esteratic site consists of an imidazole ring with a serine –OH group whereas the anionic site is made up of a glutamate residue. A choline subsite and an acyl packet are the basic components of the active centre of the molecule. Acetylcholine binds to the anionic site causing the ester bond of Ach to approximate to the ester site of AChE. After the hydrolysis of Acetylcholine, the acetyl group gets bonded to the serine group of the esteratic site and thus releasing the free choline molecule. The rapid hydrolysis of acetylated enzyme forms acetic acid and free enzyme. The hydrolysis of Ach is represented in Figure I and takes place at a rate estimate to be of 10,000 molecules per second at the active site (Priya *et al.,* 2004).

2. Pseudo cholinesterase (BuChE), majorly found in the liver, commonly known as butyrylcholinesterase, plasma cholinesterase, or acylcholine acylhydrolase. BuChE hydrolyses butyrylcholine at a higher rate than hydrolysed by Ach (Huang *et al.,* 2007). It acts by the termination of transmission of impulse at cholinergic synapse due to the rapid hydrolysis of Ach to choline and acetic acid. The degradation rate of Ach by AChE is about 25000 molecules per second, thus exhibiting greater specific catalysis for a serine hydrolase. The rate of diffusion-controlled reaction is approached due to such higher specificity (Quinn, 1987; Taylor *et al.,* 1994). BuChE is a monomer of ellipsoidal shape having measurements ~ 45 by 60 by 65, made up from 14 helices surrounding central mixed sheet of 12-strands. The structure of BuChE has a remarkable feature of a deep and narrow gorge (~20 long), which penetrates to the half of the enzyme and ends by touching its base (Manavalan *et al.,* 1985). The base of the molecule consists of the active site of AChE and is made up of two subunits- the esteratic subsite and anionic subsite which forms the choline-binding pocket and the catalytic machinery respectively (Nachmansohn *et al.,* 1951). The positive quartnery amine of choline (hydrolysed from Ach) and quartenary ligands (edrophonium, N-methylacridinium) binds to the uncharged and lipophilic anionic site acting as competitive inhibitors (Wilson *et al.,* 1958; Mooser *et al.,* 1954). The negatively charged amino acid present in the anionic site does not bind to the cationic substrates while aromatic residues (14 in number) interacts with the cationic substrates leading to line the gorge to the active site of the molecule (Froede *et al.,* 1971; Radic *et al.,* 1992; Ordentlich *et al.,*1995). Across different species, 14 amino acids present in the aromatic gorge are retained thoroughly (Ariel *et al.,* 1998). The most critical aromatic amino acid is tryptophan 84 which on substitution with alanine leads to decrease in the activity of enzyme by 3000- fold (Ordentlich *et al.,* 1993). The esteratic site consists of three amino acids known as catalytic traid of histidine 440, glutamate 327 and serine 200; where Ach is broken down to choline and acetate (Tougu *et al*., 2001).

Anticholinesterases

The drugs which delays the action of acetylcholine from the time it is liberated at the cholinergic nerve by preventing the action of butyryl cholinesterase and acetyl cholinesterase, are termed as anticholinestrases. These are classified into two types–Acid transferring and Prosthetic. Acid transferring inhibitors forms an intermediate compound by reacting with the enzyme , which cannot be degraded as easily as the acetylated compound is degraded from acetylcholine. In contrast, the prosthetic inhibitors are short lived, acting as reversible competitive inhibitors of the enzyme. Depending on the duration of action, anticholinestrases may be divided into reversible (mdium duration) and irreversible (longer acting) anticholinesterases(V Priya,2004). The pharmacological effect of AChE is induced by the inhibition of breakdown of Ach by cholinestrases. Inactivation of

cholinestrases by AChE activates the Ach receptors and increases the amount of acetylcholine in the synaptic region of nerves and neuromuscular junction. Musicarinic effects are seen due to the parasympathetic activity whereas sympathetic activity exhibits nicotinic effects. The balance between the muscarinic and nicotinic receptors exhibits the main symptoms and effects seen (Pappano, 2012). The life of the neurotransmitter is prolonged by the inhibition of AChE and thus retaining the same therapeutic effects as those of acetylcholine at its time of administration. AChE plays a major role in the treating diseases such as glaucoma, myasthenia gravis, and Alzheimer's disease. AChE can also be used as insecticides and nerve gases (Triggle *et al.,* 2006).

Pharmacological Properties (Priya, 2004; Vickers *et al.,* 1999)

Causing depression of skeletal muscle and autonomic ganglia along with the induced greater activity of cholinergic receptors in the CNS, anticholinesterases should be administered with muscarinic antagonists like glycopyrronium and atropine, which helps in nullifying the effects of excess of acetylcholine present in the synapses of bronchi, gut and CVS. Compounds like pyridostigmine and neostigmine which contains a quaternary ammonium do not have the ability to penetrate the cell membrane and the blood brain barrier, thus their main effect is seen predominantly on the muscarinic and nicotinic receptors. Organophosphates and physostigmine are lipid soluble agents which acts within the brain and also on the central cholinergic receptors.

Respiratory System: Bronchospasm and hypoxia is caused due to bronchial muscle contraction by anticholinesterases, when its secretion is increased.

Eye: Anticholinesterases causes contraction of the ciliary muscles and sphincter papillae causing miosis and blockage of the accommodation reflex. Facilitating the output of aqueous humour, the intraocular pressure is decreased.

Gastrointestinal system: Gastric motility, oesophageal motility and secretion of gastric juices are increased due to the action of anticholinesterases. The motor activity of the large and small bowel is enhanced due to the anticholinesterases High doses of anticholinesterases leads to diarrhoea, incontinence and vomiting.

Secretory glands: Anticholinesterases increases the rate of secretion of secretory glands by post ganglion cholinergic fibres such as of sweat, gastric, lacrimal, pancreatic and intestinal glands.

Cardiovascular system: Anticholinesterase increases the vagal influences on the heart which results in the shortening of the effective refractory period of atrial muscle. It also delays the conduction time and refractory period at the SA node and AV node. Accumulation of acetylcholine results in bradycardia causing the decreased blood pressure and cardiac output.

Neuromuscular junction: Anticholinesterase prolongs the residual time of Ach in neuronal synapse, thus increasing the binding ability of the transmitter with the respective receptor. In case of overdose, depolarisation blockade occurs due to the depolarization of endplate by acetylcholine. The decay time of the endplate potential is prolonged due the repeated trigger of the receptor by the excess amount of Ach present at the synapse.

Classification of Cholinesterase Inhibitors

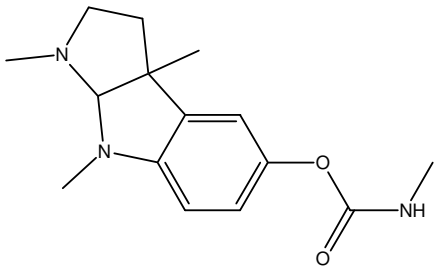
Anti-cholinestrases, also known as AChE inhibitors, prevents the breakdown of Ach by cholinesterase enzymes, thus increasing the time period and level of the neurotransmitter action. AChE inhibitors can be classified into two categories according to their mode of action: Irreversible and Reversible, as represented in Figure II. Reversible inhibitors can be grouped into competitive or non-competitive and exhibits the major therapeutic applications whereas irreversible inhibitors exhibits the toxic effects causing poisoning that may be fatal.

Reversible AChE Inhibitors

These drugs act as an important aspect in the manipulation of the pharmacological actions shown by the enzymes. This category consists of many compounds having variant functional moieties like tertiary ammonium group, carbamate, and quaternary). They play an important role in the diagnosis and the treatment of diseases such as glaucoma, myasthenia gravis , Alzehimer's disease, and myasthenia gravis. It is also used as an antidote in case of anticholinergic poisoning.

Carbamates

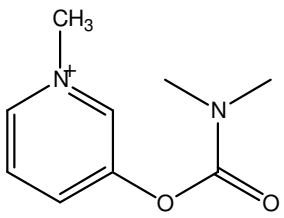
Physostigmine:



Physostigmine

It is a natural alkaloid obtained from the Calabar bean. It is the first anticholinestrase which is used in treating glaucoma. It consists of a carbamate moiety and crosses the blood brain barrier and has no uaternary ammonium group. It is used as an antidote in the anticholinergic toxicity. Plasma esterases cause the degradation of physostigmine and its excretion does not depend on the rate of renal elimination (Priya, 2004). The common side effects of physostigmine are tightness in chest, weakness of muscle, nausea, vomiting, diarrhea, stomach cramps or pain, and shortness of breath (De Sarno *et al.,* 1989). Physostigmine has a shorter t-1/2 and has variable bioavailability causing insufficient efficiency (Thai *et al.,*1983).Its activity is stronger in case of dimethyl-, allyl, benzyl-, carbamic esters of phenol-bases, methyl-; weaker in case of phenyl- and ethyl- and absent in diallylcarbamic esters and diethyl of the series. Disubstituted carbamic acid esters are the most stable compounds of this series (Habib *et al.,* 1986). Newer analogs of physostigmine are represented in the table I.

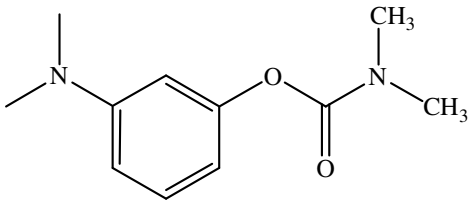
Pyridostigmine:



Pyridostigmine

It is the most common drug used in the daily treatment and the drug effect is initiated in 15-30 minutes, and the peak effect is of 1-2 hours and effect is exhibited for 3-4 hours or for greater time period. Pyridostigmine bromide (carbamate functionalised reversible AChE inhibitor) is used to guard from the action of nerve agents and is commonly used in treating myasthenia gravis. It consists of quaternary amine and is less absorbed from GIT system. Majority of the AChE inhibitors as well as pyridostigmine bromide are administered orally (Lorke *et al.,* 2018; Hegazy *et al.,* 2002; Petrov *et al.,* 2018). Analogs /derivatives of pyridostigmine are described in Table II.

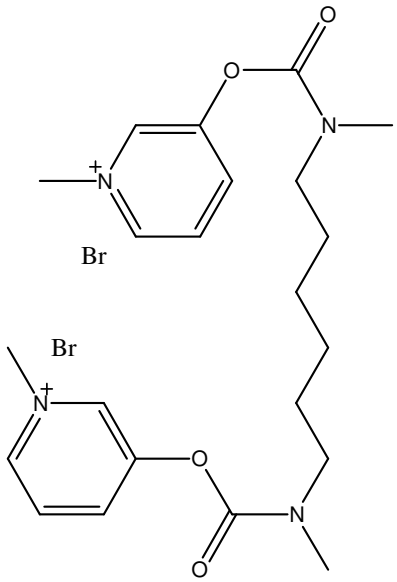
Neostigmine:



Neostigmine

Non-depolarizing neuromuscular blocking agents are reversed commonly using Neostigmine. It acts by increasing the rate of recovery from the blockade and reduces the action of residual blockage. After recovery from blockade, variant doses of this drug have chances of causing muscle weakness. Neostigmine consists of quarternary ammonium ion and is used as antidote for curare poisoning. Its onset of action is exhibited within 30 minutes (injection) and 4 hours(by mouth) and has a duration of action upto 4 hours (Churchill *et al.,*1959; Kent *et al*., 2018). Newer neostigmine analogs are represented in Table III.

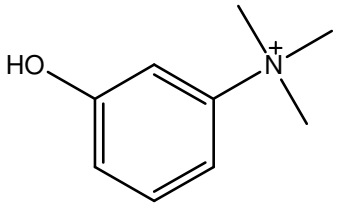
Distigmine:



Distigmine

Distigmine is reversible cholinesterase inhibitor which is derived from carbamate. It is chemically synthesised by Schmid reaction and its chemical structure consist of two molecules of pyridostigmine linked together by hexamethylene bonds.It binds competitively to the agonist binding site of muscarinic receptors and have longer duration of action as compared to neostigmine and pyridostigmine. Mainly used in treatment of myasthenia gravis and used clinically in some Asian and European countries (Schmid *et al.,* 1957; Obara *et al.,* 2017).

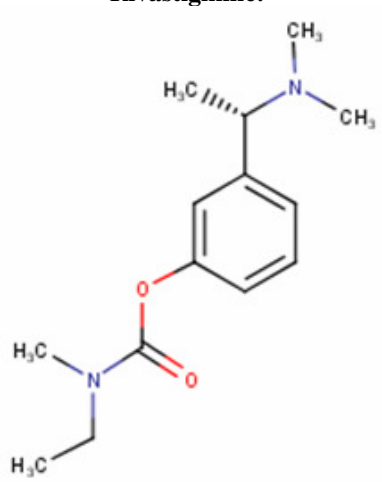
Edrophonium:



Edrophonium

Edrophonium is synthetic quaternary ammonium compound and the only drug available as short-acting anticholinesterase. It binds competitively to the anionic site of the enzyme anticholinesterase by a non-covalent bond. For antagonism of neuromuscular blockage recommended dose is 0.5-1.0 mg/kg. I.V. administration of Edrophonium attains peak affect within 0.8 – 2.0 min but have shorter period of action i.e. 10 min due to reversible binding to the anticholinesterase and rapid renal elimination.12 to 16 times less potent than neostigmine. As comparative to neostigmine, effects of edrophonium are less predictable when used to antagonize non-depolarizing neuromuscular block. To antagonize longer acting drugs, edrophonium is less preferred. Neostigmine effects are more pronounced in comparison to edrophonium at equipotent doses (V Priya,2004). Endrophonium newer derivatives are represented in Table IV.

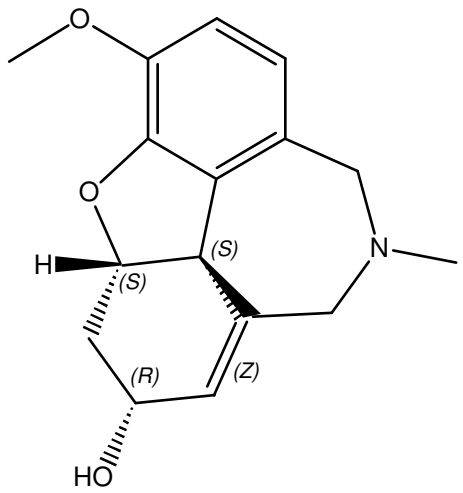
Rivastigmine:



Rivastigmine

It is a strong but slow acting carbamate inhibitor which is reversible in nature and acts by bonding with the esteratic part and thus causing blockade of cholinesterase action. It has strong efficacy to inhibit the action of both BuChE and AChE (Desai *et al.,* 2005). The pharmacokinetics of the drug states that a 3 mg dose has 40% bioavailability and a fair rate of absorption. The rate of decreasing cognitive function, daily activities and the sterness of dementia is reduced with daily dose of 6-12 mg with regular and timely treatment of Alzheimer's disease. The major side effects of this drug are syncope, diarrhoea, anorexia, abdominal pain, dizziness and nausea (Birks *et al.,* 2009; Inglis, 2002). Derivatives of Rivastigmine are represented in Table V.

Galantamine:

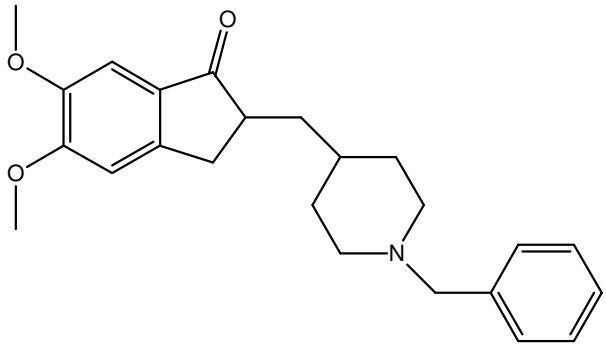


Galantamine

Galantamine is a natural alkaloid isolated from the plant *Galanthus worowii.* It is competitive, rapidly – reversible inhibitor of acetylcholinesterase which selectively binds to the anionic subsite and to the aromatic gorge (Bartlolucci *et al.,*2001; Pilger *et al.,* 2001; Kitisripanya *et al.,* 2011). In addition to the modulation which drug induces after attaching to the allosteric site of the nicotinic cholinergic receptors, it enhances the sensitivity of nicotinic receptors in acetylcholine presence (Wessler *et al.,* 2008; Pohanaka, 2011).

The pharmacokinetic parameters of galantamine are as absolute oral bioavailability between 80 and 100% and half life of 7 hours. The initial dose used for treatment is 4 mg b.d. and then dose tapering can be done upto 12 mg b.d (Tayeb *et al.,* 2012). Its major side effects are exhibited in the GIT and hence are less tolerated. The long term tolerability can be achieved with standardized and calibrated titration (Birks, 2006). It also exhibits nicotinic-potentiating effects by allosteric mechanism and thus plays a role in treatment of major depression, alcohol abuse and cognitive dysfunction (Ago *et al.,* 2011). Derivatives of Galantaminee are represented in Table VI .

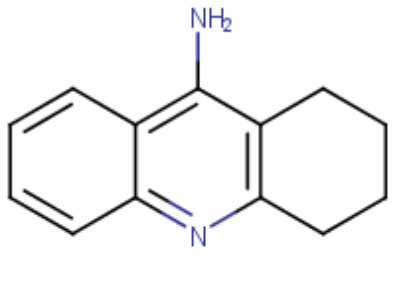
Donepezil:



Donepezil

It is a reversible AChE inhibitors which selectively binds to the peripheral anionic site, thus delays the accumulation of amyloid plaque, along with the symptomatic treatment of Alzheimer's disease (Fong *et al.,* 2015; Peera, 2015; Popa *et al.,* 2006; Arce *et al.,* 2009). Its major therapeutic action is observed in treating mild to moderate Alzheimer's disease while cognitive function is also improved , in case of severe Alzheimer's disease(Castro *et al.,* 2006). It has the maximum oral bioavailability of 100% but slower rate of excretion. It has longer duration of action with half life of about 70 hrs. The maximum administered daily dose is 23 mg (once in a day) (Winblad, 2006). The major side effects are anorexia, GIT anomalies-nausea, abdominal pain, anorexia, and causes bradycardia (Farlow *et al.,* 2010). Derivatives of Donepezil are represented in Table VII.

Tacrine (Tetrahydroaminacrine Hydrochloride):



Tacrine

For treating Alzheimer's disease, Tacrine was the frist approved drug of AChE inhibitors. Due to the greater side effects such as hepatotoxicity, its use has been limited (Birks *et al.,* 2009; Watkins *et al.,* 1994). It can pass the blood-brain barrier exhibiting central effects and has shorter duration of action. It has also been used in prolonging the activity duration of succinylcholine and has an elimination half life of 2-4 hours (V Priya, 2004). Derivatives of Tacrine are represented in Table VIII.

Clinical Applications (Priya, 2004).

(i) Alzheimer's Disease

Alzheimer's is progress, chronic as well disabling brain disease. It is indicated by disruption in the function of cortex which involves orientation, memory, capacity of learning, judgement, language (Suganthy *et al.,* 2009). This disorder refers to the deficiencies in the cholinergic system as well as the beta amyloid deposition in the plaques of amyloid and tangles of the neurofibiil. Cholinergic system is the targeted site for the drugs of Alzheimer's. Enhancement of the transmission of the cholinergic system through the inhibition of the enzyme–Acetyl cholinesterase which is responsible for the hydrolysis of acetyl choline. In addition the two enzymes Butrylcholinesesterase as well as acetyl cholinesterase help in agreegation Beta amyloid especially during the senile formation of plaque at early phase. Hence, both the former and the later enzymes are reported to be essential for the treatment of Alzheimer;'s disease. This is achieved by the elevation of acetylcholine in the brain and the declination in the deposition of Beta amyloid . The treatment drugs involved are- Donepezil, Xanthostigmine,Galantamine, Coumarin, Tacrine, Rivastigmine and many more.

(ii) Vascular Dementia

Vacular dementia and Lewy Body Demtia are often of the commonest type of demtia after Alzhermer's. The former type of dementia is indicated by the dysfunction , though memory dysfunctioning is rare or minimal (Roman 2003) while the latter is characterized by the impairment in cognitive functions as well as disturbance of neuro psychiatric functions along with hallucinations (Tiraboschi *et*

al., 2000). The symptoms involved are degeneration of neurons in the brain as well as detoriation in neurotransmission. It is reported that the replacement therapy of cholinergic is characteristic choice for the vascular dementia and LBD treatment (Poirer, 2002).

(iii) Myasthenia Gravis

Myasthenia gravis is referred to as auto-immune, chronic disease being characterised the antibody production versus to the nicotinic receptors of acetylcholine. This causes an inhibition of the post synaptic effect in stimulation of acetylcholine (Conti-Fine *et al.,* 2006). The destruction of motor –end plate occurs which further results in weakness of muscle and fatigue. Which causes decline in the decrease in level of ACH. This decline leads to cognitive effect deterioration. The one of effective and promising results is enhancing the cholinergic system transmission in these disorders likely.

(iv) Antagonism

Use of potent neuromuscular blocking agents results in residual muscle weakness which is quite common. Administration of non–depolarizing neuromuscular blocking agents to patients should be monitored throughout the anesthesia and recovery, using nerve stimulator for ensuring its antagonism. Unless the height of twitch has redeemed to more than 20% of its control, residual block antagonism should not be attempted. Also, profound antagonism requires longer duration by standard dose of anticholinesterases to put back twitch height/train-of-four response to control values.

(v) Glaucoma

Primary as well as Secondary glaucoma involves anticholinesterases treatment. They facilitate aqueous humor drainage in turn intraocular pressure decreases. Acquired cholinesterase deficiency can occur due to prolonged use of physostigmine and ecothiophate eye drops.

(vi) Paralytic ileus

Intestinal dilatation due to paralytic ileus is relieved by use of Neostigmine. In case of Peritonitis, intestinal obstruction contraindication is seen.

Conclusion

AChE inhibitors exhibits its toxic and pharmacological actions by the inactivation of the activity of the enzyme causing accretion of Ach in synapse. AChE inhibitors are divided into reversible and irreversible, which is based on its mechanism, Alzheimer's disease (AD) Treatment involves reversible inhibitors (non-competitive or competitive) serve as drug therapy for therapeutic effects. The efficacy is maintained by limiting the hydrolysis rate, thus controlling the Ach level. Thus, the loss of actions of brain cells is compensated by the use of these drugs and alongside in forebrain regions, it increases the neurotransmission of acetylcholine. AChE inhibitors have also shown tremendous affect in treating many neurological complications such as Lewy bodies, myasthenia gravis and Parkinson's disease. In contrast, carbamate reversible Anticholinesterases also show signs of toxicity and thus are in use as fungicides, insecticides and herbicides.

Table 1 : Derivates of physostigmine

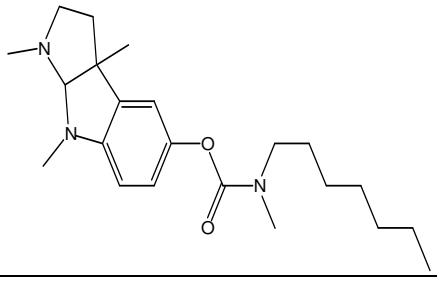
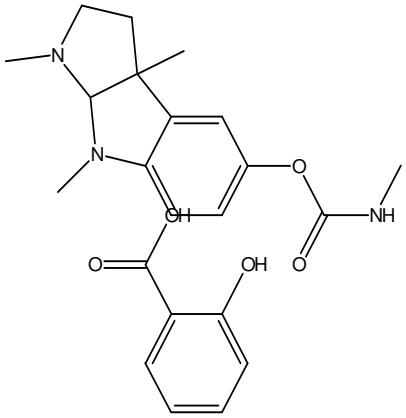
S. No	Derivative	Effect	Structure	Reference
1	Heptyl-Physostigmine	Impart prolonged anticholine-esterase activity in addition to lipophillicity		Habib *et al.,*1986
2	Physostigmine-Salicylate	Greater acetylcholine concentration		De Sarno *et l.,*1989

Table 2 : Derivatives of Pyridostigmine

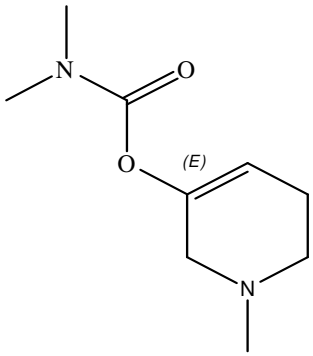
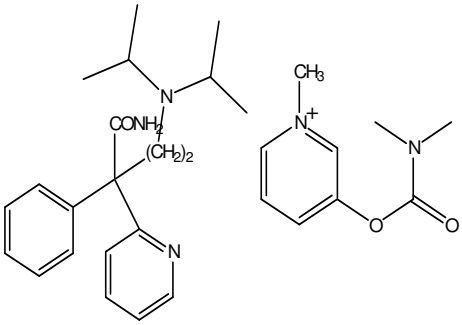
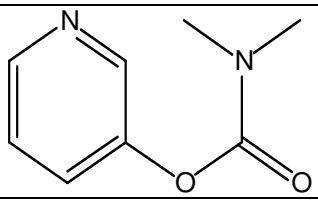
S.No	Derivative	Effect	Structure	Reference
1	Tetra-hydro-pyridostigmine	Lower toxicity and greater efficacy		(Ray *et al.,*1991)
2	Diso-pyramide Pyridostigimine	Prolonged Antiarrythmic efficacy		(Teichman *et al.,* 1987)
3	Nor-Pyridostigmine	Greater efficacy		(Arnal *et al.,*1990)

Table 3 : Derivatives of Neostigmine

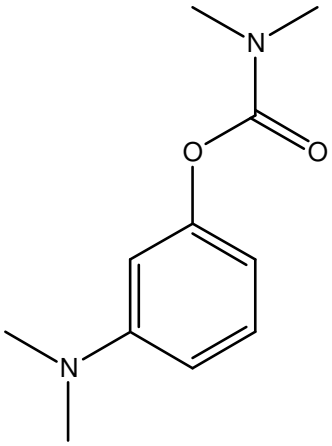
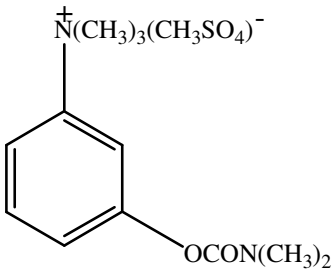
S.No	Derivative	Effect	Structure	Reference
1	Nor- neostigmine	Greater liphillic action as crosses the BBB (Blood Brain Barrier); Less efficacy		(Kent *et al.,* 2018)
2	Neostigmine Methylsulfate	Effect of Analgesia		(Hood *et al.,* 1995)

Table 4 : Derivates of Endrophomium

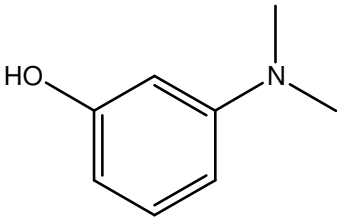
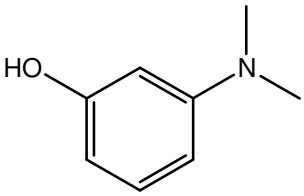
S.No	Derivative	Effect	Structure	Reference
1	3-Hydroxyphenyltrimethylammonium	Greater action		(Roseiro *et al.,* 2012
2	3-(Dimethylamino)phenol	Expanded and sustained inhibitory action		(Denkewalter *et al.,* 2013)

Table 5 : Derivatives of Rivastigmine

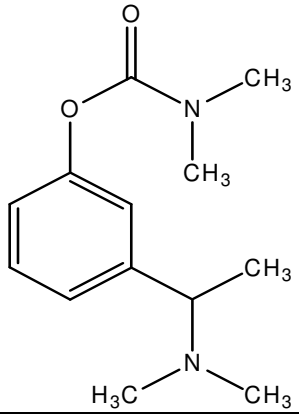
S.No	Derivative	Effect	Structure	Reference
1	3-(1-(Dimethylamino) ethyl) phenyl – dimethyl carbamate	Selctive Inhibitor		(Bar *et al.,* 2002)

Table 6 : Derivatives of Galantamine

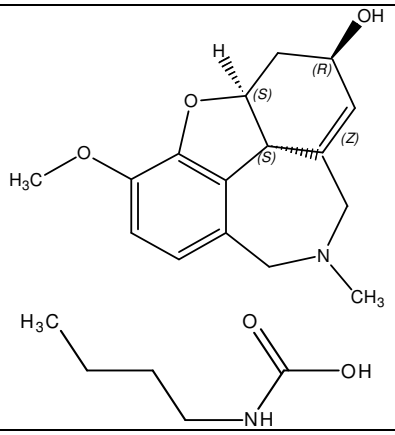
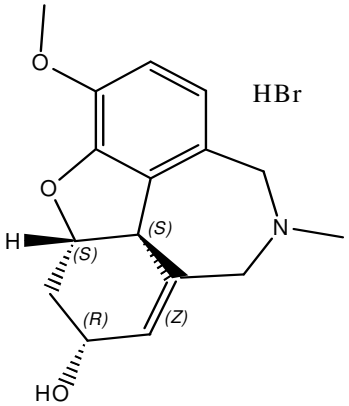
S.No	Derivative	Effect	Structure	Reference
1	*galantamine n-butylcarbamate*	Elevation in Anticholinesterase action		(Peera *et al.,* 2013)
2	*Galantamine Hydro-bromine*	Sustained Release		(Fong *et al.,* 2015)

Table 7 : Derivatives of Donepezil

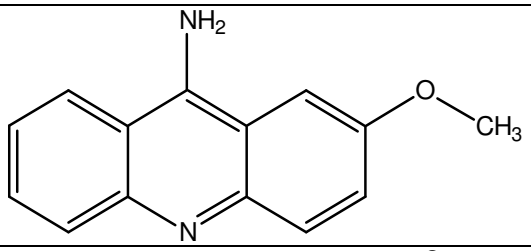
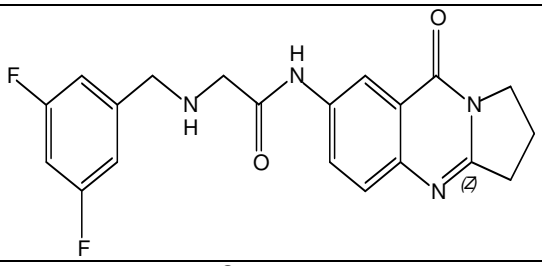
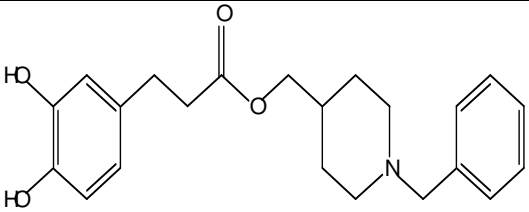
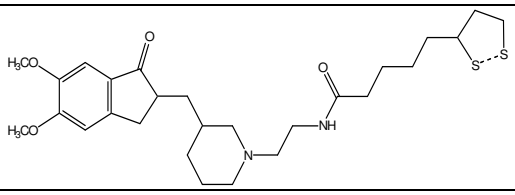
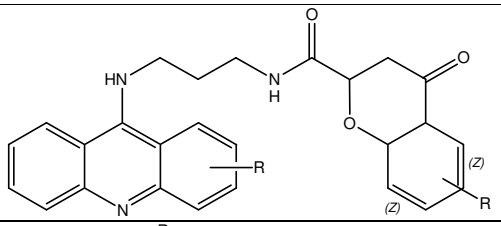
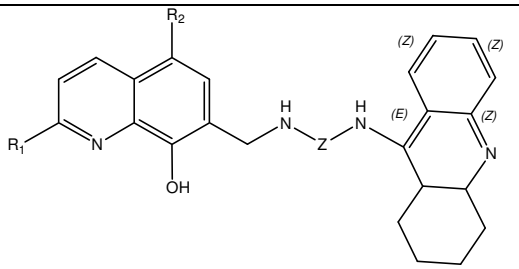
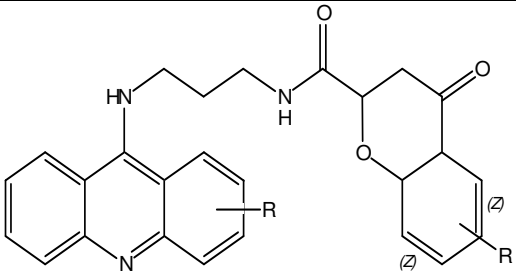
S.No	Derivative	Effect	Structure	Reference
1	7-Methoxytacrine	Interaction with anionic as well cationic sites of Anti-cholieesterase		(Korabecny *et al.,* 2014)
2	Deoxyvasicinone –Donepezil	Alzheimer's Multitargetting drug		(Du, *et al., 2019)*
3	feruloyl-donepezil	Show Inhibitory activity		(Dias *et al.,* 2017)
4	Donepezil-Lipoic Acid	Potent against BuCHe as well as Ache (HUMANS)		(Terra *et al.,* 2018)

Table 8 : Derivatives of Tacrine

S.No	Derivative	Effect	Structure	Reference
1	Tacrine-Ferulic Acid	Greater AChE selectivty		(Fu, Y *et al.,* 2016)
2	*tacrine-8-hydroxyquinoline*	Beta-amyloid level decreases		(Fernandez *et al., 2010)*
3	tacrine-4-oxo-4H-chromene	Increases permeability and anti-oxidant properties		(Watkins *et al.,* 1994)

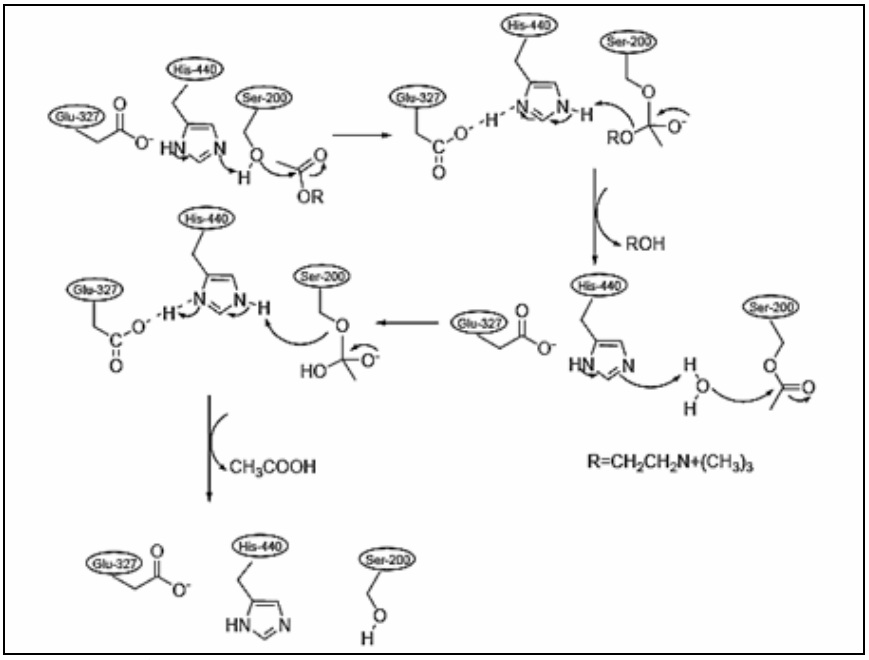


Fig. 1 : Mechanism of Ach hydrolysis catalyzed by AChE

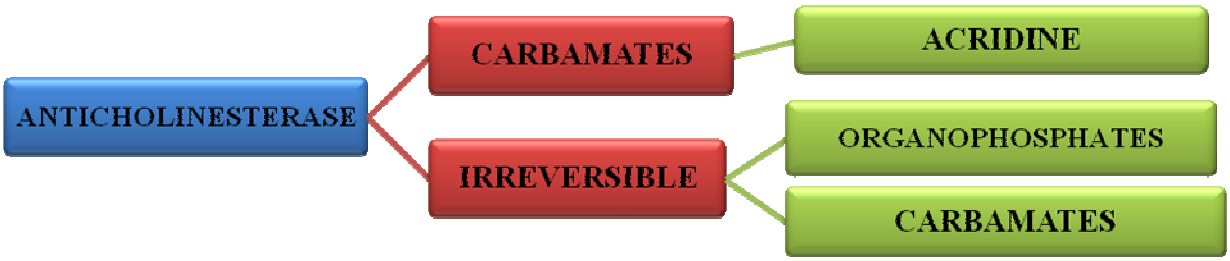


Fig. 2 : Classification of Cholinesterase Inhibitors

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