Summary and Conclusion
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Acetylcholinesterase inhibitors such as donepezil, galantamine, rivastigmine and tacrine approved by the U.S. FDA to treat AD, which act by limiting the degradation of synaptic Ach levels to activate cholinergic receptors.

However, AChEIs efficacy in enhancing cognition is failed so far, in part because of central and peripheral adverse effects that are due to activation of the other subtype of muscarinic Ach receptors mAChRs such as M2 to M5 and/or direct agonism action. Recent research suggests that selective stimulation of M1 receptors, but not other subtypes, is a beneficial strategy to treat AD without producing adverse effects.

There are five receptor subtypes in the muscarinic family (M1-M5) that differ in terms of their localization, signaling activity and presumed function. Among the five existing mAChR subtypes, M1 is predominant in the many memory related brain regions, including the cortex, hippocampus, and striatum.

Thus selective M1 receptor drug targeting could play important role in regulating higher cognitive function. There is difficulty in developing highly selective M1 receptor agonists due to the high sequence homology among the orthosteric binding sites of mAChR subtypes. The alternative novel approach is to achieve high subtype selectivity is by targeting allosteric binding sites that are distinct from the ACh binding sites.

In this approach many GPCRs, including mAChRs, have allosteric binding sites bound by molecules that activate the receptor in the absence of ligand (allosteric agonist) or enhance the response to native ligand (PAM).

BQCA is a novel highly selective potent PAM of M1 receptor. It reduces the concentration of ACh required to activate M1 as well as it has no effect on potentiation, agonism or antagonism activity on other subtypes of mAChRs and does not show unwanted peripheral cholinergic stimulation.

BQCA enhances the memory function and reverses the cognitive impairment in scopolamine-induced memory deficits, suggested that the M1 receptor PAM BQCA has therapeutic potential for the treatment of AD.

It is also worth noting that drug discovery programs centered on small molecules, be it orthosteric or allosteric, share common problems concerning solubility and formulation, generation of active metabolites, clearance, lack of brain penetrance due to its highly...
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hydrophilic nature (due to highly lipophilic nature of the blood-brain barrier (BBB)) and necessitating frequent dosing due to its narrow biological half-life in brain.

A sensitive, rapid HPLC method was developed and validated for the estimation of BQCA in SD rat plasma. A simple PPT technique was employed to analyse the plasma and tissue samples. High sample throughput and good sensitivity (2.0 ng/mL in plasma and 5.0 ng/g in tissues) was achieved using the presented method.

BQCA absorbed into the systemic circulation with maximum concentration (~8000.0 ng/mL) within 1.5 h following i.p. administration. The order of AUC from the tissue distribution study was kidney > lung > liver > brain > spleen > heart. BQCA was meteorically taken up into the brain and bring off a maximal brain concentration at 1.5 h and maintained up to 3-4 h. The method was successfully applied for the analysis of BQCA in plasma and tissue samples followed by the i.p. administration of SD rats at 10mg/kg dose.

BQCA loaded PLGA NPs were prepared using modified nanoprecipitation with narrow size distribution (<100 nm) and higher entrapment efficiency. In vitro release was found to follow Fickian-diffusion transport diffusion kinetics.

The high concentrations of BQCA achieved in the brain when the drug administered in form of PS 80-BQCA PLGA NPs. The developed formulations may also reduce the total dose required for the therapy with concurrent reduction in dose related toxicity.

Administration of BQCA solution in streptozotocin-induced animals did not result in any noticeable improvement in learning and memory capacities, whereas BQCA administration in form of PS 80-BQCA PLGA NPs in streptozotocin-induced animals significantly (P<0.001) decreased escape latency. These results indicated that, compared to BQCA solution and uncoated NPs, the PS 80 coated PLGA NPs of BQCA resulted in faster memory regain in streptozotocin-induced animals.

These preliminary results indicate that PS 80-BQCA PLGA NPs could be effective in brain targeting and sustaining BQCA release for a prolonged period and could be a significant improvement for treating Alzheimer’s disease. Further studies are needed to support the findings of pharmacodynamic studies in transgenic mouse model and to confirm the performance of NPs on non-amyloidogenic APP processing pathway.