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Review Article

Designing arecoline analogues as M1 receptor stimulant to treat Alzheimer's dementia: Review

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Abstract

The cholinergic hypothesis of Alzheimer's disease (AD) has spurred the development of numerous structural classes of compounds with different pharmacological profiles aimed at increasing central cholinergic neurotransmission, thus providing a symptomatic treatment for this disease. Indeed, the only drugs currently approved for the treatment of AD cholinomimetics with the pharmacological profile of acetylcholinesterase inhibitors. Recent evidence of a potential disease modifying role of acetylcholinesterase inhibitors and M1 muscarinic agonists have led to a revival of this approach, which might be considered as more than a symptomatic treatment. From one of the research studies (Bratt et al. 1996), arecoline showed significant cognitive improvements in AD patients, this led to the development of many derivatives in this class and most of them have either cholinergic toxicity or lack of specificity to the M1 receptor. Therefore, this paper attempts to modify different structural problems existing in currently available arecoline derivatives.

General Introduction to AD

Alzheimer's disease (AD) is, an irreversible, progressive brain disorder that occurs gradually and results in memory loss (Fisher 2000), unusual behavior, personality changes and a decline in thinking abilities. It is a neurodegenerative disorder clinically characterized by progressive loss of cognitive functions, including memory, language, praxis, judgment and orientation. These losses are related to the death of brain cells and the breakdown of the connections between them. Many patients also show significant noncognitive symptoms such as depression, psychosis, agitation, and personality changes .The etiology of AD remains unknown. Several hypotheses (e.g., amyloid deposition, tau hyperphosphorylation, metabolic dysfunctions, loss of synapses, increased oxidative stress, immunological changes, and RNA mutations) have been proposed to account for the neurodegenerative process, although the integration

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of all these different hypotheses into one etiopathogenetical cascade requires further work. One characteristic deficit in AD is the reduction of cholinergic transmission. Basal forebrain neurons, which provide the majority of cholinergic innervations in the cortex and hippocampus, start to degenerate early during the course of AD (Growdon 1997). The cortex and hippocampus show a marked decline in choline acetyltransferase (ChAT), the enzyme responsible for the synthesis of acetylcholine. The number of basal forebrain neurons and the level of ChAT have been shown to correlate with the severity of dementia and the loss of synapses in AD. Recent investigations have documented additional cholinergic insufficiencies in other brain regions such as the amyloid complex and putamen. AD is the most common cause of dementia among people age 65 and older. The prevalence of AD doubles every 5 years beyond age 65. Prevalence is the number of people in a population with a disease at a given time infact, some studies indicate that nearly half of all people ages 85 and older have symptoms of AD (Bratus et al. 1980).

Currently used therapeutic agents

The cholinergic deficit in AD has been a target for pharmacological treatment. Several possible strategies have been explored (Heidrich and Rosler 1999).

a. Acetylcholine precursors.

b. Choline uptake enhancers.

c. Acetyl group donors.

d. Acetylcholine releasers.

e. Acetylcholinesterase inhibitors.

f. Cholinergic receptor agonists (muscarinic, nicotinic).

Two cholinesterase inhibitors, tacrine and donezepil are currently available and approved by U.S, Food and Drug Administration (FDA). The efficacy of acetylcholinesterase inhibitors depends on the availability of sufficient acetylcholine and number of presynaptic neurons, which produce and release acetylcholine. The availability of presynaptic neurons limits the efficacy of acetylcholinesterase inhibitors in AD, since neurons degenerate with the progression of the disease. The direct stimulation of cholinergic receptors (muscarinic, nicotinic) might be more efficient under these circumstances. The investigation of possible muscarinic receptor agonists began with compounds that were not specifically designed for use in AD (arecoline, pilocarpine, bethanechol, oxotremorine). Among these, first generation muscarinic agonists, arecoline

showed memory enhancing effects in patients with mild to moderate AD. Arecoline was administered by continuous intravenous infusion. Due to its rapid invivo hydrolysis, arecoline has a short plasma half-life and negligible activity by oral administration, recently a series of arecoline derivatives has been synthesized with the goal to find compounds (tetrahydropyridinealdoximes, milameline, or E-1-methyl-1, 2, 5, 6 tetrahydro-pyridine-3-carboxaldehyde-O-methyloximehydrochloride, CI-979/RU-35926/PD-129409),
with adequate oral activity and a long duration of action. From this new class of drugs, further studies and possible development of antidementia drug is required.

Muscarinic receptor1 (M1 receptor) and Alzheimer disease

M1 receptor is a G protein coupled receptor, is located on outer surface of the cell membrane of neurons in the brain. It is a glycoprotein with molecular weight approximately 64 KD. Stimulation of the same will subside the formation of neurotoxic β amyloid via secondary messengers. Amyloid formation is an early event in brain's of AD patients and defines much of the histopathology of AD. β Amyloid is deposited in cerebral blood vessels, as they diffuse to extra cellular space may trigger neuritic reaction. The $\alpha\beta$ amyloid fragment deposited in AD brains is neurotoxic where as the N-terminal portion of APP may have neuroprotective and neurophilic effects formed by stimulation of M1 receptor (Johnson and Hartigan 1998).

Linkage of M1 receptor, β amyloid and tau phosphorylation

The cholinergic hypofunction in AD may lead to the formation of amyloid, which might impair the coupling of M1 receptor with G proteins (Sadot et al. 1996). This disruption in coupling may lead to formation of amyloid transduction, to a reduction in levels of trophic amyloid precursor protein (αAPPs) and generation of more β amyloid that can also suppress Ach synthesis and release, aggravating further cholenergic deficiency (Genis et al. 1999). Tau microtubule associated protein is neuronal specific and its expression is necessary for neurite outgrowth. Hyperphosphorylation tau proteins in response to β amyloid, is the principal fibrous component of the neurofibrillary tissue tangle pathology in AD.

M1 agonists

As therapeutic agents, M1 agonists in the short term may palliate symptoms of AD and improve memory function. In long term, M1 agonists have the potential to modify the underlying pathophysiology of AD, and there by prevent or retard the course of dementia. Several M1 agonists, including AF series were tested in various animal models. In this context, the M1 agonists from the AF series restored memory and learning deficits in several animal models that mimic cholinergic and/or other deficits reported in AD. They also have the advantage of not producing central and peripheral adverse side effects at effective doses and showing a relatively wide margin of safety. The therapeutic potential of M1 selective muscarinic agonist including AF102B, AF150 (S), AF267B (the AF series have basic arecoline structure) is evaluated and compared with several FDA approved acetylcholinestrase inhibitors (Lovestone and Reynolds 1997). These M1 agonists can elevate APPs, hyperphosphorylation in *in vitro* and *in vivo* studies, and restore cognitive impairments in several animal models in AD. Based on the early studies, arecoline had positive acute effects on some areas of cognition in two small studies. But its uses are limited because of intravenous administration (gets easily hydrolyzed in stomach), as a carcinogen and lack of specificity to M1 receptor. Even other cholinergic agonists including oxtremorine, muscarine, RS86, milameline, and sabcomeline, which do not discriminate among subtypes of cholinergic receptors. Thus cannot be termed as M1 specific agonists. Some of the tested M1 agonists like alvameline are very weak agonists of M1 receptor, and also produces cholinergic adverse reactions like vomiting and increased secretions (Fisher 2000). The duration of action of the cholinergic drugs is short and the range of effective doses is small. Currently available agents suffer from, nonspecificity towards M1 receptor; pose serious adverse side effects, bioavailability problems. Hence, the search of novel orally bioavailable antidementia drug with improved therapeutic potential over existing agents is of utmost need.

General structure activity relationship studies of arecoline bioisters

Extensive database have been developed and continued for better pharmacodynamic and pharmacokinetic parameters. Database developed is as follows:

1. In arecoline (**1**) ester group is prone to acid hydrolysis in stomach, it lacks specificity to M1 receptor and also it is carcinogenic according to studies reported (Nieschulz and Schmersahl 1968).

2. Quaternization of nitrogen of the arecoline produces equipotent M1 receptor agonist as compared to arecoline itself (Krogsgaard and Bundgaard 1991).

3. The secondary amine of norarecoline (absence of CH_3 group on ester of arecoline) is weaker muscarinic agonist (Bieger et al. 1970; Sauerberg et al. 1986).

4. In case of ester substituent on ester ($-$COOR), the affinity and biological activity increases in this order. Where, the triple bond of propargyl* ester contributes to the receptor binding (Lambrecht and Mutschler 1981).

$$\mathrm{R} = \mathrm{CH_3} < \mathrm{C_2H_5} < \mathrm{nC_3H_7} < -\mathrm{CH_2} - \mathrm{CH} = \mathrm{CH_2} <= \mathrm{CH_2} - \mathrm{C} \equiv \mathrm{CH}^*$$

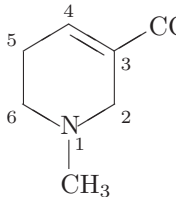
5. Reduction or removal of the ring double bond (between three and four position) reduces the muscarinic agonist activity by 250 to 1000 times (In 1, if the nitrogen of the arecoline is substituted by sulphur (bioisoster, in 1 where $N \Rightarrow S$), activity is retained, but not active as nitrogen in arecoline (Moser et al. 1983).

6. Introduction of another nitrogen in the ring of arecoline, to produce basic structures that is pyrimidine analogue, which gives less potent derivatives than arecoline itself (Messer et al. 1992).

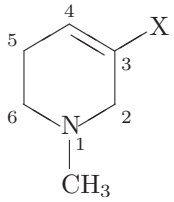
7. $\mathrm{N} - \mathrm{CH_3}$ group of arecoline produces selectivity of the basic structure to M1 receptor (Moltzen et al. 1994).

8. Substitution at 3^{rd} position of the ring increases the biological activities but at 4^{th} substitution antagonizes M1 receptor activity and other substitution doesn't have significant effect.

   The ligand is designed as tertiary nitrogen, which facilitates bioavailability (passage through blood brain barrier), and after the passage the ligand is

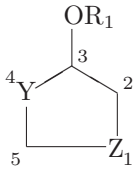


1.

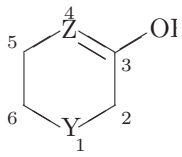


2.

Where $R = CH_3$ **for arecoline and X may be 2a or 2b**



2a.



2b.

Where $R_1 = H$**, alkyl, aryl etc; Y=Z=O, N, S**

Figure 1: General Structures of arecoline bioisters.

expected to be convert positive nitrogen (Nitrenium ion) *in vivo* oxidation in presence of mono amino oxidase. As supported by structurally related drugs or ligands (Eg. MPTP or Arecoline) and hence the, molecules will be highly reactive. Because of the above structural and functional relations to M1 receptor, this basic structure and its analogues are selected for study.

9. 3-Acetoxy quinuclidines are potent muscarinics and also thianium, piperidine derivatives of quinuclidine also provides potent muscarinic activity. An alternative and better strategy to design arecoline derivatives, is by substituting the ester (because of non-specificity to the receptor, hydrolysis in the body and carcinogenic in nature) by five or six membered heterocyclic ring (Lambrecht and Mutschler 1981) to produce better muscarinic agonist.

In five membered heterocycles 2a

a. Electronegative atom at 1^{st} position increases the biological activity. Order of biological activity with respect to hetero atom, is as follows (Sauerberg et al. 1991). $N > S > 0$.

b. Presence or absence of electronegative atom at 5^{th} position of the arecoline ring doesn't change the biological activity.

c. Electronegative atom as a part of the ring at 4^{th} position, increases the biological activity, in the order. N > S > O.

d. SR, OR, group attached to 3^{rd} position increases the biological activity. As the increase in the carbon number of R in SR or OR up to 6 number, increases the biological activity. [Hydrophobic nature increases binding to receptor, and avoids being washed out from receptor]

In six membered heterocycles 2b

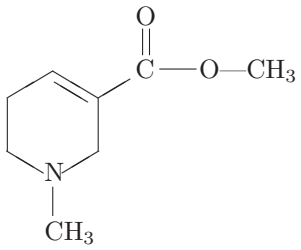
a. Electronegative atom at 1^{st} position as part of ring of sublead increases the biological activity, in the order, N > S > O (Ward et al. 1992).

b. Electronegative atom at 4^{th} position as a part of ring of sublead increases the biological activity, in the order, N > S > 0.

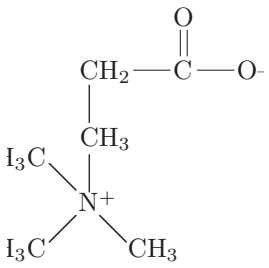
c. SR, OR attached at 3^{rd} position increases the biological activity. As the increase in the carbon number of R in SR or OR at 2^{nd} position of sublead up to 6 numbers, increases the agonistic activity.

Different class of arecoline molecules in research and their muscarinic activity

Arecoline stimulate muscarinic receptor because of its structural similarity with that of acetylcholine as shown below 3 and 4.

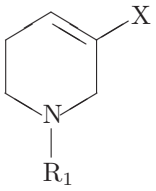


3.



4.

Arecoline bioisosters have general formulae as shown in 5 and the basic nucleus is tetrahydropyridine.

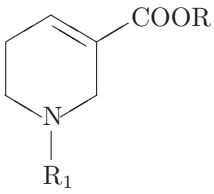


5.

Both affinity and efficacy are significantly enhanced by tetrahydropyridine series to M1 receptor, provides semirigid template, which has good affinity for the muscarinic receptor (Showell et al. 1991). If the molecule is flexible as that of acetylcholine, it interacts with different class of muscarinic receptors and lacks the specificity to interact with a specific muscarinic receptor. If the molecule is rigid, it is unable to stimulate different class of muscarinic receptors. Tetrahydropyridines are semirigid class can bind specifically to M1 receptor, also provides some kind of flexibility to stimulate M1 receptor. N-methyl group on tetrahydropyridines makes the molecule selective towards M1 than M2 receptor.

I. SAR of arecoline bioisters in which arecoline nucleus linked to different substituents (R) through various functional groups

A. Ester linkage



6.

Ester linkage is prone to hydrolysis and some of its derivatives are carcinogenic.

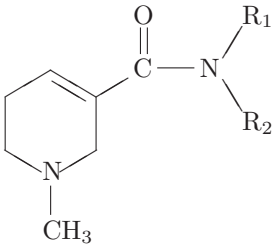
1. When R substituent is H, straight or branched alkyl from one to six carbon atoms or cycloalkyl from four to eight carbon atoms, muscarinic activity

increases up to two carbon atoms, beyond which the activity decreases (Butler et al. 1988).

2. When R substituent is straight or branched alkenyl from one to six carbon atoms, as carbon number increases, correspondingly activity also decreases.

3. When R is phenyl alkyl where in, the alkyl portion is straight or branched from one to six carbons and the phenyl ring may be unsubstituted or substituted with halogen, hydroxy, alkyl from one to six carbon atoms, or alkyloxy from one to four carbon atoms, muscarinic activity decreases as the carbon length increases, as the substituted group on phenyl ring become electronegative, agonistic activity also increases.

B. Amide linkage



7.

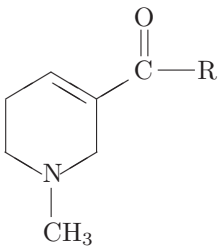
1. When R_1 and R_2 are independently hydrogen or alkyl from one to four carbon atoms, muscarinic activity decreases as carbon length increases in R_1 and R_2 independently (Butler et al. 1988).

2. When group R_1 is hydrogen and R_2 is cycloalkyl from three to eight carbon atoms, muscarinic activity decreases as the carbon length increases in cycloalkyl ring.

3. Group R_1 is H and group R_2 is benzyloxy, it increases the activity (Kelly et al. 2001).

4. Group R_1 is H and group R_2 is phenyl alkyl where in, the alkyl portion is straight or branched from one to six carbon atoms, phenyl ring may be unsubstituted or substituted with halogen, hydroxy, alkyl from one to six carbon atoms or alkyloxy from one to four carbon atoms, as carbon length decreases in alkyl portion and electronegativity of substituent on phenyl ring increases, proportionately muscarinic activity increases.

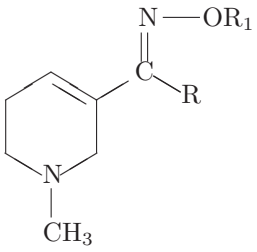
C. Ketone linkage



8.

1. When R is pyrrolidinyl, piperidinyl, 4-diphenyl methylene piperzinyl, azepinyl, morpholinyl, thiomorpholinyl, isoxazolyl, piperazinyl, pyrrolidinyl and isoxzolyl rings show good Muscarinic action than six numbered heterocyclic rings.
2. When R is 4-alkyl piperazinyl ring where the alkyl group may be straight or branched alkyl from one to six carbon atoms, as the carbon length of alkyl chain increases, muscarinic activity decreases (Bergmeir et al. 1995).

D. Oxime ether linkage

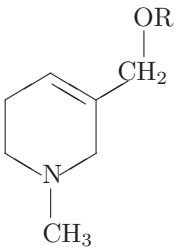


9.

1. When R is straight or branched alkyl chain having one to four carbon atoms, muscarinic activity decreases as carbon length increases (Bergmeir et al. 1995).
2. When R_1 substituent is straight or branched alkyl from one to six carbon atoms optionally substituted with hydroxyl or alkoxyl from one to four carbon atoms, as carbon length of alkyl chain increases and electronegativity of group attached to alkyl chain increases, Proportionally muscarinic activity increases.

3. When R_1 is cycloalkyl of from three to eight carbon atoms where hydrocarbon chain of from one to four carbon atoms, muscarinic activity decreases as the carbon number increases in cycloalkyl ring.

E. Methyl ether linkage



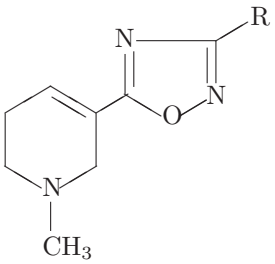
10.

1. When R is straight or branched alkyl from one to six carbon atoms, optionally substituted with hydroxy or alkyl of from one to four carbon atoms, as carbon length increases, the muscarinic activity also increases (Walther et al. 1995).

2. Group R is cycloalkyl from three to eight carbon atoms where hydrocarbon chain of one to four carbon atoms, as ring expands from three to eight carbon, muscarinic activity decreases.

II. SAR of Arecoline bioisosters in which arecoline nucleus is attached to different ring systems.

A. 1, 2, 4 Oxadiazole ring

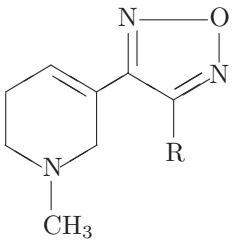


11.

1. When R is unbranched alkyl chain, show strong affinity into binding assay in rat brain membranes (Ngur et al. 1992).

2. When R is branched or a cyclic systems, which are Muscarinic antagonists and analogs in which the R group contains an ether moiety (e.g. $CH_2 - O - CH_3$) are muscarinic agonist, but they have lower receptor binding affinity than alkyl derivatives.

B. 1, 2, 5 Oxadiazole ring



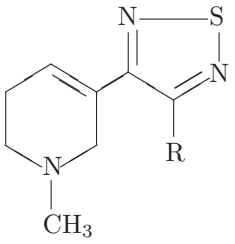
12.

1, 2, 5 oxadiazole show M1 receptor efficacy may be related to the magnitude of electrostatic potential located over the nitrogen's and also influences the M1 efficacy of the compounds by determining the energetically favourable conformers for rotation about bond connecting the tetrahydropyridyl ring (Ngur et al. 1992).

1. When R is branched or unbranched alkyl chain up to their carbon chain, central muscarinic affinity increases and R with n-butyl or n-hexyl, show low affinity to the muscarinic receptor.

2. When R is branched or unbranched alkoxy or alkylthio from one to eight carbon chain, as the carbon chain increases, a receptor affinity also increases.

C. 1, 2, 5 Thiadiazole ring



13.

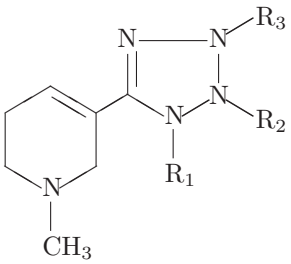
M1 efficacy of 1, 2, 5 thiadiazole analogues are similar to that of 1, 2, 5 oxodiazole analogues (Ngur et al. 1992).

1. When R is alkyl chain from one to eight carbon chain, or branched chain carbon from three to six carbons, branched alkyl chain with higher carbon number shows high potency (Sauerberg et al. 1992).

2. When R is alkoxy or alkylthio from one to six carbon chain, among alkoxy substituents, pentyloxy show maximum receptor affinity, whereas alkylthio, thiohexyl substituent show greater affinity to muscarinic receptor.

When alkyl R and alkoxy (thioalkyl) R substituent analogues are compared for their muscarinic activity, either derivative with some carbon length as that of alkyl derivatives, show 10 to 100 times high affinity to central muscarinic receptor.

D. Tetrazoline ring

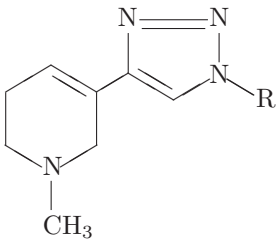


14.

1. When R_1, R_2 and R_3 are independently unbranched alkyl from one to eight carbons or branched from three to eight carbons, whereas R_2 substituent is methyl group, it shows high affinity and R_1 methyl group shows less affinity, but bulky R_2 substituent decreases the muscarinic activity (Moltzen et al. 1994).

2. When R_2 is unsaturated unbranched chain from five to six carbon atoms, propargyl derivatives show maximum affinity, where as vinyl derivative shows less affinity to the receptor.

E. Triazole ring

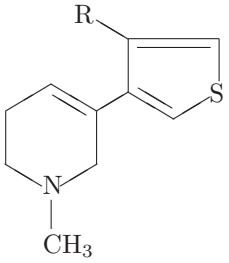


15.

1. When R is unbranched alkyl of from one to six carbon atoms alkyl chain with less carbon show good affinity with the receptor (Moltzen et al. 1994).
2. When R is alkoxy or thioalkyl from one to six carbon atoms, analogues with higher carbon show good affinity with the receptor.
3. When R is unsaturated unbranched chain from one to six carbon atoms while propargyl derivative shows maximum affinity and vinyl with low affinity to the receptor.

F. Thiophene ring

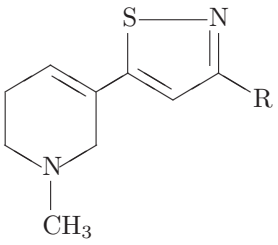
1. When R is unbranched alkyl chain from one to six carbons, as carbon chain increases, muscarinic activity decreases (Ngur et al. 1992).



16.

2. When R is alkoxy from one to eight carbon, as carbon chain increases up to seven, agonistic activity increases.

G. Thiazole ring

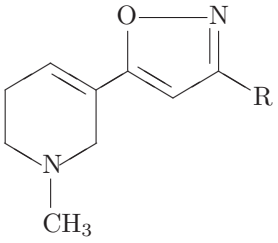


17.

1. When R is unbranched alkyl chain from one to six carbons, as carbon chain increases muscarinic activity decreases (Ngur et al. 1992).

2. When R is alkoxy from one to eight unbranched carbon chains, as carbon chain increases up to six, muscarinic activity also increases.

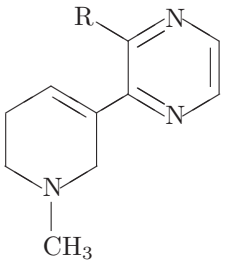
H. Oxazole ring



18.

1. When R is alkoxy from one to eight unbranched carboxyl chain, as carbon chain increases up to six, muscarinic activity increases (Ngur et al. 1992) .

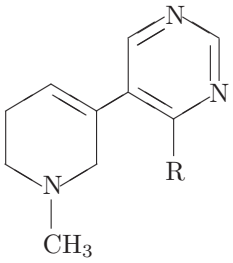
I. Pyrazine ring



19.

1. When R substituent is alkoxy from one to seven unbranched carbon chain, as carbon length increases up to six, muscarinic activity increases (Ward et al. 1992).

J. Pyrimidine ring



20.

1. Where R is alkoxy or thioalkyl from one to six unbranched carbons, as carbon length increases, affinity to receptor increases (Lin et al. 1995).

Interaction mechanism of arecoline bioisosteres with muscarinic receptor-1

Arecoline is a cyclic 'reverse ester' bioisoster of acetylcholine, containing a tertiary amino group, it is approximately equipotent with its quatranised analogue N-methyl arecoline, as a muscarinic Ach receptor agonist, at pH 7.1 arecoline is partially protonated and which can be calculated by equation **(1)** shown below.

$$\% \text{ Ionized} = \frac{100}{\text{Antilog}\,(\text{pH} - \text{pka})} \qquad (\mathbf{1})$$

Arecoline is 83% ionized and 17% unionized at pH 7.1. The presence of a fraction of unionized arecoline molecule (17%) allows it to penetrate through Blood Brain Barrier and after penetration (figure 2), ionized to form (protonated form 83%) is assumed to bind and activate muscarinic AChE receptor-1. Same concept can be applied to arecoline bioisoters (Krogsgaard and Bundgaard 1991).

Arecoline binds to muscarinic receptor because it is structurally related to acetylcholine and muscarine, they have similar dimension (4.4A° units) between positively charged nitrogen and oxygen as shown in figure 3. In general rigid ligands may not have required flexibility to evoke the conformational change of the receptor protein necessary for a full agonist response, since conformational changes of both the agonist and receptor may be required.

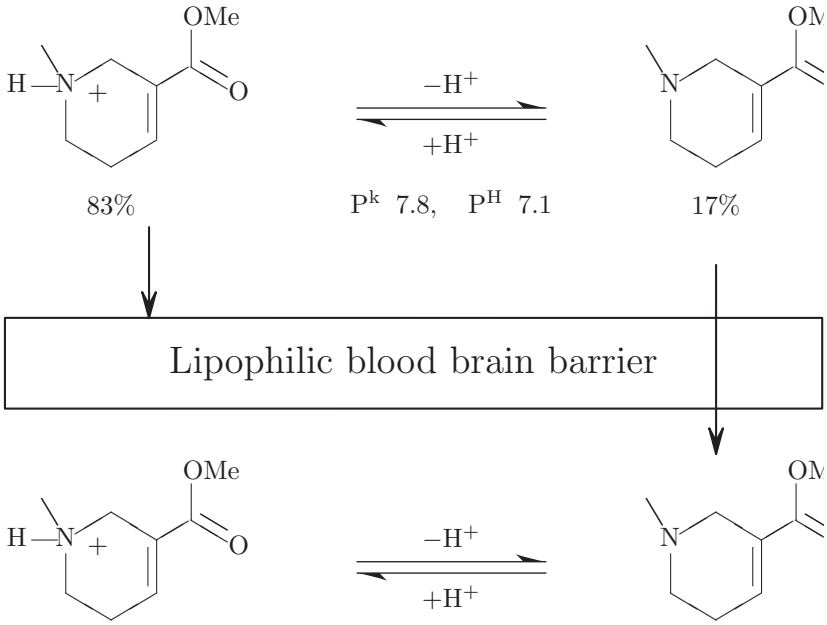


Figure 2: Ionization of arecoline and its penetration through blood brain barrier.

The crystal structure of oxadiazole (11) showed that one of the oxygen atoms of carboxylic acid group of amino acid of the muscarinic receptor forms a hydrogen bond at N1 with -0- H-N = 2.81A° and q = 160.5°. Acetyl choline itself cannot form hydrogen bond, but would form an electrostatic interaction with the aspartate of M1 receptor. In order to probe further into the pocket of

the receptor, occupied by the acetyl methyl group of acetylcholine **(4)**, various analogues were synthesized to study the hydrogen bond donating/acceptor properties of M1 receptor site. The presence of hydroxyl groups as hydrogen bond donor reduced affinity for both sites of the receptor by approximately 10 fold, whereas fluoro ethyl analogue (designed as a bond acceptor) retained a more acceptable level of affinity and predicted efficacy. Not only hydrogen bond donating group is required, but also concomitant secondary lipophilic binding is essential (e.g. quinaclidinyl benzilate).

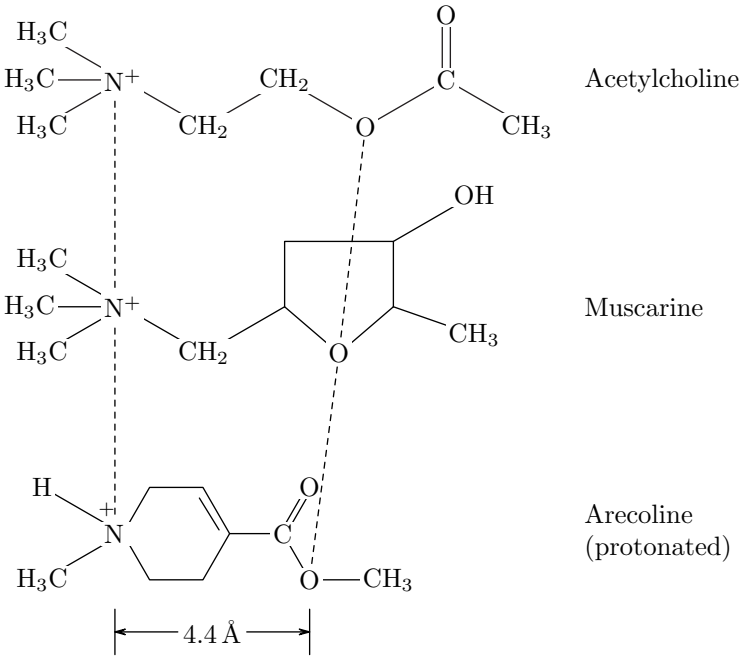


Figure 3: Structured similarities of arecoline, acetylcholine & muscarine

Quantum mechanical calculations revealed difference between the secondary and tertiary amines of tetrahydropyridines **(5)**. Area of positive electrostatic potential around the protonated ring of nitrogen and have delocalized charge over a wide area including N_1, C_2 and C_6. In contrast the tertiary amines have more distinct areas of positive charge around the N-methyl group N_1, C_2 and C_6. The affinity and potency depends mainly on the length of alkyl chain for space filling properties. The optimum substituents were found to be unbranched C_{5-6} alkoxy/alkyl thio side chain. It is probable that this chain fits into a widening lipophilic cavity in the receptor whose occupancy is rightly beneficial for activating the M1 receptor. Oxygen and sulfur di-

rectly attached to the 1, 2, 5 thiadiazole ring **(13)** probably influence the electronic and conformational properties of the 1, 2, 5 thiadiazole to obtain optimum agonist receptor interaction. The length of alkyl chain is probably also responsible for the separation of the M1 and M_2 functional agonist activity.

Replacement of either one or two nitrogens in the 1, 2, 5 thiadiazole ring **(13)** reduced the affinity for the muscarinic agonist conformational state appropriately 350 fold. The affinity for M1 receptors was also reduced, but only about 100 fold. A similar reduction in muscarinic receptor affinity was observed, when N_5 nitrogen in 1, 2, 5 oxadiazole is removed. The 1, 2, 5 thiadiazole moiety is largely responsible for the high M1 receptor affinity and efficacy. Alteration of the aromatic heterocyle led to the compounds with lower affinity. The sulfur atom in the 1, 2, 5 thiadiazole **(13)** is apparently important for the receptor interaction, since the 1, 2, 5 oxadiazole have much lower M1 receptor affinity. The nitrogens or at least the N_5 nitrogen is also very important for optimal receptor recognition. The exchange of N_5 nitrogen for carbon as in the thiazole **(17)** caused an even significant decrease in muscarinic receptor affinity than the sulfur/oxygen exchange.

Exchange of the second nitrogen as in the thiophenes did not alter the receptor affinity significantly, indicating that the N_5 nitrogen perhaps is more important for receptor interaction than the N_3 nitrogen. For the 1, 2, 5-oxadiazole **(12)** muscarinic ligands, a correlation between the electrostatic potentials adjacent to the nitrogens and the receptor affinity has been demonstrated. For the 1, 2, 5 thiadiazole ligands it was concluded that the methyl group was the preferred size of lipophilic substituent for binding to the high affinity state of the receptor. The SAR of the five membered aromatic heterocycles supports the hypothesis that the 1, 2, 5 thiadiazole moiety is a unique isoster to the arecoline ester functionality.

Quaternary ammonium nitrogen of the acetyl choline or tertiary nitrogen of the arecoline with muscarinic receptor forms electrostatic attraction (E), hydrogen bonding (P) with the ester oxygen of acetyl choline or with the ester oxygen of arecoline, hydrophobic (H) and van der waals (W) interaction with the methyl group of acetyl choline or arecoline (figure 4).

The essential structure of muscarinic agents is a quaternary ammonium group and a methyl group. In general, these agents have chain of five atoms attached to the quaternary nitrogen. One pair of unshared electrons that can participate in hydrogen bonding and alkyl group, which participate in hydrophobic and van der waals interactions (Chothia 1970).

(E) = Electrostatic attraction. (P) = Hydrogen bonding.

(H) = Hydrophobic interaction. (W) = Van der Waals interaction.

In 1983, Schulman and co-workers proposed the theoretical model for the muscarinic receptor. In their model, acetylcholine and cholinergic agents

interact with a muscarinic receptor through (figure 5) two sites; the anionic site P and electrophilic site Q. The optimal distance between P and Q [6.7A°] is practically invariable in the receptor active conformation (Schulman et al. 1983). The angle PNOQ (108 degree) defines the drug orientation at the receptor and owing to structural similarity of agonists, it should remain almost constant during drug receptor interaction.

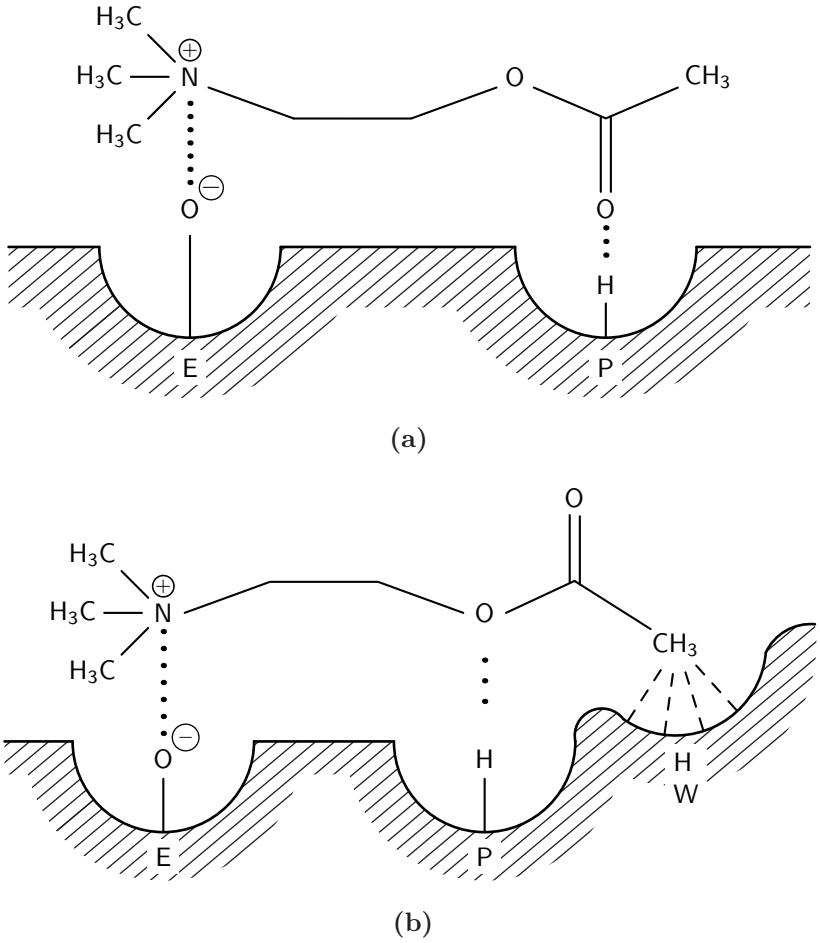


Figure 4: Interaction of acetylcholine or arecoline with muscarinic receptor.

a. Acetylcholine interacting with the receptors carboxylate oxygen and electrophilic group, such as a hydrogen-bonding proton.

b. The oxygen is indicated symbolically by P while electrophilic site is located

at the point of minimum electrostatic potential near the oxygen, denoted by α. The interaction dihedral angle PNOQ is indicated by α.

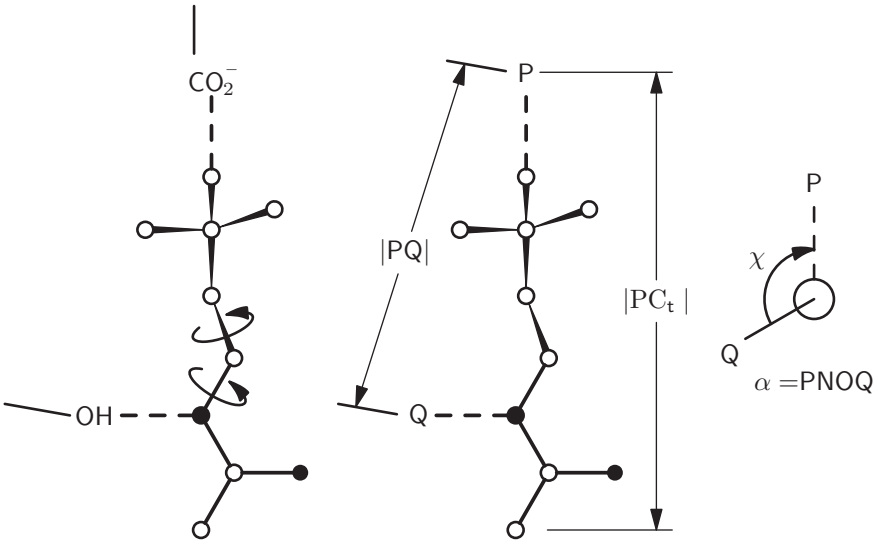


Figure 5: Interaction of acetylcholine and cholinergie agents with muscarinic receptor.

Overview of the SAR

It can be drawn from the above discussion that semirigid ring substituents or acyl functional groups with variable number of carbon chain and/or alkoxy (thioalkyl) group with certain number of carbon atoms having electronegative substitutents placed at proper position and optimization of these substituent parameters on arecoline lead molecule can help to over come the limitations of existing molecules tested for A.D.

Glossary

1. **Agonist:** A drug capable of combining with receptors to initiate drug action; it possesses affinity and intrinsic activity.

2. **Amyloid:** A protein (probably combined with chondroitin sulphuric acid) that is microscopically homogeneous but which is composed of fine fibrils seen by electron microscope. occurs characteristically as pathologic extra

cellular deposits beneath the endothelium of capillaries or sinusoids, in the walls of arterioles, and especially in association with recticuloendothelial tissue.

3. **Blood brain barrier:** The walls of the capillaries that perfuse the brain.
4. **Cholinergic:** Relating to nerve fiber that cause effects similar to those induced by acetylcholine.
5. **Muscarinic:** Having muscarine like action, i.e, producing effects that resemble post ganglionic parasympathetic stimulation.
6. **Neuritic:** Inflammation of a nerve, marked by neuralgia, hyperesthesia, anesthesia, or parasthesia, paralysis, muscular atrophy in the region supplied by the effected nerve, and by abolition of the refluxes.
7. **Neurophilic (Neurotrophic):** Relating to trophic conditions under nerve influence.
8. **Presynaptic neuron:** Neuron receiving the signal at a synapse.
9. **Putamen:** The outer, larger, and darker gray of the three portions into which the band lenticular nucleus is divided by laminae of white fibers; it is connected by intervening of gray substance with the caudate nucleus.
10. **Receptor:** The component of the cell or organism that interact with a drug and intiates the chain of biochemical events to the drug's observed effects.

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