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Muscarinic agonists and antagonists in the treatment of Alzheimer's disease☆

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease characterized by cognitive impairment and personality changes. The development of drugs for the treatment of the cognitive deficits of AD has focused on agents which counteract loss in cholinergic activity. Although symptoms of AD have been successfully treated with acetylcholinesterase inhibitors (tacrine, donepezil, rivastigmine, galanthamine), limited success has been achieved with direct M_1 agonists, probably due to their lack of selectivity versus other muscarinic receptor subtypes. Muscarinic M_2 antagonists have been reported to increase synaptic levels of acetylcholine after oral administration to rats (e.g. BIBN-99, SCH-57790), but their selectivity versus other muscarinic receptor subtypes is modest. Exploration of a series of piperidinylpiperidines has yielded the potent and selective M_2 antagonist SCH-217443. This antagonist has excellent bioavailability in rats and dogs and shows activity in a rat model of cognition.

Keywords: Alzheimer's disease; Muscarinic; Cholinergic; M_2 Receptors

Alzheimer's disease (AD) is a neurodegenerative disease characterized by cognitive impairment and personality changes which affects from 5 to 10% of the adult population over 65 years of age. One of the consistent findings in brains of AD patients is loss of cholinergic markers, including levels of acetylcholine (ACh) and choline acetyltransferase (CAT). The cholinergic approach to treatment of AD involves counteracting this loss in cholinergic activity by pharmacological intervention to increase cholinergic transmission [1].

The most widely explored approach to cholinergic therapy is the use of inhibitors of acetylcholinesterase (AChE), which block the major enzyme involved in the degradation of ACh (Fig. 1). Currently, there are four AChE inhibitors approved for use, tacrine, donepezil, rivastigmine and galathamine, and others such as the natural product huperzine A appear likely to follow (Fig. 2a) [2]. The clinical experience with these drugs has been promising, although their efficacy is modest, and side-effect issues continue to be of concern. The success of the AChE inhibitors has helped to validate the cholinergic approach to the treatment of AD.

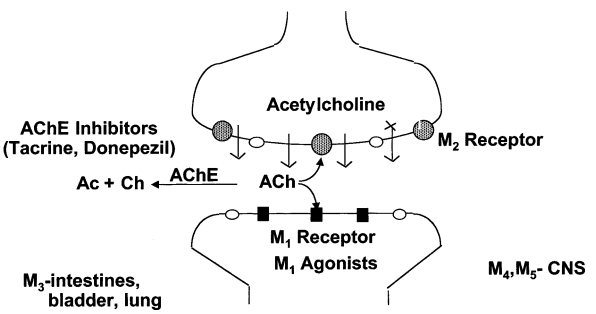

Fig. 1. The cholinergic hypothesis.

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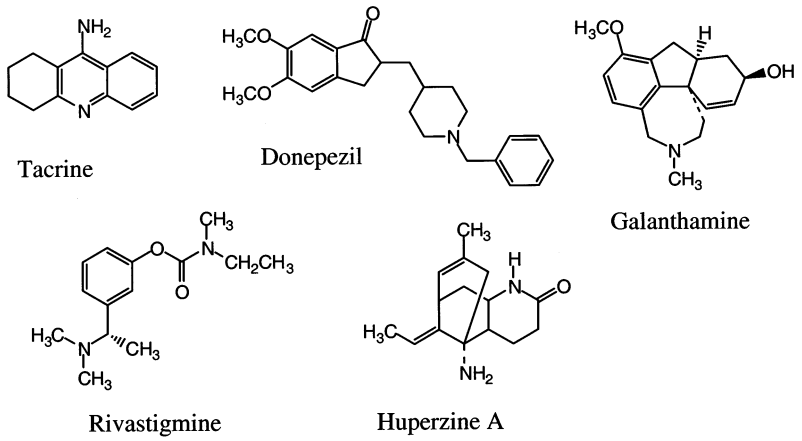


Fig. 2a. Muscarinic M_1 receptor agonists.

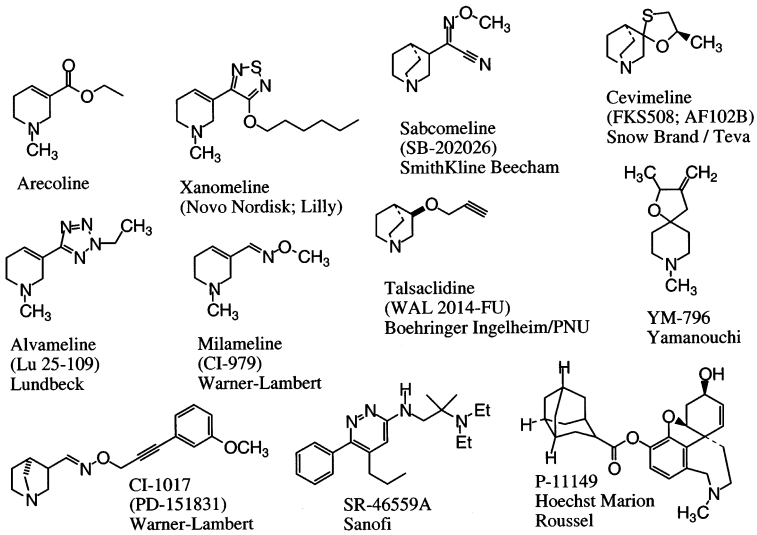


Fig. 2b. Acetylcholinesterase inhibitors.

A second cholinergic approach to AD has been the development of direct agonists of postsynaptic M_1 receptors [3]. Stimulation of these receptors has been shown to have cognition-enhancing effects in animals. Although a substantial effort has been devoted to the development of M_1 agonists, the promise of this approach has not been fully realized, in part because many of the agonists shown only modest selectivity for the M_1 receptor. This results in a variety of muscarinic side effects, due to activation of M_3 receptors in the intestines, bladder and lung (Fig. 1). Non-selective M_1 agonists may also interact with M_4 and M_5 receptors in the CNS with (as yet) unknown consequences. The lack of selectivity of current M_1 agonists also limits their efficacy, since non-selective agonists also activate presynaptic M_2 autoreceptors, thereby reducing release of ACh (Fig. 1). Many of the current M_1 agonists (Fig. 2b) were derived from the naturally occurring alkaloid arecoline, and have modest M_1 selectivity. At least six agonists from this class have been advanced into late-stage clinical trials (Fig. 3), and most have shown efficacy, as measured by standard cognition or behavioral scores. Many others have advanced into early clinical trials or have undergone preclinical evaluation [3]. It is possible that more-selective M_1 agonists can be found which will show improved efficacy, while producing fewer side effects.

A third, less-popular cholinergic approach to AD has been the development of antagonists of the postsynaptic M_2 autoreceptors [4,5]. Studies in animals have demonstrated that the blockade of these receptors results in increased levels of ACh, and improvements in assays measuring cognition. Although a number of potent M_2 antagonists have been reported [5], only a few have shown selectivity versus other muscarinic receptor subtypes. The most interesting of these is BIBN-99 (Fig. 4), which produces release of ACh and improves learning ability in age-impaired rats after s.c. administration [4].

Agonist	Sponsor	Status	Efficacy*	Comments
Arecoline		P-II	Yes	Short half-life; discontinued
Xanomeline	Novo Nordisk / Lilly	P-III	Yes	GI side-effects; transdermal product under investigation
Milameline (CI-979; RU35926)	Parke-Davis / HMR	P-III	Yes	Non-selective agonist (M_1, M_2); discontinued
Sabcomeline (SB202026)	SmithKline Beecham	P-III	Yes	M_1 full agonist; M_2 partial agonist; discontinued
Cevimeline (FKS 508;AF102B)	Snow Brand / Teva / Forest	P-III	Yes	
Talsaclidine; (WAL 2014-FU)	Boehringer Ingelheim	P-III	Yes	GI side-effects; discontinued
Alvameline (Lu 25-109)	H. Lundbeck A/S / Forest	P-III	No	M_1 agonist; M_2/M_3 antagonist; discontinued
SR 46559A	Sanofi	P-II	-	Modest selectivity versus M_2/M_3 (M_2 antagonist)
YM-796	Yamanouchi	P-II	-	
CI-1017 (PD-151832)	Parke-Davis / Pfizer	P-II	-	Highly M_1 selective in vitro

* Reported to improve cognition or behavior as measured by standard scores (e.g. ADAS-Cog)

Fig. 3. Muscarinic M_1 agonists which have entered clinical studies.

Our goal at Schering-Plough was to identify a potent M_2 receptor antagonist with 100-fold selectivity versus the M_1 and M_3 receptors, and at least 30-fold selectivity versus the M_4 and M_5 receptors. Ideally, the antagonist would have high selectivity versus other G-protein-coupled receptors, and acceptable ($>20\%$) oral bioavailability in rats and monkeys, with plasma half-life sufficient to predict once-daily dosing in Alzheimer's patients. Modifications of a modestly potent, non-selective lead structure allowed SCH-57790 (Fig. 5) to be identified [6]. Oral administration of SCH-57790 in rats (10 mg/kg) causes the release of ACh [7], and produces activity in a rodent model of cognition (passive avoidance response — 'PAR') [8].

Following the discovery of a potent piperidinylpiperidine analog **1** [9], a diverse set of piperidine analogs was prepared in order to identify antagonists with improved selectivity. The result of this effort was the exceedingly potent and selective antagonist SCH-76050 (Fig. 6), which unfortunately displayed poor plasma levels in rats after oral administration [10]. Examination of metabolites found in rat bile demonstrated that extensive metabolism takes place at the methylenedioxy moiety, at the central piperidine ring and on the (2-methyl)benzoyl group. Further development of the piperidinylpiperidine series focused on reducing the rate of clearance by introduction of groups to block these sites of metabolism.

One successful direction involved introduction of a ketal group at the benzylic carbon atom of SCH-76050 and the replacement of the methylenedioxy group with a 4-methoxy substituent [11]. Of high interest was a series of antagonists which incorporate an anthranilic acid amide in place of the (2-methyl)benzoyl group of SCH-76050 [12]. One of these antagonists, SCH-217443, shows potency and selectivity which met our criteria (Fig. 7), and was chosen for further evaluation.

SCH-217443 showed excellent oral bioavailability in rats (80%, 10 mg/kg), with i.v. $t_{1/2} = 6$ h, and produced a dose-related (3, 10, 30 mg/kg) release of ACh in rats, as measured by microdialysis, after oral administration (vehicle = 0.4% methocel). Activity was demonstrated in a rodent model of cognition at low oral doses (0.001, 0.01, 0.1 mg/kg) [8]. It is known that M_2 receptors are present in cardiac tissue, where they are linked to heart rate. As expected, SCH-217443 (at doses of 3 mg/kg and above) increased heart rate in rats. It is important to note that this effect occurs at doses at least 30-fold higher than those active in cognition.

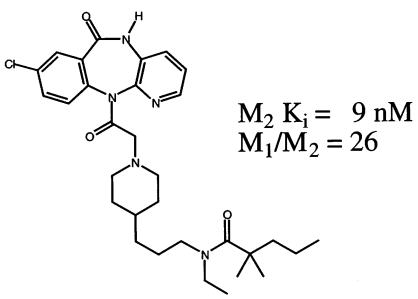


Fig. 4. M_2 antagonist BIBN-99.

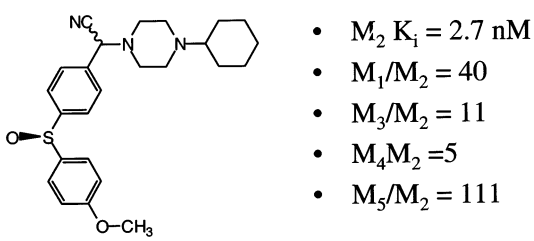
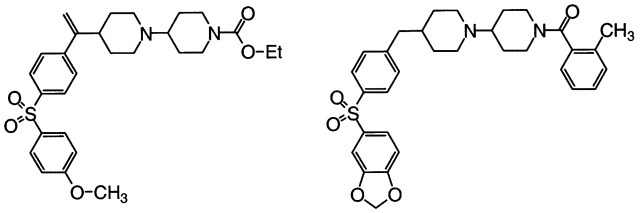


Fig. 5. SCH-57790.



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- M_2 K_i = 0.11 nM
- M_1 / M_2 = 59
- M_3 / M_2 = 34

SCH-76050

M_2 K_i = 0.02 nM

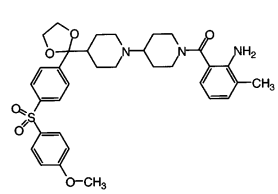
M_1 / M_2 = 1,400

M_3 / M_2 = 730

M_4 / M_2 = 37

M_5 / M_2 = 280

Fig. 6. Piperidinylpiperidine M_2 antagonists.



- M_2 K_i = 0.4 nM
- M_1/M_2 = 623
- M_3/M_2 = 250
- M_4/M_2 = 35
- M_5/M_2 = 58
- M_2 - K_b = 1 nM (adenylate cyclase inhibition)

Fig. 7. SCH-217443.

SCH-217443 is a potent and selective M_2 receptor antagonist which has promising pharmacokinetics and activity in an animal model of cognition. It is hoped that M_2 receptor antagonists such as SCH-217443 will prove to be of utility in the treatment of AD, either alone or in combination with AChE inhibitors.

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