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Review

Alzheimer's disease and age-related memory decline (preclinical)

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ABSTRACT

An unfortunate result of the rapid rise in geriatric populations worldwide is the increasing prevalence of age-related cognitive disorders such as Alzheimer's disease (AD). AD is a devastating neurodegenerative illness that is characterized by a profound impairment of cognitive function, marked physical disability, and an enormous economic burden on the afflicted individual, caregivers, and society in general. The rise in elderly populations is also resulting in an increase in individuals with related (potentially treatable) conditions such as "Mild Cognitive Impairment" (MCI) which is characterized by a less severe (but abnormal) level of cognitive impairment and a high-risk for developing dementia. Even in the absence of a diagnosable disorder of cognition (e.g., AD and MCI), the perception of increased forgetfulness and declining mental function is a clear source of apprehension in the elderly. This is a valid concern given that even a modest impairment of cognitive function is likely to be associated with significant disability in a rapidly evolving, technology-based society. Unfortunately, the currently available therapies designed to improve cognition (i.e., for AD and other forms of dementia) are limited by modest efficacy and adverse side effects, and their effects on cognitive function are not sustained over time. Accordingly, it is incumbent on the scientific community to develop safer and more effective therapies that improve and/or sustain cognitive function in the elderly allowing them to remain mentally active and productive for as long as possible. As diagnostic criteria for memory disorders evolve, the demand for pro-cognitive therapeutic agents is likely to surpass AD and dementia to include MCI and potentially even less severe forms of memory decline. The purpose of this review is to provide an overview of the contemporary therapeutic targets and preclinical pharmacologic approaches (with representative drug examples) designed to enhance memory function.

Contents

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1. Introduction

According to the United Nations (UN, 2007) the World Health Organization (WHO, 2008) and the United States Centers for Disease Control and Prevention (CDC, 2003), a combination of declining fertility and increasing life expectancies is a phenomenon that is resulting in an unprecedented growth of elderly populations worldwide. An unfortunate result of this trend is the concomitant rise in the number of people suffering from age-related forms of dementia such as Alzheimer's disease (AD). In the United States alone the number of individuals with AD could be considered epidemic at approximately 5.3 million (Hebert et al., 2003), and unfortunately, this number is expected to increase dramatically in the near future due to the number of aging baby boomers (CDC, 2007; Kinsella and He, 2009). This issue has many dimensions at both the individual level and on societies as a whole. On an individual level, AD significantly shortens life expectancy and it is one of the major causes of physical disability, institutionalization, and decreased quality of life among the elderly (reviewed Qiu et al., 2009). On a societal level, the marked rise in the number of dementia patients is likely to create an extraordinary (potentially unsustainable) economic burden and demand on social systems and health care-related institutions. It is also important to note that the population estimates (for AD) highlighted above do not include individuals with related (potentially treatable) conditions such as "Mild Cognitive Impairment" (MCI) which is characterized by a less severe (but abnormal) level of cognitive impairment (reviewed Petersen, 2004) and a high-risk for developing dementia (reviewed, Luck et al., 2010). Even in the absence of a diagnosable disorder of cognition (e.g., AD and MCI), the perception of increased forgetfulness and declining memory function is a clear source of distress, embarrassment, and low self esteem in the elderly (Imhof et al., 2006; Ohman et al., 2008, see also review, Ballard, 2010). Undoubtedly these factors have (at least in part) driven sales of over the counter nutritional supplements (e.g., ginkgo biloba and phosphatidyl serine) that promise improved memory function (now a billion dollar industry in the United States alone), despite the lack of any clear evidence of their effectiveness (Kennedy, 2004, see also review, Lanni et al., 2008).

Collectively, the information discussed above indicates that it is incumbent on the scientific community to develop safer and more effective pro-cognitive agents that could allow even the oldest in our societies to remain socially active and productive. The purpose of this review is to provide a brief overview of the contemporary therapeutic targets and preclinical pharmacologic approaches (with representative drug examples) designed to enhance memory function. The pharmacologic agents reviewed are not all-inclusive but represent examples from the more actively pursued (i.e., current) areas of investigation. The review does not address the wide variety of potentially exciting disease modifying (mechanism-based) treatments that are in development for AD based on the amyloid cascade hypothesis (vaccines, β and γ secretase inhibitiors), or therapies targeting tau and neurofibrillary tangle formation, neuroinflammation, etc.

2. Current treatments

Since the FDA approval of the acetylcholinesterase inhibitor (AChEI) tacrine in 1993, the primary therapeutic approach to the cognitive loss associated with AD (and other forms of dementia) has been that of a cholinergic replacement strategy. This approach is based on studies spanning more than 35 years in both humans and lower animals indicating that acetylcholine (cholinergic) pathways in the brain modulate a number of important processes including attention, working memory, and other aspects of cognition (reviewed, Terry and Buccafusco, 2003). Furthermore, the brains of cognitively impaired elderly patients and those who suffered from AD commonly exhibit damage or abnormalities in cholinergic pathways. Both postmortem and antemortem studies in aged humans and AD patients, as well as animal experiments (i.e., in aged animals and AD-related animal models) show decreased high affinity choline uptake; decreased acetylcholine synthesis and release, and decreased numbers of nicotinic and muscarinic acetylcholine receptors (Auld et al., 2002). Collectively such findings have led to the so called "Cholinergic Hypothesis of AD" (reviewed, Bartus, 2000). With the exception of the relatively recent FDA approval of the NMDA antagonist, memantine (see below) in the United States, only the clinical data derived from studies based on the cholinergic hypothesis (more specifically, with AChEIs) have provided convincing evidence of an adequate level of efficacy and reliability in AD balanced with an acceptable burden of side effects.

2.1. AChEIs

FDA-approved therapy with donepezil, rivastigmine, and galantamine is based on several large clinical studies in patients diagnosed with mild to moderate AD (Boada-Rovira et al., 2004; Mintzer and Kershaw, 2003; Raskind et al., 2000; Winblad et al., 2001). The compounds produced subtle but statistically significant cognitive improvements in the AD study patients. Further, there are some (albeit controversial) retrospective data to suggest that these agents may enhance activities of daily living and improve behavioral disturbances in AD (reviewed, Standridge, 2004). However, there are a number of limitations associated with AChEI's. This drug class can be associated with a number of peripheral side effects (e.g., nausea, vomiting, diarrhea, and tremors) and it is only effective in a limited number of patients. In addition, few would argue that the compounds in this class have potent neuroprotective activity, the ability to

preserve cognition over significant periods of time, or to prevent the inevitable outcome of the illness.

2.2. Memantine

Memantine, the other FDA-approved therapeutic agent for the cognitive symptoms of AD is a low to moderate affinity uncompetitive (open-channel) NMDA receptor antagonist which binds preferentially to the NMDA receptor-operated cation channels. These actions are believed support the therapeutic effects of memantine by combating the persistent activation of N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate in the brain, a process thought to contribute to the symptomatology of AD. Approval of memantine was based on three randomized, double-blind, placebo-controlled clinical trials in moderate to severe AD (reviewed, Thomas, 2009). The clinical data indicate that memantine is a relatively safe drug with few major side effects and a negligible risk of drug–drug interactions, but only small clinically-relevant effects on cognition, global functioning and activities of daily living have been observed, mainly in patients with moderate AD (reviewed, van Marum, 2009). Memantine is recommended both as monotherapy and in combination with AChEIs, and the later approach is very commonly used, despite a lack of clear evidence that one approach is superior to the other (reviewed, Thomas, 2009).

3. Novel cholinergic-based strategies

Please see Table 1 for a summary of the variety of cholinergic-based strategies for cognitive enhancement.

3.1. New AChEIs

There is a variety of compounds that have been synthesized as analogs of the currently marketed AChEIs, or as analogs of older AChEIs with well-characterized pharmacological profiles such as physostigmine (originally derived as an alkaloid of the Calabar bean). One such compound, TAK-147, is a derivative of donepezil which has been shown to produce pro-cognitive effects in rats performing a scopolamine reversal task in the Morris water maze (Xu et al., 2002; Chen et al., 2002). The compound has also shown cognitive enhancing effects in a rat based chronic cerebral ischemia cognitive deficit model similar to donepezil (Xu et al., 2002). TAK-147 has also been shown to ameliorate deficits induced by diazepam on passive avoidance and restore performance in a scopolamine deficit model in delayed-matching-to-position task in rats (Miyamoto et al., 1996). BZYX is another donepezil derivative with a dialkylbenzyl amine moiety from rivastigmine that was designed to function as a dual binding site AChE inhibitor (Sheng et al., 2009). This compound is capable of reversing scopolamine, $NaNO_2$, and ethanol induced deficits in rats in a radial arm maze (Zhang et al., 2009). Further, BZYX seems to have neuroprotective properties by scavenging reactive oxygen species produced by H_2O_2 and preventing the loss of mitochondria membrane potential (Zhang et al., 2009).

Phenserine, a derivative of physostigmine is a long-acting AChEI and has shown considerable cognitive enhancing abilities. In the Morris water maze, phenserine has displayed pro-cognitive properties in rats by significantly decreasing travel distance and lowering latencies to reach the platform (Janas et al., 2005). In a dog delayed-non-matching-to-sample task, phenserine has demonstrated the ability to reverse scopolamine induced deficits on task accuracies (Araujo et al., 2005; Studzinski et al., 2005). The compound has also been shown to enhance cognition in rats using a 14 unit T-maze by reducing the number of errors it took to complete the maze (Ikari et al., 1995). Interestingly, phenserine is also able to overcome deficits induced by the NMDA receptor antagonist 3-((±) 2-carboxypiperzin-4-yl) propyl phosphonic acid (CPP) in the same 14-unit T-maze (Patel et al., 1998). Similarly, eptastigmine, a derivative of physostigmine, and ganstigmine (CHF2819), a derivative of geneserine (a closely related compound to physostigmine), have both shown cognitive

Table 1
Cholinergic-based compounds.

Compound name	Receptor	Mechanism	References
AChE inhibitors			
TAK-147	AChE	Inhibitor	Xu et al. (2002a,b)
BZYX	AChE	Inhibitor	Sheng et al. (2009)
Phenserine	AChE	Inhibitor	Janas et al. (2005)
CHF2819	AChE	Inhibitor	Trabace et al. (2007)
Eptastigmine	AChE	Inhibitor	Imbimbo (2001)
Huperzine A	AChE	Inhibitor	Wang et al. (2010)
Loganin	AChE	Inhibitor	Lee et al. (2009)
NP-0361	AChE	Inhibitor	Buccafusco (2009)
Pseudoberberine	AChE	Inhibitor	Hung et al. (2008)
Memoquin	AChE	Inhibitor	Cavalli et al. (2007)
PMS777	AChE	Inhibitor	Bate et al. (2004)
Nicotinic			
SIB-1508Y	α4β2	Agonist	Schneider et al. (1999)
SIB-1553A	α2β4	Agonist	Scheider et al. (2003)
ABT-418	α4β2	Agonist	Prendergast et al. (1998a,b)
ABT-594	α4β2	Agonist	Buccafusco et al. (2007)
S-38232	α4β2	Agonist	Howe et al. (2010)
ABT-089	α4β2	Partial agonist	Decker et al. (1997)
Ispronicline/ AZD-3480	α4β2	Partial agonist	Gatto et al. (2004)
Varenicline/ Chantix®	α4β2/α7	Partial agonist/full agonist	Rollema et al. (2009)
GTS-21	α7	Partial agonist	Buccafusco and Terry (2009)
MEM-3454/ RG-3487	α7	Partial agonist	Callahan et al. (2006), Rezvani et al. (2009) and Wallace et al. (2011)
MEM-63908/ RG4996	α7	Partial agonist	Taly et al. (2009)
AZD-0328	α7	Partial agonist	Sydserff et al. (2009)
AR-R17779	α7	Agonist	Van Kampen et al. (2004)
S-24795	α7	Partial agonist	Lopez-Hernandez et al. (2007)
SSR-180711	α7	Partial agonist	Taly et al. (2009)
SEN12333 (WAY-317538)	α7	Agonist	Roncarati et al. (2009)
NS-1738	α7	Positive allosteric modulator	Timmermann et al. (2007)
Compound 6	α7	Positive allosteric modulator	Ng et al. (2007)
PNU-120596	α7	Positive allosteric modulator	Hurst et al. (2005)
2087101	α4β2/α7	Positive allosteric modulator	de Filippi et al. (2010)
Cotinine	α4β2/α7	nAChR desensitization	Buccafusco et al. (2009) and Terry et al. (2005a)
JWB1-84-1	α4β2/α7	nAChR desensitization	Buccafusco et al. (2009) and Sood et al. (2007)
JAY2-22-33	α4β2/α7	nAChR desensitization	Buccafusco et al. (2009) and Sood et al. (2007)
Muscarinic			
Talsaclidine	M1	Agonist	Clader and Wang (2005)
Xanomeline	M1	Agonist	Clader and Wang (2005)
Cevimeline/ AF102B	M1	Agonist	Fisher et al. (2002)
AF150(S)	M1	Agonist	Fisher et al. (1998)
AF267B	M1	Agonist	Caccamo et al. (2006)
CI-1017	M1	Agonist	Tecle et al. (2000)
WAY-132983	M1	Agonist	Bartolomeo et al. (2000)
EUK-1001	M1	Agonist	Cui et al. (2008a)
MCD-386	M1	Agonist	Buccafusco (2009)
AC-42	M1	Positive allosteric modulator	Spalding et al. (2006)
77-LH-28-1	M1	Agonist	Langmead et al.
TBPB	M1	Positive allosteric modulator	Jones et al. (2008)
SCH 57790	M2	Antagonist	Carey et al. (2001)
SCH 72788	M2	Antagonist	Lachowicz et al. (2001)
BIBN-99	M2	Antagonist	Rowe et al. (2003)

enhancing properties by reversing scopolamine induced deficits (Dawson et al., 1991; Rupniak et al., 1992; Trabace et al., 2007).

Huperzine A, another alkaloid, isolated from the Chinese herb *Huperzia serrata*, is a potent inhibitor of AChE and has been shown to have a pro-cognitive effect in a wide number of preclinical animal models including the Morris water maze task (Wang et al., 2006, 2010) and the radial arm maze task (Wang and Tang, 1998). The compound has also shown cognitive enhancing properties in a delayed response task in monkeys (Ye et al., 1999; Ou et al., 2001). Further, Huperzine A has been used to reverse scopolamine induced deficits (Wang and Tang, 1998; Gao et al., 2000) and produce pro-cognitive effects in aged rodents and monkeys (Ye et al., 1999; Ye et al., 2000). Two other compounds of interest are loganin, an iridoid glycoside isolated from the *Cornus officinalis* fruit and pseudoberberine, isolated from *Corydalis turtschaninovii*. Both are AChE inhibitors and have displayed cognitive enhancing properties (Hung et al., 2008; Lee et al., 2009). Loganin displays cognitive enhancing properties when tested in a scopolamine induced deficit reversal task using the Y-maze and passive avoidance task (Kwon et al., 2009). Loganin has also been shown to improve learning and spatial memory in rats tested in the Morris water maze task (Lee et al., 2009). Pseudoberberine has also been shown to reverse scopolamine induced cognitive impairments in mice in both a passive avoidance task and in a water maze task (Hung et al., 2008).

Recently there has been renewed interest in AChE inhibitors as they have been shown to modulate the processing of APP away from production of the toxic amyloid beta peptide (De Ferrari et al., 2001; Racchi et al., 2005; Peng et al., 2007; Rizzo et al., 2010). This has led to the synthesis of novel AChE inhibitors many of which hit multiple targets relevant to AD (Fernández-Bachiller et al., 2010; Mohamed and Rao, 2010; Huang et al., 2010; Kikuchi et al., 2010; de Los Ríos et al., 2010; Samadi et al., 2010; Pisani et al., 2010). Many of these compounds are still in their infancies, requiring much more thorough examination before they prove their worth in the treatment of AD. Still, expect to see more interest in this area of research as these AChE inhibitors, as well as their derivatives, continue to be tested in the months and years ahead.

3.2. Muscarinic acetylcholine receptor (mAChRs) ligands

mAChRs are metabotropic receptors that are coupled to G-proteins. Agonist binding to mAChRs results in decoupling of the G-protein prompting a signal transduction cascade that leads to either excitatory or inhibitory actions on the cell. There have been five types of mAChRs identified, labeled M1–M5 (Levey et al., 1991). The M1, M3, and M5 receptor subtypes are coupled to Gq proteins that activate the phospholipase C (PLC) pathway, which results in protein kinase C (PKC) activation leading to intracellular calcium release and excitatory actions on the cell. The M2 and M4 subtypes are coupled to Gi proteins that when activated inhibit adenylyl cyclase activity, resulting in a reduction of cAMP and inhibitory actions on the cell. The M1 receptor subtype has been the dominant target for cognition enhancement therapy, due to its wide expression in the cortex and hippocampus (Levey et al., 1991), and because the receptor subtype seems to be retained longer than other mAChRs in AD (Flynn et al., 1995).

3.2.1. Muscarinic receptor agonists

There have been numerous M1 receptor agonists evaluated in preclinical studies as possible treatments for cognitive impairment associated with AD and age-related memory decline (Clader and Wang, 2005). The first generation of M1 agonists were analogs of the mAChR agonist arecoline, a class of compounds that includes talsaclidine, sabomeline, xanomeline, and cevimeline, among others. Many of these compounds showed positive cognitive effects in preclinical tests. However, a lack of sufficient selectivity for the M1 receptor over the M3 and M5 receptors hindered further development efforts for many of these compounds for AD therapy, due to potential cholinergic side effects. Indeed, this problem has hindered much development of subtype selective mAChR agonists/antagonists, owing to the high amount of sequence homology shared by the orthosteric binding sites of mAChRs subtypes (Hulme et al., 1990). However, the M1 receptor continues to be an attractive target for cognition therapy.

Significant preclinical data supporting M1 receptors as valid targets for cognition enhancement were obtained through studies utilizing the "AF" compounds, a series of M1 partial agonists composed of derivatives of cevimeline. Early studies revealed that treatment with cevimeline, also known as AF102B, produced positive outcomes in a broad range of animal models of AD and cognitive impairment (Clader and Wang, 2005). The analogs developed from AF102B are more efficacious at M1 receptors with greater selectivity. Treatment with AF150(S) abolished cognitive impairments associated with ApoE knockout mice, a strain of mice that shows cognitive deficits resembling AD pathology (Fisher et al., 1998). Other studies with AF150(S) demonstrated memory and cognition improvements in young and old rodents in the delayed matching-to-position task, Morris water maze task, as well as the radial arm maze (Brandeis et al., 1999; Ruske and White, 1999). When administered to 3xTG-AD mice, a mouse model of AD characterized by Aβ plaque buildup, neurofibrillary tangles, and deficits in cognition, the compound AF267B recovered deficits in spatial working memory seen in the Morris water maze test after 2 months of treatment (Caccamo et al., 2006). Treatment with AF267B was also effective in reducing cognitive deficits in animals with lesions in the nucleus basalis (Beach et al., 2003). Other analogs of AF102B include AF125 and AF151 (Fisher et al., 1993). Adding to the appeal of these more selective M1 compounds was an apparent lack of peripheral side effects in preclinical models as well as a longer half life and high bioavailability (Fisher et al., 2002).

Efforts continue to develop newer, more selective M1 agonists for cognition therapy in AD that also have a low potential for undesirable peripheral cholinergic effects. A newly synthesized class of arecoline analogs, N-alkyl/aryl substituted thiazolidinone arecoline derivatives, showed significant affinity for M1 receptors, and improved scopolamine-induced impairments in the passive avoidance step down task and elevated plus maze transfer latency (Sadashiva et al., 2009). Other arecoline derivatives with M1 receptor selectivity are also currently being synthesized and tested in preclinical models of AD (Kumar et al., 2008; Malviya et al., 2008, 2009). The novel derivative of xanomeline, EUK1001, improved novel object recognition and fear cognition in a passive avoidance task in aged mice (Cui et al., 2008a; Si et al., 2010). EUK1001 was also shown to have higher affinity for M1 receptors than xanomeline coupled with a significantly lower side effect profile (Cui et al., 2008b). It will remain to be seen whether these newer compounds succeed in any clinical setting. However, a great promise still holds for compounds in this pharmacological class, assuming a given new molecular entity carries sufficient selectivity for M1 receptors over other mAChR subtypes.

3.2.2. Muscarinic receptor antagonists

Both in vitro and in vivo (e.g., $M2R^{-/-}$ knockout mice) studies suggests that M2 muscarinic receptors in the mammalian hippocampus and cortex serve as presynaptic autoreceptors mediating the inhibition ACh release. This evidence supports the hypothesis that antagonists at central M2 autoreceptors might enhance cognition by increasing synaptic acetylcholine levels (see Wess et al., 2007 for review). Consistent with this notion are studies indicating that specific M2 receptor-preferring antagonists such as SCH 57790, SCH 72788, and BIBN-99 can improve learning and memory-related tasks in animal models (Carey et al., 2001; Lachowicz et al., 2001; Rowe et al., 2003). However, $M2R^{-/-}$ mice were found to exhibit deficits in some cognitive tasks suggesting that complete pharmacological blockade of central M2 receptors might (in fact) have negative effects

on cognition (Tzavara et al., 2003). Several hypotheses have been proposed to explain these discrepant findings. One possibility is that the M2 receptor-preferring antagonists evaluated to date may only serve as partial antagonists of central M2 receptors. Another is that there are both presynaptic and postsynaptic M2 receptor-signaling pathways in the CNS that may have different sensitivities to the antagonists used (see Wess et al., 2007 for review). Thus, additional studies are needed to determine which strategy (M2 antagonism versus enhancement) will be likely to provide a therapeutic benefit in disorders of cognition.

3.2.3. Muscarinic positive allosteric modulators

The lack of sufficient selectivity of orthosteric ligands for targeted muscarinic receptor subtypes has driven research for compounds that act as positive allosteric modulators (PAMs) on the receptor, targeting binding sites away from the orthosteric site (see Nicotinic positive allosteric modulators section below for a complete discussion). There have been several mAChR PAMs that have been identified in in vitro studies (Jones et al., 2008; Conn et al., 2009). Many of these compounds have been reported as possessing very high selectivity for the targeted receptor. However, to date only a small number of these compounds have been studied in animal models for cognition enhancement, though promising results have recently been published (Bradley et al., 2010). With the continuing need for new therapies addressing the cognitive decline associated with AD and advanced age, these compounds in this class will surely garner much attention for future preclinical cognition studies.

3.3. Nicotinic acetylcholine receptor (nAChR) ligands

nAChRs are ionotropic receptors that open in response to agonist binding. The result of agonist binding to the receptor is the transfer of cations into, and out of, the cell, notably the influx of sodium and to a lesser degree calcium, and the efflux of potassium. The end result of nAChR activation is membrane depolarization. Nicotinic receptors are composed of five membrane-spanning subunits that form a pentameric arrangement around a water-filled pore (Jones et al., 1999; Karlin 2002; McGehee and Role, 1995). Neuronal nicotinic receptors are formed through a combination of α and β subunits composing heteromeric receptors, or through homomeric α configurations. Although there have been nine α (α2–α10) and three β (β2–β4) subunits currently identified that can form many different combinations, for the purposes of this review, the heteromeric α4β2 and homomeric α7 nAChR subtypes will be primarily discussed. These two subtypes have been the targets for the majority of cognition enhancing drugs for AD and age-related memory decline, as both subtypes are highly expressed in the cerebral cortex and hippocampus. Targeting other nAChR subtypes has been associated with efficacy and side effect issues, owing to their distribution in other brain areas such as the nucleus accumbens (Buccafusco, 2004).

3.3.1. Nicotinic receptor agonists

The ability of nicotine to improve cognition in animal models as well as in humans has been known for over two decades, and has been extensively studied and reviewed (Elrod et al., 1988; Levin, 2002; Murray and Abeles, 2002). However, the use of nicotine clinically for any purpose other than smoking cessation was severely limited by concerns over serious side effects (Benowitz, 1986). The goal for cognition enhancement through nAChRs is to develop receptor subtype selective agonists that do not possess the undesirable side effects accompanied by the use of nicotine, particularly the abuse and addiction potential. Compounds selective for the α4β2 subtype were the first to be developed for cognition enhancement and studied in preclinical studies.

Two of the first α4β2 agonists tested for cognition enhancement were SIBIA Neuroscience's SIB-1508Y and Abbott's ABT-418. These compounds showed great promise in pre-clinical animal models of cognitive impairment (Schneider et al., 1999; Prendergast et al., 1998a,b). However, a lack of selectivity for the α4β2 receptor hindered further development for these compounds. ABT-089, a follow-up compound to ABT-418, was shown to improve Morris water maze performance in aged rats, and when tested in young rats with septal lesions improved acquisition in a spatial discrimination water maze task (Decker et al., 1997). In the same study, ABT-089 improved cognitive performance in young and aged monkeys in the delayed matching-to-sample task. Although ABT-089 has less affinity for α4β2 nAChRs than either nicotine or ABT-418, the compound was shown to be as potent as nicotine in evoking hippocampal ACh release from rat synaptosomes (Sullivan et al., 1997). However, despite ABT-089's comparable effects to nicotine for ACh release, the compound does not share nicotine's potency at inducing dopamine release in the ventral tegmental area (VTA), perhaps owing to the compound's pharmacological profile as a partial agonist. ABT-594, an α4β2 agonist currently being studied for analgesic potential, was shown to improve delayed matching-to-sample task performance when studied in non-human primates (Buccafusco et al., 2007). The α4β2 partial agonist varenicline (Chantix®), already FDA approved for smoking cessation has also been considered a candidate for potential cognition enhancement. In pre-clinical tests, varenicline improved sustained attention task performance in rats, a model which tests top-down control of attention (Rollema et al., 2009). Deficits in top-down attention control are a prominent feature of age-related memory decline. Rats administered varenicline also demonstrated improvements in the novel object recognition task compared to vehicle treated animals in the same study. Ispronicline (AZD-3480), another α4β2 partial agonist, improved working memory in rodents, even after a single dose (Gatto et al., 2004). This improvement was observed for up to 18 h despite a half life of only 2 h, highlighting prolonged effects present even after elimination of the compound. Finally, a recently published study highlights the positive effects of the agonist S-38232 in a distractor version of the sustained attention task in rodents, though no effect was observed in a standard sustained attention task paradigm (Howe et al., 2010). These recent studies demonstrate the continuing appeal of targeting α4β2 nAChRs for cognition enhancement in preclinical research.

Compounds targeting the homomeric α7 nicotinic receptor subtype have yielded some promising results for cognition enhancement and are a major focus of current preclinical research (Leiser et al., 2009). The distribution of α7 nAChRs is limited primarily to the hippocampus, certain cortical layers, and the hypothalamus, making these receptors intriguing targets for cognition enhancement (Freedman et al., 1995). Activation of α7 nAChRs does not appear to be involved in the rewarding effects of nicotine, suggesting that targeting these receptors has limited abuse potential (Brioni et al., 1996). Also, while not the focus of this review, the extrasynaptic localization of α7 nAChRs suggests a role for the receptor subtype in cell viability. The α7 partial agonist and anabaseine synthetic derivative GTS-21 (3-[(2, 4 dimethoxy) benzylidene]-anabaseine, or DMXBA) is a well studied compound and was poised to perhaps become the first synthetic nicotinic compound to market for cognition enhancement. The compound has been shown in preclinical models to enhance cognitive processes, including studies in rodents and non-human primates (Buccafusco and Terry, 2009; Chen et al., 2010; Rodefer et al., 2007). This cognition enhancement by GTS-21 is accompanied by a low potential for side effects (Kem, 2000). What has made GTS-21 particularly interesting is the compound's relative specificity for cognition enhancement versus its inactivity in behavioral tasks in which nicotine is effective (Briggs et al., 1997). The most significant effects of GTS-21 reported to date have been observed in tasks of attention, working memory, and episodic secondary memory. The results of preclinical tests using compounds like GTS-21 have driven the development of newer, more selective α7 receptor agonists for use in

cognition enhancement. The Memory Pharmaceuticals (acquired by Roche) compound MEM 3454 (known as RG-3487) is an α7 nAChR partial agonist with 5-HT_3 receptor antagonist properties that has been shown to enhance task performance in young and aged-cognitively impaired rodents as well as young and aged non-human primates (Callahan et al., 2006; Wallace-Boone et al., 2009; Wallace et al., 2011) across multiple cognition domains (episodic, attention, executive function, spatial reference and working memory). RG-3487 was also shown to improve sustained visual attention in rodents, a property shared by nicotine but not galanthamine (Rezvani et al., 2009). Moreover, the improvements in cognitive performance were shown to be reflective of the observed increases in acetylcholine and dopamine efflux in cortical and hippocampal brain regions (Huang et al., 2006). These positive preclinical observations translated into significant improvements in cognition, as measured by the cognitive drug research (CDR) test battery in healthy human volunteers and mild to moderate AD subjects during phase I and phase IIA clinical testing (Callahan et al., 2006). Another α7 nAChR partial agonist from Memory Pharmaceuticals, MEM 64368, demonstrated robust cognitive enhancing properties in rodents and non-human primates (Rodefer et al., 2007; Wallace-Boone et al., 2007). This α7 nAChR partial agonist was characterized as a low intrinsic activity agonist (~30%) with moderate affinity (Ki ~ 300 nM) at α7 nAChR receptors compared to that of RG-3487 (Ki = 6 nM; intrinsic activity ~68%) and displayed a 10-fold selectivity for α7 nAChR over 5-HT_3 receptors (Wallace-Boone et al., 2007; Wallace et al., 2011). In addition, AstraZeneca's α7 nAChR compound AZD-0328 improved spatial working memory in mice in a novel object recognition task, an improvement that was partly attributed to enhanced midbrain and cortical dopamine release (Sydserff et al., 2009). The novel α7 agonist SEN12333 (WAY-317538) has also been shown to improve novel object recognition performance in rats (Roncarati et al., 2009). This improvement was observed even under scopolamine or MK-801-induced amnesia, representing relevant cholinergic and glutamatergic deficits commonly seen in AD. In the same study, SEN12333 recovered deficits in a passive avoidance task induced by scopolamine. Results similar to these have been observed in preclinical cognitive tests using a host of α7 nAChR agonists (Table 1).

3.3.2. Nicotinic positive allosteric modulators

Due to the historical difficulty in developing compounds with sufficient selectivity for the orthosteric ligand binding site of nAChR subtypes, there has been considerable interest directed toward allosteric modulators for targeting nAChRs. Positive allosteric modulators avoid direct receptor activation by utilizing binding sites away from the orthosteric site targeted by traditional agonists. Though allosterically-acting compounds have been more difficult to discover than compounds acting at orthosteric sites, the existence of these compounds has been known for several years and their use has recently been suggested as a favorable strategy for targeting nicotinic receptors (Albuquerque et al., 2009). The emergence of more advanced techniques for investigating molecular site interactions, as well as in silico screening of large compound libraries for receptor targets, has generated interest in this approach in certain drug discovery arenas. However, only a few compounds in this class have been studied in vivo. The drug galantamine, an acetylcholinesterase inhibitor currently in use for AD treatment, has also been demonstrated to act as a positive allosteric modulator of nAChRs (Coyle et al., 2007).

The allosteric potentiating ligands (APLs) of nAChRs that have been tested in preclinical memory and cognition models have demonstrated great potential for this class of compounds. The compound NS-1738, classified as an α7 selective positive allosteric modulator (PAM), recovered scopolamine-induced deficits in the Morris water maze task in rats as well as improving the animals performance in a social recognition model (Timmermann et al., 2007). The PAM known as compound 6 also targets α7 nAChRs, and when administered to rats significantly improved their performance in the radial arm maze task compared to vehicle treated control animals (Ng et al., 2007). Compound 6 also showed positive results in sensory gating deficits, a property shared by another nAChR PAM, PNU-120596 (Hurst et al., 2005).

3.3.3. Desensitization of nicotinic-acetylcholine receptors (nAChRs)

As is apparent in the preceding paragraphs, drug discovery efforts for pro-cognitive agents in the nicotinic field to date have focused on agonists, partial agonists and allosteric modulators (i.e., all efforts designed to increase activity of nAChRs). These approaches have (for the most part) been based on the idea that enhanced activity at nAChRs promotes the release of neurotransmitters in relevant brain regions which results in the desired behavioral effect (improved cognition). However, in a number of settings, nAChR agonists and antagonists can have very similar physiologic effects (see review, Buccafusco et al., 2009), and further, a large discrepancy often exists between the high concentrations of nicotinic drugs required to activate nicotinic responses in vitro and the lower doses used to induce various behavioral responses in vivo. Nicotine can both activate and desensitize its receptors over a relatively short time course leading to the question of whether (in fact) nAChR desensitization when compared to receptor activation, plays an equal if not more important role in the behavioral effects. Recent studies in our laboratories (Sood et al., 2007; Buccafusco et al., 2009) indicated that nicotine, the major nicotine metabolite, cotinine, and two novel analogs of choline, JWB1-84-1 [2-(4-(pyridin-3-ylmethyl)piperazin-1-yl)ethanol] and JAY2-22-33 [2-(methyl(pyridine-3-ylmethyl) amino)-ethanol], improved working memory in a delayed match to sample task (DMTS) in monkeys. JWB1-84-1 also reduced the number of errors involved in completing a radial arm water maze (RAWM) task in AD-Tg mice that over-express Abeta beginning around 7 months of age (Sood et al., 2007). The effectiveness of the four aforementioned compounds (nicotine, cotinine, JWB1-84-1 and JAY2-22-33) in the DMTS task was linearly related to their effectiveness in producing desensitization of a nAChR agonist response in rats. Only nicotine evoked an agonist-like action in these studies indicating that it is possible to develop new chemical entities (e.g., choline analogs and cotinine analogs) that have the ability to desensitize nAChRs without an antecedent agonist action. Since the side effects of nicotine (e.g., cardiovascular and gastrointestinal) are often associated with its agonist effects, such an approach could offer the advantage of better tolerability.

4. Phosphodiesterase inhibitors

Please see Table 2 for a summary of the variety of phosphodiesterase-based strategies for cognitive enhancement.

Initially, phosphodiesterase (PDE) inhibitors (e.g., papaverine) were examined for their ability to increase cerebral blood flow in an attempt to improve cerebral metabolism and thereby, improve cognitive function in aged patients (for review see Yesavage et al., 1979). More recently, research has concentrated on the ability of PDE inhibitors to modulate the second messenger molecules cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Eleven subclasses of PDE inhibitors (PDE1–PDE11) have been identified with most having one or more isoforms (e.g., PDE4A, PDE4B, PDE4C and PDE4D) and each isoform may have multiple splice variants (e.g., PDE4D1–PDE4D9). Overall, more than 100 human PDEs exist (Bender and Beavo, 2006). All PDEs have a common catalytic domain, but PDE4, PDE7 and PDE8 hydrolyze cAMP whereas PDE5, PDE6 and PDE9 hydrolyze cGMP. PDE1, PDE2, PDE3, PDE10 and PDE11 are capable of hydrolyzing both cAMP and cGMP. PDE inhibitors (PDE-I) increase intracellular levels of cAMP and/or cGMP which can lead to gene transcription by activating the CREP signaling pathways (Impey et al., 1996; Lu and Hawkins, 2002; Tully

Table 2
Phosphodiesterase inhibitors.

Compound name/ identifier	Reference
PDE2 inhibitors	
BAY 60-7550	Boess et al. (2004), Domek-Lopacinska and Strosznajder (2008), Rutten et al. (2007) and van Donkelaar et al. (2008)
PDE4 inhibitors	
HT-0712	Bourtchouladze et al. (2003)
L-454,560	Huang et al. (2007)
MEM1018	Zhang HT et al. (2005) and Zhang M et al. (2005)
MEM 1091	Zhang HT et al. (2005) and Zhang M et al. (2005)
Rolipram	Barad et al. (1998), Comery et al. (2005), Egawa et al. (1997), Gong et al. (2004), Rutten et al. (2007, 2008), Zhang and O'Donnell (2000) and Zhang et al. (2000)
PDE5 inhibitors	
Sildenafil	Devan et al. (2004, 2006), Domek-Lopacinska and Strosznajder (2008), Prickaerts et al. (2002, 2005), Rutten et al. (2008) and Shafiei et al. (2006)
Vardenafil	Prickaerts et al. (2002), Rutten et al. (2007) and van Donkelaar et al. (2008)
Zaprinast	Prickaerts et al. (1997) and Domek-Lopacinska and Strosznajder (2008)
PDE9 inhibitors	
BAY 73-6691	Van der Staay et al. (2008)
PDE10 inhibitors	
MP-10	Grauer et al. (2009)
Papaverine	Hebb et al. (2008) and Rodefer et al. (2005)
TP-10	Schmidt et al. (2008)

et al., 2003). Activation of the cAMP/PKA/CREB and cGMP/PKG/CREB pathway has been implicated in synaptic plasticity such as long-term potentiation (LTP) and cognitive function (Frey et al., 1993; Son et al., 1998; Blokland et al., 2006). Despite 11 subclasses of PDEs, research has focused on PDE2, PDE4, PDE5, PDE9 and PDE10 and their potential involvement in learning and memory processes (see Rose et al., 2005 and Reneerkens et al., 2009 for a comprehensive review). To date, BAY 60-7550 is the only known selective PDE2-I that has been tested in animal models of cognition. BAY 60-7550 increased CA1 hippocampal LTP without affecting basal synaptic transmission (Boess et al., 2004). This PDE2-I improved object recognition acquisition and consolidation memory in rats and mice as well as social recognition memory performance in rats (Boess et al., 2004; Domek-Lopacinska and Strosznajder, 2008; Rutten et al., 2007). Cognitive enhancing effects of BAY 60-7550 was also observed in aged-impaired 24 month old rats in the object recognition task (Domek-Lopacinska and Strosznajder, 2008) and was shown to reverse the object recognition memory deficits of acute tryptophan depletion in rats (van Donkelaar et al., 2008). Moreover, BAY 60-7550 reversed the NMDA antagonist MK 801-induced working memory deficit in the spontaneous alternation T-maze task in mice (Boess et al., 2004). Of the PDE subtypes, PDE4 has been extensively characterized. PDE4-Is selectively inhibit the hydrolysis of cAMP and strong evidence exists for the cAMP/PKA/CREB pathway in mediating the cognitive effects of PDE4-I (Rose et al., 2005; Tully et al., 2003). Rolipram has been the most extensively studied PDE4-I. Rolipram has been shown to facilitate hippocampal LTP function in young and aged rodents (Barad et al., 1998; Navakkode et al., 2004), reverse β-amyloid (Aβ1–42) peptide impairment (Vitolo et al., 2002) and counteract the inhibitory effects of high levels of Aβ on synaptic plasticity in the transgenic APP/PS1 mouse model of AD (Gong et al., 2004). Behaviorally, rolipram has shown improvements in object recognition, spatial reference, working and associative memory behavioral tasks in young and aged rodents (Bach et al., 1999; Barad et al., 1998; Monti et al., 2006; Ramos et al., 2003; Rutten et al., 2006, 2007) as well as improvements in working and executive memory function in young (Ramos et al., 2003; Rutten et al., 2008) but not aged adult monkeys (Ramos et al., 2003). Rolipram also restores working and reference memory in the radial arm maze task and associative memory in the passive avoidance task following administration of scopolamine (Egawa et al., 1997; Ghelardini et al., 2002; Imanishi et al., 1997; Zhang and O'Donnell, 2000), MK-801 (Zhang et al., 2000; Zhang HT et al., 2005; Zhang M et al., 2005), MAPK/ERK kinase (MEK) inhibition (Zhang et al., 2004) or anisomycin (Randt et al., 1982). Further, rolipram is capable of reversing cognitive impairments in genetic mouse models of human disorders such as Rubinstein–Taybi syndrome (Bourtchouladze et al., 2003) and AD (Gong et al., 2004; Comery et al., 2005). In addition to rolipram, several newly developed PDE4-Is have been evaluated for their potential involvement in learning and memory processes. HT-0712 has been shown to increase cAMP thereby enhancing the CREB signaling pathway leading to improved memory performance in young mice in the object recognition and fear conditioning tasks as well as aged mice in a trace conditioning behavioral task (Bourtchouladze et al., 2003; Helicon Therapeutics.com). Moreover, HT-0712, like rolipram, was shown to reverse the object recognition deficit in a genetic mouse model of Rubinstein–Taybi syndrome (Bourtchouladze et al., 2003). L-454,560 improved cognitive performance in the delayed matching to position (DMTP) version of the Morris water maze task (Huang et al., 2007). MEM 1018 and MEM 1091 were efficacious in reversing the MK-801-induced working and reference memory deficits in the rat radial arm maze and each compound antagonized the amnesic effect of MK-801 on passive avoidance behavior (Zhang HT et al., 2005; Zhang M et al., 2005). Although PDE5-Is were originally developed for the treatment of erectile dysfunction (e.g., sildenafil (Viagra), vardenafil (Levitra) and tadalafil (Cialis); Setter et al., 2005), recent preclinical evidence has suggested a potential role in cognition. PDE5-Is selectively inhibit the enzymatic activity of PDE5 leading to increase intracellular levels of cGMP (Bender and Beavo, 2006). PDE5-Is have been shown to enhance memory function in the object recognition task in rats (Domek-Lopacinska and Strosznajder 2008; Prickaerts et al., 2002; 2005; Rutten et al., 2007) and mice (Rutten et al., 2005). The PDE5-I sildenafil also improved executive memory performance in monkeys using the prefrontal cognition object retrieval paradigm (Rutten et al., 2008). In pharmacological deficit models, PDE5-Is, sildenafil and vardenafil, have reversed recognition, spatial and associative memory performance impairments produced by acute tryptophan depletion (van Donkelaar et al., 2008), nitric oxide synthase (NOS) inhibition (Devan et al., 2006; Prickaerts et al., 1997), scopolamine (Devan et al., 2004; Shafiei et al., 2006) and diabetic neuropathy (Patil et al., 2004). Currently, only two PDE9-Is, SCH 81566 and BAY 73-6691, have been reported and only BAY 73-6691 has been characterized in animal models of cognition (van der Staay et al., 2008). PDE9-Is, like PDE5-Is, inhibit the degradation of the second messenger cGMP. BAY 73-6691 treatment increased hippocampal LTP function in young and aged rats and produced pro-cognitive effects in the object recognition and social recognition tasks in rats and mice. Further, BAY 73-6691 reversed the scopolamine-induced passive avoidance deficit as well as the MK-801-induced deficit in the working memory T-maze task (van der Staay et al., 2008). Lastly, PDE10A-Is have been suggested as a target for cognition particularly in the treatment of cognitive dysfunction associated with schizophrenia (Rodefer et al., 2005). PDE10A-Is regulate the activity of both cAMP and cGMP and while PDE10A-Is like papaverine, TP-10 (Schmidt et al., 2008) and MP-10 (Grauer et al., 2009) possess greater pharmacological similarity to that of the traditional antipsychotics (Grauer et al., 2009; Schmidt et al., 2008), there is evidence for a role in modulating cognitive function. Papaverine has been shown to reverse the executive memory deficits of subchronic phencyclidine following washout in the attentional set-shifting paradigm which is a rodent model analogous to the Wisconsin Card Sorting task in humans (Rodefer et al., 2005). Further, papaverine, but not MP-10 enhanced object recognition memory

following a 48 h delay interval in rats (Grauer et al., 2009) and both compounds attenuated the MK-801-induced social odor recognition deficits in mice (Grauer et al., 2009). Despite these encouraging results following acute administration of PDE10A-I, chronic administration of papaverine to mice disrupted spatial reference memory and reversal learning using the Morris water maze task (Hebb et al., 2008).

Overall, the preclinical evidence clearly demonstrates that PDE-Is for the PDE2, PDE4, PDE5, PDE9 and PDE10 subclasses are involved in learning and memory processes. It is now up to the pharmaceutical industry to develop safe and viable compounds to assess these preclinical effects on cognition in clinical trials in humans.

5. Serotonin receptors

Please see Table 3 for a summary of the variety of serotoninergic-based strategies for cognitive enhancement.

Serotonin (5-hydroxytryptamine; 5-HT) receptor systems are expressed throughout the peripheral and central nervous systems and are involved in a multitude of physiological functions such as cardiovascular and gastrointestinal regulation, thermoregulation, affective disorders as well as learning and memory (Barnes and Sharp, 1999; Cassel and Jeltsch, 1995). Within the 7 classes of 5-HT receptors (5-HT_{1-7}) there are at least 13 distinct G protein-couple receptors (GPCRs) and one ligand-

Table 3
Serotoninergic-based compounds.

Compound name	Receptor	Reference
5-HT_{1A}		
8-OH-DPAT	Agonist	Meneses and Perez-Garcia (2007) and Ogren et al. (2008)
Buspirone	Partial agonist	Meneses (1999) and Ogren et al. (2008)
MDL 73005	Agonist	Bertrand et al. (2001)
S15535	Agonist	Millan et al. (2004)
Lecozotan/SRA-333	Antagonist	Schechter et al. (2005)
NAD-299	Antagonist	Luttgen et al. (2005) and Misane and Ogren (2003)
WAY 100635	Antagonist	Harder and Ridley (2000), Misane and Ogren (2003) and Pitsikas et al. (2003)
5-HT_{2A}		
WAY 101405	Antagonist	Hirst et al. (2008)
MDL 100,907	Antagonist	Meneses (1999), Roth et al. (2004), Williams et al. (2002) and Winstanley et al. (2003)
EMD 281014	Antagonist	Terry et al. (2005b)
Ketanserin	Antagonist	Levin and Rezvani (2007)
Mianserin	Antagonist	Roth et al. (2004)
5-HT_3		
DAU 6215	Antagonist	Pitsikas et al. (1993) and Pitsikas and Borsini (1996).
Granisetron	Antagonist	Naghdi and Harooni (2005) and Pitsikas and Borsini (1997)
Ondansetron	Antagonist	Arnsten et al. (1997), Barnes et al. (1990), Carli et al. (1997), Domeney et al. (1991) and Pitsikas and Borsini (1997)
RS-56812	Antagonist	Terry et al. (1996)
SEC 579	Antagonist	Meneses (1999)
WAY 100289	Antagonist	Hodges et al. (1995)
5-HT_4		
RS 67333	Partial agonist	Marchetti et al. (2004), Fontana et al. (1997), Kulla and Manahan-Vaughan (2002) and Levallet et al. (2009)
SC 53116	Partial agonist	Matsumoto et al. (2001)
SL 65.0155	Partial agonist	Hille et al. (2008), Moser et al. (2002) and Spencer et al. (2004)
BIMU1	Partial agonist	Galeotti et al. (1998)
VRX 03011	Partial agonist	Mohler et al. (2007)
RS 17017	Agonist	Terry et al. (1998)
GR 125487	Antagonist	Galeotti et al. (1998), Lamirault and Simon (2001) and Spencer et al. (2004)
RS 67532	Antagonist	Marchetti et al. (2004) and Fontana et al. (1997)
SDZ 205,557	Antagonist	Galeotti et al. (1998)
5-HT_6		
Ro-04-6790	Antagonist	King et al. (2004, 2005, 2009), Meneses (2001) and Woolley et al. (2004)
Ro-4368554	Antagonist	Schreiber et al. (2007)
SB 271046	Antagonist	Callahan et al. (2004), Foley et al. (2004), King et al. (2004), Loiseau et al. (2008), Marcos et al. (2008), Rodefer et al. (2008) and Routledge et al. (2000)
SB 357134	Antagonist	Rogers and Hagan (2001) and Stean et al. (2002)
SB 399885	Antagonist	Hatcher et al. (2005), Hirst et al. (2006) and Rowe et al. (2008)
SB 742457	Antagonist	Callahan et al. (2009), Maher-Edwards et al. (2010), Rowe et al. (2009) and Upton et al. (2008)
MEM 68626	Antagonist	Rowe et al. (2008)
MEM 34551	Antagonist	Rowe et al. (2008)
PRX-07034	Antagonist	Gannon et al. (2006)
SB 742457	Antagonist	Callahan et al. (2009), Maher-Edwards et al. (2010), Rowe et al. (2009) and Upton et al. (2008)
EMD 386088	Agonist	Kendall et al. (2010) and Meneses et al. (2008)
E-6801	Agonist	Kendall et al. (2010) and Romero et al. (2006)
R-13c	Agonist	Fone (2008)
WAY 181187	Agonist	Burnham et al. (2010), Callahan et al. (2009), Loiseau et al. (2008), Rowe et al. (2009), Schechter et al. (2008) and West et al. (2009)
WAY 208466	Agonist	Schechter et al. (2008)
SB 399885	Antagonist	Hatcher et al. (2005), Hirst et al. (2006) and Rowe et al. (2008)

gated ion channel (5-HT_3; Barnes and Sharp, 1999; Hannon and Hoyer, 2008). Several of the 5-HT receptor subtypes (i.e., 5-HT_{1A}, 5-HT_{2A}, 5-HT_3, 5-HT_4 and 5-HT_6) have been implicated in learning and memory processes (for review see King et al., 2008; Terry et al., 2008) and are expressed in key brain regions (e.g., amygdala, cortex, hippocampus and striatum) where they modulate the neurotransmitter release of acetylcholine, dopamine, GABA and glutamate and noradrenaline (Barnes and Sharp, 1999).

5.1. 5-HT_{1A} receptors

The 5-HT_{1A} receptor functions as both a somatodendritic inhibitory autoreceptor involved in raphe nuclei regulation as well as a postsynaptic heteroreceptor modulating neuronal release (Barnes and Sharp, 1999). For the most part, 5-HT_{1A} receptor agonists (e.g., 8-OH-DPAT and buspirone) have been shown to disrupt learning and memory processes (Meneses and Perez-Garcia, 2007; Ogren et al., 2008), although there are reports of 5-HT_{1A} receptor agonists (MDL 73005 and S15535) showing improvements in cognitive function (Bertrand et al., 2001; Millan et al., 2004). The real interest within 5-HT_{1A} receptor pharmacology stems from the observations that selective "silent" 5-HT_{1A} receptor antagonists (e.g., lecozotan (SRA-333), NAD-299, WAY 100635 and WAY 101405) reverse anatomical lesions (e.g., fornix and hippocampal) and pharmacological impairments (e.g., scopolamine and MK 801) as well as possess stand-alone improvements across a broad spectrum of behavioral models of cognition in rodents and non-human primates (Harder et al., 1996; Harder and Ridley, 2000; Hirst et al., 2008; Luttgen et al., 2005; Misane and Ogren, 2003; Pitsikas et al., 2003; Schechter et al., 2005). Although the exact mechanism underlying the observed pro-cognitive effects of 5-HT_{1A} receptor antagonists is not completely known, it is thought that modulation of cholinergic and/or glutamatergic transmission is involved. Interestingly, the 5-HT_{1A} receptor antagonist lecozotan (SRA-333) was shown to be safe and well tolerated in healthy young and elderly subjects (Patat et al., 2008) and a clinical phase II trial in mild to moderate AD patients was recently completed, though the outcome hasn't been reported (Sabbagh, 2009).

5.2. 5-HT_{2A} receptors

5-HT_{2A} receptors are expressed in brain regions (e.g., cortex, striatum and hippocampus) known to be involved in cognition and perception and $5HT_{2A}$ receptor antagonists appear to be involved in cognitive processes (Terry et al., 2005b; Williams et al., 2002; Winstanley et al., 2003). For example, medial prefrontal cortex infusions with the selective $5HT_{2A}$ receptor antagonist MDL 100,907 improved visuospatial attention and decreased impulsivity in the rat 5-choice serial reaction time task (Winstanley et al., 2003) and oral administration of the $5HT_{2A}$ receptor antagonist EMD 281014 improved medium and long retention interval performance in the delayed matching-to-sample task in young and aged rhesus monkeys (Terry et al., 2005b). However, the $5HT_{2A}$ receptor antagonist ketanserin failed to show improvements in the radial arm maze or operant signal detection task in rats and co-administration of ketanserin with either acute or chronic administration of nicotine attenuated the enhanced attentional performance produced by nicotine (Levin and Rezvani, 2007). Interestingly, the $5HT_{2A}$ receptor antagonists mianserin and MDL 100,907 have shown modest, but promising effects on cognition in schizophrenic patients (Roth et al., 2004). Additional research and interest from the pharmaceutical community is required to truly assess the potential of this drug target.

5.3. 5-HT_3 receptors

The 5-HT_3 receptor and in particular, 5-HT_3 receptor antagonists have also generated interest as putative cognitive enhancers given their ability to increase acetylcholine release (Diez-Ariza et al., 2002; Ramirez et al., 1996) and improve certain aspects of cognitive function (Meneses, 1999; Terry et al., 2008). Overall, 5-HT_3 receptor antagonists (e.g., DAU 6215, granisetron, ondansetron, RS-56812, SEC 579 and WAY 100579) appear to be efficacious in reversing pharmacologically-induced impairments (e.g., atropine, scopolamine and ibotenate acid forebrain lesions) as well as produce stand-alone improvements in cognitive function across multiple cognition behavioral models in young and aged rats (Barnes et al., 1990; Carli et al., 1997; Fontana et al., 1995; Hodges et al., 1995; Pitsikas and Borsini 1996; 1997; Pitsikas et al., 1993) and non-human primates (Arnsten et al., 1997; Barnes et al., 1990; Carey et al., 1992; Domeney et al., 1991; Terry et al., 1996). Despite these encouraging results, several studies have failed to support the pro-cognitive effects of 5-HT_3 receptor antagonists (Bratt et al., 1994; Naghdi and Harooni, 2005; Pitsikas et al., 1993; Pitsikas and Borsini, 1997). Whereas ondansetron was found to be inactive in an AD clinical trial (Dysken et al., 2002), a renewed interest has been initiated for the cognitive dysfunction associated with schizophrenia (Akhondzadeh et al., 2009; Zhang et al., 2006).

5.4. 5-HT_4 receptors

The concentration of 5-HT_4 receptors in limbic structures (e.g., cortex, amygdala, septum and hippocampus), along with modulation of cholinergic neuronal activity (Bockaert et al., 2004; Bonaventure et al., 2000; Vilaro et al., 2005) and neurochemical release of acetylcholine (Consolo et al., 2004; Matsumoto et al., 2001; Mohler et al., 2007) within these brain regions makes it an attractive target for restoration of cognitive dysfunction. 5-HT_4 receptors are positively linked to adenylate cyclase and activation leads to increased intracellular levels of cAMP, a fundamental component in synaptic long-term potentiation (LTP; Frey et al., 1993). Indeed, 5-HT_4 receptor partial agonists (e.g., RS 67333, SC 53116 and SL 65.0155) enhance the activity of cAMP (Eglen et al., 1995) facilitate hippocampal (Kulla and Manahan-Vaughan, 2002; Marchetti et al., 2004; Matsumoto et al., 2001) and amygdala LTP function (Huang and Kandel, 2007). Moreover, 5-HT_4 receptor agonists were capable of reversing hippocampal deficient LTP synaptic transmission in transgenic mice overexpressing the amyloid β peptide (Spencer et al., 2004). Behaviorally, 5-HT_4 receptor agonists produce pro-cognitive effects in animal models of learning and memory (King et al., 2008; Meneses, 1999). The 5-HT_4 receptor partial agonists (e.g., BIMU 1, SC 53116, RS 67333, SL 65.0155 and VRX 03011) have been shown to reverse the amnesic effects of scopolamine and atropine on passive avoidance and spatial navigation performance in rats and mice (Fontana et al., 1997; Galeotti et al., 1998; Matsumoto et al., 2001; Moser et al., 2002), enhance place and object recognition memory in young and aged rats (Lamirault and Simon, 2001; Levallet et al., 2009; Moser et al., 2002), enhance delayed spontaneous alternation behavior (Mohler et al., 2007) and reverse the aged related deficit observed in the linear maze in rats (Moser et al., 2002). Additionally, SL 65.0155 improved attentional performance in the rat 5-choice serial reaction time task (Hille et al., 2008) and RS 17017 enhanced attentional and working memory performance in young and aged monkeys in the delayed matching-to-sample task (Terry et al., 1998). The ability of selective 5-HT_4 receptor antagonists (e.g., GR 125487, RS 67532 and SDZ 205,557) to block the pro-cognitive actions of 5-HT_4 receptor agonists across several behavioral models strengthens the role of 5-HT_4 receptors in cognitive processes (Fontana et al., 1997; Lamirault and Simon, 2001; Moser et al., 2002). Lastly, synergistic effects with cholinesterase inhibitors (e.g., donepezil, galanthamine and rivastigmine) and 5-HT_4 receptor agonists have been observed in animal models of cognition (Cachard-Chastel et al., 2008; Mohler et al., 2007; Moser et al., 2002) suggesting therapeutic utility for AD. In addition to providing potential symptomatic relief, activation of the 5-HT_4 receptor in vitro stimulates the secretion of the soluble form of amyloid precursor protein (sAPPα), a neuroprotective protein in the brain (Lezoualc'h

2007; Robert et al., 2001) and in vivo, 5-HT_4 receptor agonists have been shown to increase sAPPα levels in cortex and hippocampus in young adult and transgenic APP-overexpressing mice (Cachard-Chastel et al., 2007; 2008). Taken together, these data provide strong preclinical support for 5-HT_4 receptor involvement in the treatment of AD symptomatology and pathology.

5.5. 5-HT_6 receptors

The 5-HT_6 G-protein coupled receptor was first cloned from rat striatum using RT-PCR techniques in the early 1990s and its activation stimulates cAMP production and protein kinase A (Kohen et al., 1996; Monsma et al., 1993; Ruat et al., 1993). 5-HT_6 receptor expression is almost exclusively within the central nervous system (CNS) thereby limiting any potential peripheral side effects. Receptor distribution resides within brain areas (e.g., striatum, cortex, hippocampus and hypothalamus) responsible for mediating many of its observed preclinical effects on anxiety and depression (Svenningsson et al., 2007; Wesolowska and Nikiforuk 2007), epilepsy (Routledge et al., 2000), obesity (Heal et al., 2008) and the current topic, learning and memory (Fone, 2008; King et al., 2008). Initial evidence supporting the involvement of 5-HT_6 receptors in cognitive processes was derived from the finding that receptor knockdown after intracerebroventricular treatment with 5-HT_6 receptor antisense oligonucleotides (AO) improved retention of the learned hidden platform position during probe trials in the water maze task in normal rats (Bentley et al., 1997; Woolley et al., 2001). The significance of this receptor blockade was later confirmed when administration of 5-HT_6 receptor antagonists Ro-04-6790, SB 271046 and SB 357134 led to improved probe trial, but not acquisition learning performance in normal adult rats (Marcos et al., 2008; Rogers and Hagan, 2001; Stean et al., 2002; Woolley et al., 2001). Conversely, in aged rats 5-HT_6 receptor antagonists are capable of enhancing both acquisition learning and retention probe trial performance (Foley et al., 2004; Hirst et al., 2006; Stean et al., 2002) suggesting that within the water maze task 5-HT_6 receptor antagonists may have a greater influence on declining cognitive function especially as it relates to cholinergic activity. Indeed, these aged-related findings were extended by classifying the aged rat population as either being aged cognitively-impaired or aged cognitively-unimpaired based upon their acquisition water maze performance to that of young adult rats (Rowe et al., 2007). In these cognitively-impaired aged rats, hippocampal acetylcholine levels are significantly decreased compared to their cognitively-unimpaired cohort and therefore, represent a model of "natural" aged-related cognitive decline, akin to that observed in humans suffering from Mild Cognitive Impairment (MCI) or AD (Quirion et al., 1995). Administration of 5-HT_6 receptor antagonists (e.g., MEM 68626, MEM 34551, SB 271046 and SB 742457) completely reversed the acquisition learning and probe retention trial water maze performance deficits observed in this aged cognitively-impaired cohort (Callahan et al., 2004; Rowe et al., 2008, 2009). SB 742457 and MEM 68626 were also shown to reverse the spatial working memory deficits of aged cognitively-impaired rats in the 8-arm radial water maze task (Rowe et al., 2008). Moreover, synergistic effects were demonstrated with a sub-threshold dose of the acetylcholinesterase inhibitor donepezil in combination with SB 271046 on spatial memory performance (Callahan et al., 2004), whereby the drug combination enhanced acquisition and probe trial performance of the aged cognitively-impaired animal over that performance observed for either drug given alone. These results suggest that 5-HT_6 receptor antagonists administered along with cholinesterase inhibitors may provided added beneficial effects in the treatment of cognitive dysfunction in humans. In addition to spatial reference and working memory improvements, 5-HT_6 receptor antagonists are active across multiple behavioral models reflecting various cognitive domains (e.g., episodic, associative, executive function, and working memory) and brain regions (e.g., cortical, hippocampal, striatal and amygdalar). 5-HT_6 receptor antagonists reverse pharmacologically-induced deficits (e.g., scopolamine, MK 801 and phencyclidine) as well as possess stand-alone effects in young and aged rats in the following tasks, object recognition (Callahan et al., 2004, 2009; Gannon et al., 2006; Hirst et al., 2006; King et al., 2004, 2005, 2009; Schreiber et al., 2007; Wolff et al., 2002), social recognition (Loiseau et al., 2008; Mitchell et al., 2006; Schreiber et al., 2007), social discrimination (Schreiber et al., 2007), operant autoshaping (Meneses 2001; Perez-Garcia and Meneses, 2005; Schreiber et al., 2007), passive avoidance (Bos et al., 2001; Callahan et al., 2004; Foley et al., 2004; Riemer et al., 2003; Schreiber et al., 2007), attentional set-shifting (Hatcher et al., 2005; Rodefer et al., 2008) and radial arm maze (Wolff et al., 2002). Moreover, the pro-cognitive effects observed in rodents have been extended to include non-human primates, though a limited number of studies of been published to date. SB 271046 was shown to improve accuracy in aged rhesus monkeys in the delayed matching-to-sample task and in marmosets, SB 271046 reversed the MK 801-induced deficits on both perceptual visual and visuospatial discrimination tasks (Upton et al., 2008). Many of the behavioral effects on cognition in young and aged animals can be attributed to the ability of 5-HT_6 receptor antagonists to increase the release of acetylcholine (Hirst et al., 2006; Riemer et al., 2003; Shirazi-Southall et al., 2002; Zhang et al., 2007), glutamate (Dawson et al., 2000; Dawson et al., 2001) and the monoamines (Lacroix et al., 2004; Li et al., 2007) in brain regions involved in learning and memory processes. Collectively, these preclinical findings along with the recent positive phase II clinical trial effects with SB 742457 in mild to moderate AD subjects (Maher-Edwards et al., 2010; Upton et al., 2008) suggest that 5-HT_6 receptor antagonists may be viable drug candidates for the symptomatic relief of cognitive dysfunction associated with age-related cognitive decline, AD and possibly, schizophrenia.

More recently, 5-HT_6 receptor agonists (e.g., EMD 386088, E-6801, R-13c, WAY 181187 and WAY 208466) have been identified (Cole et al., 2005; Mattsson et al., 2005; Romero et al., 2006; Schechter et al., 2008) and their potential involvement on cognitive processes assessed (Burnham et al., 2010; Callahan et al., 2009; Fone, 2008; Kendall et al., 2010; Loiseau et al., 2008; Meneses et al., 2008; Rowe et al., 2009). Initial studies have yielded controversy with reports showing pro-cognitive effects on attentional set-shifting (Burnham et al., 2010) and object recognition (Fone, 2008; Kendall et al., 2010) while others have demonstrated either cognitive impairment on social recognition (Loiseau et al., 2008) and autoshaping (Meneses et al., 2008) or no effects on cognition in object recognition, passive avoidance and water maze (Callahan et al., 2009; Rowe et al., 2009). In many cases, co-administration of a selective 5-HT_6 receptor antagonist has been used to either reverse the agonist-induced deficit (Loiseau et al., 2008) or agonist-induced improvement (Burnham et al., 2010). In the object recognition task, Kendall et al. (2010) showed that both 5-HT_6 receptor agonists and antagonists enhanced recognition memory at a 4 h delay and that combining sub-optimal doses of each led to enhanced memory performance, whereas Callahan et al. (2009) showed that object recognition memory was neither affected at a short 1 h delay or enhanced at a 48 h delay by the 5-HT_6 receptor agonist WAY 181187. Moreover, the pro-cognitive effect observed at the 48 h delay interval by the antagonist SB 742457 was dose-dependently blocked by co-administration of WAY 181187. Further, whereas SB 742457 dose-dependently reversed the age-related cognitive impairment in Fischer rats, WAY 181187 was ineffective in reversing the natural age-related cognitive deficit (Rowe et al., 2009). Given that these investigators have shown pro-cognitive effects with 5-HT_6 receptor antagonists (as well as other drug classes) in the same behavioral models used to characterize 5-HT_6 receptor agonists, simply stating methodological differences across laboratories appears to be an unlikely reason for the present disparity. Additionally, one might argue that the differences stems from the use of non-selective 5-HT_6 receptor agonists, however many of the investigators have used the same 5-HT_6 receptor agonist, WAY 181187 (Burnham et al., 2010; Callahan et al., 2009; Loiseau et al., 2008; Rowe et al., 2009), although a few have reported on less well characterized compounds (e.g., EMD 386088, E-6801 and R-13c; Fone, 2008; Kendall et al., 2010; Meneses et al., 2008) especially with respects to

neurochemical profiling. For example, the high affinity and receptor selective 5-HT_6 agonist WAY 181187 has been showed to increase GABA release in rat frontal cortex, hippocampus, striatum and amygdala. Effects that are blocked by SB 271046 administration (Schechter et al., 2008), thus supporting the proposed disinhibitory action by 5-HT_6 receptor antagonists on cholinergic and glutamatergic activity. WAY 181187 has also been shown to decrease dopamine and serotonin release in rat cortex and striatum and inhibit potassium-stimulated glutamate release from hippocampal slices (Schechter et al., 2008), effects opposite to 5-HT_6 receptor antagonists. Additionally, WAY 181187 has been shown to attenuate CA1 hippocampal LTP function, an effect blocked by SB 399885 (West et al., 2009). Generally, pro-cognitive drugs (e.g., 5-HT_4 receptor agonists, Matsumoto et al., 2001) enhance LTP activity which represents the synaptic basis for learning and memory (Bliss and Collingridge, 1993). Taken together, these data suggest that 5-HT_6 receptor agonists would either have no effect on cognition or impair cognitive performance. Conversely, it's been argued that the cognitive enhancing properties of 5-HT_6 receptor agonists occur by direct activation of 5-HT_6 receptors located on cholinergic and/or glutamatergic neurons, however autoradiography (Roberts et al., 2002), immunohistochemical (Woolley et al., 2004) and cholinergic lesion studies (Marcos et al., 2006) suggest little 5-HT_6 receptor expression on cholinergic neurons (as well as glutamate neurons) and that the observed increase in acetylcholine and glutamate release by 5-HT_6 receptor antagonists is due to an indirect disinhibitory effect on GABAergic neurons. If 5-HT_6 receptor agonists directly modulate cholinergic and/or glutamatergic release then microdialysis studies will provide the much needed proof of concept for the proposed mechanism of action. Alternatively, 5-HT_6 receptor agonists could be activating second messenger intraneuronal signaling cascades such as cAMP and/or cGMP which are widely known to be involved in learning and memory processes (Reneerkens et al., 2009; Rose et al., 2005). 5-HT_6 receptors are functionally coupled to cAMP and agonists would be expected to facilitate cAMP production triggering downstream protein kinase A (PKA) or mitogen-activated protein (MAP) kinase activity thereby leading to activation of transcription factor cAMP-response element binding protein (CREB) and subsequently gene expression and protein synthesis which is necessary for long-term memory formation (Tully et al., 2003). 5-HT_4 receptors, like 5-HT_6 receptors, trigger this cAMP/PKA signaling pathway which is regulated by phosphodiesterases (PDEs) and it was recently demonstrated that the cognitive improvement in object recognition memory by the 5-HT_4 receptor agonist RS 67333 was due to a direct stimulation of prefrontal cortex and hippocampal PDE activity (Levallet et al., 2009). It is therefore plausible to suggest that the observed pro-cognitive effects associated with 5-HT_6 agonists may involve modification of this second messenger system and in particular, PDE activity. Similar studies will need to be executed with 5-HT_6 agonists to verify this potential mechanism of action.

6. Histamine H_3 receptor antagonists

Histamine is an important neurotransmitter involved in many physiological functions (e.g., allergies, gastric acid secretion, immunomodulation and neurotransmitter release; Leurs et al., 2005). Histamine exerts its effects through four G-protein-coupled histamine receptor subtypes (H1, H2, H3 and H4).The histamine H3 receptor (H3R) and, in particular, H3R antagonists are being pursued as potential drug targets for the treatment of cognitive dysfunction associated with age-related cognitive decline, AD, attentional deficit hyperactivity disorder (ADHD) and schizophrenia (Esbenshade et al., 2008; Witkin and Nelson, 2004). H3Rs are expressed almost exclusively in mammalian brain with high densities in cortex, hippocampus, striatum and hypothalamus, areas involved in wakefulness, attention, vigilance and cognition (Martinez-Mir et al., 1990; Pollard et al., 1993). H3Rs are presynaptic autoreceptors that regulate the synthesis and release of histamine from histaminergic neurons (Arrang et al., 1983; 1987). H3Rs also function as heteroreceptors and mediate the release of not only histamine but other neurotransmitters such as acetylcholine, dopamine, noradrenaline and serotonin (Leurs et al., 2005; Schlicker et al., 1994) and inhibition of H3Rs with selective antagonists can augment the release of neurotransmitters involved in cognition. (Fox et al., 2005; Galici et al., 2009; Medhurst et al., 2007a). Due to the high constitutive activity of native H3Rs and the ability of H3R antagonists to inhibit G-protein-coupled receptor signaling, some H3R antagonists have been termed "inverse agonist" (e.g., ciproxifan, thioperamide, ABT-239, BF 2.649, and GSK 189254; Fox et al., 2005; Leurs et al., 2005; Ligneau et al., 2007; Medhurst et al., 2007a), however, not all H3R antagonists show this intrinsic activity and are considered to be "neutral" antagonists (e.g., JNJ-5207852; JNJ-10181457; Barbier et al., 2004; Galici et al., 2009) (Table 4).

In preclinical behavioral models of cognition, a variety of H3R antagonists have proven to be efficacious in restoring and/or enhancing cognitive performance (for comprehensive reviews see Esbenshade et al., 2008; Leurs et al., 2005; Witkin and Nelson 2004). For example, studies with the first generation H3R antagonists such as thioperamide, ciproxifan or clobenpropit were shown to reverse passive avoidance (Giovannini et al., 1999; Miyazaki et al., 1997), object recognition (Giovannini et al., 1999; Pascoli et al., 2009), two-choice discrimination water maze, Barnes maze (Komater et al., 2005) and radial arm maze (Chen, 2000) impairments produced by scopolamine treatment. Additional support for cholinergic modulation came from the observation that newly developed H3R antagonists like BF 2.649, GSK 207040, GSK 334429, GSK 189254 and JNJ-10181457 were also efficacious in reversing scopolamine-induced passive avoidance (Medhurst et al., 2007a,b), object recognition (Ligneau et al., 2007) and delayed non-matching to position (DNMTP; Galici et al., 2009) performance deficits. Working and reference memory deficits produced by MK-801 administration have also been attenuated by clobenpropit in the rat radial arm maze task suggesting an interaction of histamine on NMDA function (Huang et al., 2004). H3R antagonists are also capable of enhancing cognitive performance of young and aged animals in the absence of pharmacological impairment. Administration of ciproxifan has been shown to improve attention and decrease impulsivity in the rat 5-choice serial reaction time test (5-CSRTT) which is analogous to the continuous performance test (CPT) widely used to assess attention in humans (Day et al., 2007; Ligneau et al., 1998). Thioperamide, BF 2.649 and GSK 189254 have been shown to enhance object recognition memory in young rats and mice when drug is given prior to training (Ligneau et al., 2007; Medhurst et al., 2007a; Rowe et al., 2006) but a recent report by Pascoli et al. (2009) using ciproxifan and thioperamide showed that recognition memory was only enhanced when drug was given immediately before the retention test session. The authors indicated that the H3R antagonists were unable to enhance recognition memory when the drugs were given prior to or immediately after the training trial. Additional work is required to clarify these observed differences. The H3R antagonists A-304121, A-317920, ABT-239 and JNJ-10181457 improved attention in a repeated acquisition inhibitory avoidance task in spontaneously hypertensive (SHR) rat pups (Bonaventure et al., 2007; Fox et al., 2003, 2005) and A-304121, A-317920 and ABT-239 also improved short-term memory recall in young adult (Fox et al., 2003, 2005) and aged rats (Fox et al., 2005) with a potency similar to that of ciproxifan. ABT-239 was also able to reverse the scopolamine-induced spatial memory deficit in a two-choice discrimination water maze task (Fox et al., 2005). Similarly, GSK 189254 improved water-maze acquisition latency and probe trial performance in aged rats (Medhurst et al., 2007a). Moreover, when aged rats are screened and classified as either aged cognitively-impaired or aged cognitively-unimpaired based upon their water-maze acquisition latency performance to that of young rats and testing occurs in the aged cognitively-impaired cohort, the H3R antagonist thioperamide is capable of completely reversing the acquisition latency and probe trial performance deficits (Rowe et al., 2006). Rowe et al. (2006) extended this positive effect of thioperamide on cognitive restoration of spatial memory in aged cognitively-impaired

Table 4
Histamine (H_3) receptor ligands and miscellaneous categories.

Compound name	Receptor/mechanism	Reference
H_3 receptor ligands		
Ciproxifan	Inverse agonist/antagonist	Day et al. (2007), Ligneau et al. (1998) and Pascoli et al. (2009)
Thioperamide	Inverse agonist/antagonist	Giovannini et al. (1999), Meguro et al. (1995) and Rowe et al. (2006)
ABT-239	Inverse agonist/antagonist	Esbenshade et al. (2008) and Fox et al. (2005)
BF 2.649	Inverse agonist/antagonist	Ligneau et al. (2007)
GSK 189254	Inverse agonist/antagonist	Medhurst et al. (2007a)
GSK 207040	Antagonist/antagonist	Medhurst et al. (2007b) and Southam et al. (2009)
GSK 334429	Antagonist/antagonist	Medhurst et al. (2007b)
JNJ-5207852	Neutral antagonist	Barbier et al. (2004) and Bonaventure et al. (2007)
JNJ-10181457	Neutral antagonist	Bonaventure et al. (2007)
Clobenpropit	Inverse agonist/antagonist	Giovannini et al. (1999) and Huang et al. (2004)
A-304121	Inverse agonist/antagonist	Esbenshade et al. (2008) and Fox et al. (2003)
A-317920	Inverse agonist/antagonist	Esbenshade et al. (2008) and Fox et al. (2003)
ABT-239	Inverse agonist/antagonist	Esbenshade et al. (2008) and Fox et al. (2005)
Multi-functional compounds		
Ladostigil	AChEI/MAOI	Reviewed, Buccafusco (2009) and reviewed, Youdim and Buccafusco (2005)
Dimebolin	AChEI/ NMDA, H_3, and $5HT_6$ antagonist	Bachurin et al. (2001), Grigorev et al. (2003) and Schaffhauser et al. (2009)
JWS-USC-75IX	AChEI/M_2 antagonist	Terry et al. (1999) and Terry et al. (2011)
Memoquin	AChEI/coenzyme Q activity	Cavalli et al. (2007) and Bolognesi et al. (2009)
PM5777	AChEI/platelet activating factor inhibitor	Li et al. (2006)
Other agents and targets		
EVP 0334	HDAC inhibitor	Hahnen et al. (2008)
	Angiotensin converting enzyme inhibitiors and receptor blockers	Reviewed, Gard and Rusted (2004)
	Glycine transporter, mGluR2/3, somatostatin receptor, estrogen receptor, D2 receptor, calcium channels α receptors, and GABA	Reviewed, Buccafusco et al. (2009)

mice and thioperamide also improved avoidance learning in senescence-accelerated mice (Meguro et al., 1995). In addition to the positive behavioral effects of H3R antagonists across multiple cognitive domains and the therapeutic possibilities to treat ADHD, age-related cognitive decline, AD and various sleep disorders, H3R antagonists may also play an important role in the treatment of schizophrenia. H3R antagonists have been demonstrated to reduce the hyperlocomotor effects of dopamine agonists (e.g., amphetamine, apomorphine and methamphetamine; Akhtar et al., 2006; Clapham and Kilpatrick, 1994; Fox et al., 2005), reduce apomorphine-induced climbing behavior (Akhtar et al., 2006) and in some cases (Akhtar et al., 2006; Pillot et al., 2002) but not all (Zhang HT et al., 2005; Zhang M et al., 2005) potentiate the cataleptic effects of antipsychotics. H3R antagonists have also been shown to reverse the inherent sensorimotor gating deficits of DBA/2J mice in prepulse inhibition of startle (PPI; Browman et al., 2004) and hippocampal N40 sensory gating (Fox et al. 2005). Additionally, the H3R antagonist GSK 207040 attenuated the isolation rearing-induced deficit in PPI in rats (Southam et al., 2009) and GSK 189254 enhanced cognitive flexibility and executive memory function in the attentional set-shifting paradigm (Medhurst et al., 2007a). Taken together, these data strongly support a role for H3R antagonists in modulating the neurophysiological attributes associated with schizophrenia.

7. Multiple drug targets and multifunctional compounds

In complex illnesses such as AD, it could be argued that a multiple drug target approach to therapy is necessary to address the complex pathophysiology of the disease and its diverse symptoms. However, even if the strategy of combining drugs with different therapeutic targets is feasible, the development of multi-functional compounds would circumvent the challenge of administering multiple drugs with potentially different degrees of bioavailability, pharmacokinetics, and metabolism (reviewed, Youdim and Buccafusco, 2005). An additional advantage to single drugs with multiple actions is the simplification of the therapeutic regimen and improved compliance (an important consideration, especially for individuals who suffer from memory-related disorders). Another advantage is the potential to treat multiple symptoms including both cognitive deficits and non-cognitive behavioral symptoms. This is especially important given that the currently available AD therapeutic agents (in addition to modest efficacy and adverse side effects), do not effectively treat the very problematic non-cognitive behavioral symptoms (e.g., agitation) of the illness. Such behavioral symptoms are thus; often managed clinically by potent antipsychotic drugs which are particularly problematic in older patients since they are associated with movement disorders and/or a wide variety of metabolic abnormalities (e.g., weight gain, hyperglycemia, and hyperlipidemia, reviewed, Miyamoto et al., 2005) as well as an increase in mortality (Ballard et al., 2009). Thus, a compound exhibiting pro-cognitive and antipsychotic properties might be specialty valuable in AD as well as conditions like schizophrenia which is characterized by abnormal behavioral symptoms as well as cognitive deficits. There would also be a number of advantages to an agent that exhibits both pro-cognitive and neuroprotective activity or other disease modifying action. The obvious advantages would be enhanced cognition (and improved day to day quality of life) while at the same time delaying or preventing the progression of the illness (properties not observed in the currently available therapies). One potential advantage of a multifunctional compound over a disease-modifying agent that has no acute pro-cognitive actions pertain to the design and length of clinical trials (reviewed, Buccafusco, 2009). Clinical trials of disease modifying agents (by definition) require long evaluation periods which are often

cost-prohibitive. A pro-cognitive compound (with disease-modifying actions) could be approved for cognition enhancement in shorter clinical trials, providing a return on the manufacturer's investment while the more lengthy evaluations of disease-modifying actions could be carried out.

7.1. Ladostigil

Ladostigil is a multi-functional compound designed to incorporate the cognitive enhancing properties of rivastigmine (Ohara et al., 1997; Ballard and McAllister, 1999; Wesnes et al., 2002) with the neuroprotection properties of rasagiline (Maruyama et al., 2001; Weinreb et al., 2004). As such, the carbamate moiety of rivastigmine was introduced in the 6 position of rasagiline and a compound conveying inhibition at both acetylcholinesterase and monoamine oxidase (MAO) was born (Weinstock et al., 2000; Sterling et al., 2002; Buccafusco et al., 2003). MAO is a family of enzymes which catalyze the oxidation of biogenic amine neurotransmitters such as norepinephrine, dopamine and 5-HT. Ladostigil is a brain specific inhibitor of MAO-A and MAO-B and has thus been linked to an increase norepinephrine, dopamine and 5-HT levels in the brain after administration (Buccafusco et al., 2003; Sagi et al., 2003; Weinstock et al., 2003). Because of this MAO inhibition, ladostigil has been shown to be effective in animal models to assess antidepressant activity. (Weinstock et al., 2002) More importantly to the treatment of AD, ladostigil has been shown to be neuroprotective similar to other MAO inhibitors (Weinstock et al., 2001; Yogev-Falach et al., 2002; Sagi et al., 2003). Another interesting neuroprotective property of ladostigil centers on its ability to modulate APP processing through mitochondrial membrane potential stabilization and regulation of PKC and mitogen-activated protein kinase (MAPK) dependant signaling pathways (Yogev-Falach et al., 2002; Weinreb et al., 2008; Bar-Am et al., 2009) to reduce the production of neurotoxic amyloid beta (Yogev-Falach et al., 2006). Ladostigil also increases catalase activity and has thus been shown to protect against oxidative stress related apoptosis (Weinreb et al., 2008). Further, ladostigil can convey neuroprotection by increasing brain-derived nerve factor (BDNF) mRNA expression and production (Van der Schyf et al., 2007). Ladostigil has also shown pro-cognitive effects in a wide range of preclinical animal models (Buccafusco et al., 2003; Shoham et al., 2007; Luques et al., 2007; Weinstock et al., 2009) Administration of ladostigil was capable of preventing glial activation and cognitive deficits in object and place recognition tasks in a streptozotocin (STZ) model of AD (Shoham et al., 2007). More recently, ladostigil has been shown to enhance spatial memory in the Morris water maze by increasing proNGF, prevent age related increases in activation of astrocytes and microglia, and prevent age related reductions in cortical AChE activity in the hippocampus of aged rats. (Weinstock et al., 2009) Ladostigil has also shown pro-cognitive effects in a delayed matching-to-sample (DMTS) distracter task, as well as a DMTS titrating task in monkeys (Buccafusco et al., 2003). Similarly, ladostigil has shown positive cognitive effects in a cytochrome oxidase model of AD by preventing the decrease in choline acetyltransferase (CHaT) and restoring memory deficits in a object recognition task (Luques et al., 2007). Due to ladostigil's positive effects on such a wide range of Alzheimer's related targets (i.e. neuroprotective activity, regulatory effects on APP processing, stimulatory effects on PKC and MAPK, and effects on BDNF production), it is easy to see why taking a more encompassing approach in future drug design could be beneficial in AD drug development.

7.2. Dimebolin

Dimebolin originally developed and used for its anti-histaminergic properties since the early 1980s in Russia, has recently enjoyed a new found interest as a potential treatment for AD. Dimebolin is a multifunctional drug enjoying a broad range activity profile on many targets relating to the treatment of AD. Dimebolin is a weak acetylcholinesterase ($IC_{50} = 7.9\ \mu M$) and butyrylcholinesterases ($IC_{50} = 42\ \mu M$) inhibitor (Bachurin et al., 2001). The compound also displays antagonistic properties at the glutamatergic NMDA (Bachurin et al., 2001; Wu et al., 2008) receptor and has shown positive modulation of glutamate AMPA receptors (Grigorev et al., 2003). Further, dimebolin administration is able to protect neurons from the damaging effects of excessive cell stimulation through antagonistic action ($IC_{50} = 50\ \mu M$) at L-type Ca^{2+} channels (Lermontova et al., 2001). Dimebolin is also an antagonist to the brain 5-HT_6 receptor and has been shown to improve social recognition memory similar to other 5-HT_6 receptor antagonists (Schaffhauser et al., 2009). Dimebolin has also shown to be neuroprotective through attenuating amyloid beta induced neurotoxicity in rat cortical neuron cultures (Lermontova et al., 2001) and through its regulation of mitochondrial pores after neurotoxic insult (Bachurin et al., 2001). Dimebolin has also shown pro-cognitive effects on behavior in a senescence-accelerated mouse prone 10 (SAMP 10) model of aging by enhancing short-term memory assessed by a passive avoidance task (Grigorev et al., 2003, 2009). Similarly, the compound has been shown to improve cognition in a rat novel object recognition task by improving retention punitively through 5-HT_6 receptor antagonism. However, the exact mechanism through which dimebolin produces its cognitive enhancing effects is not know. Still dimebolin is active at many targets (AChE inhibition, NMDA antagonism, H_3 receptor antagonism, and 5-HT_6 receptor antagonism) that related to cognitive enhancement and has shown positive results in several preclinical models of cognition as well as in AD patients (Doody et al., 2006) Other reports have failed to see this improvement in AD patients treated with dimebolin (Miller, 2010). Whether or not dimebolin will prove itself as a viable treatment for AD is still uncertain. However, there remains an active interest in finding multi-functional drugs to treat AD.

7.3. JWS-USC-75-IX

Several years ago, our collaborators (Valli et al., 1992) synthesized a series of analogs of the ranitidine (an H_2 antagonist commonly used to treat duodenal ulcers) for the purpose of creating non-toxic AChEIs. The impetus for this work was the prior observation that ranitidine (a histamine H_2 antagonist commonly used to treat duodenal ulcers) had mild AChEI properties in vitro (Gwee and Cheah, 1986). Several of the compounds from this series of ranitidine analogs were subsequently found to possess potent AChEI properties as well as low toxicity profiles. Of this series, one compound, JWS-USC-75-IX (3-[[[2-[[(5-dimethylaminomethyl)-2-furanyl]methyl]thio]ethyl]amino]-4-nitropyridazine) was found to possess AChEI activity in vitro ($IC_{50} \sim 0.47\ \mu M$) as well as potent M_2 receptor antagonist activity in mouse cerebral cortex ($IC_{50} \sim 60$ nM). As had been suggested previously (Quirion, 1993; Mash et al., 1985), an M_2 (autoreceptor) antagonist might be very useful given in conjunction with an AChEI in AD to prevent the acetylcholine from decreasing its own release. JWS-USC-75-IX, thus, combined both features in a single molecule and offered a significant potential for improved reliability as a treatment of diseases where cholinergic function is impaired (e.g., AD). Later we (Terry et al., 1999) evaluated JWS-USC-75-IX for effects in memory-related tasks in rodents. The compound was found to enhance spatial learning, inhibitory avoidance, and working memory. More recent studies in our laboratories indicate that JWS-USC-75-IX has the potential to improve other domains of cognition in rodents (e.g., recognition memory) as well as attention and working memory in non-human primates (Terry et al., 2011).

7.4. Additional multifunctional compounds

The compound memoquin resulted from a multi-targeted approach, combining the radical scavenger moiety of coenzyme Q (CoQ) with the

polyamine backbone of caproctamine conferring AChE inhibition properties. The rationale was to produce a single molecular entity that combined the neuroprotective qualities of CoQ with the cognitive enhancing properties of AChE inhibition. The result was a molecule that has been shown to simultaneously reduce the neurodegenerative pathology and rescue the behavioral impairment in an object recognition task in a mouse (AD11 mice) model of AD (Cavalli et al., 2007). Similarly, PMS777 is a multiple target AChE inhibitor that displays dual inhibition of AChE and platelet-activating factor (PAF). PAF is thought to participate in the neurodegeneration related AD (Bazan et al., 2002; Bate et al., 2004). Thus, the rationale for PMS777 is to act through neuroprotection as well as cognitive enhancement. PMS777 has been shown to alleviate scopolamine induced impairment in mice (Li et al., 2006).

8. Other targets

For several years chromatin modifications, especially histone-tail acetylation, have been implicated in modulating synaptic plasticity and long-lasting changes of neural circuits that contribute to memory formation. Moreover, increased histone-tail acetylation induced by inhibitors of histone deacetylases (HDACis) has been observed to facilitate learning and memory in wild-type mice as well as in mouse models of neurodegeneration (Guan et al., 2009). Accordingly, selective inhibitors HDAC (e.g., Bayer's compound EVP 0334) have been suggested as treatments for neurodegenerative diseases, including AD (Hahnen et al., 2008).

Both angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blocker (ARB) drugs have been shown to improve cognitive function in animal models (reviewed, Gard and Rusted, 2004) and as a result have been in various stages of development for AD over the last 15 years. While no such agent has progressed very far in clinical trials to date, recent observations that ARBs are associated with a significant reduction in the incidence and progression of AD and dementia (Li et al., 2010) may suggest that such a strategy remains viable.

While psychostimulant drugs (e.g., amphetamine and methylphenidate) have been employed for many years as effective treatments for ADHD and narcolepsy, their potential as pro-cognitive agents in other disorders has been equivocal. Interest in newer ADHD and narcolepsy-related treatments such as the norepinephrine transporter (NET) inhibitor atomoxetine and the psychostimulant modafinil, respectively, is accruing and based on recent published evidence. For example atomoxetine was observed to improve reversal learning in rats and monkeys (Seu et al., 2009) while modafinil has been observed to improve cognition in several domains including working memory and episodic memory in both rodent models and humans (reviewed, Minzenberg and Carter, 2008).

There is a host of additional therapeutic targets that have been investigated or are in various stages of investigation for the symptomatic treatment of AD, MCI and cognitive deficits associated with schizophrenia. Unfortunately, a full overview of these targets is beyond the scope of the present review and we refer the reader to additional articles (Gallagher et al., 1985; Minzenberg and Carter, 2008; Buccafusco, 2009; Lynch et al., 2011) that discuss examples such as glycine transporter related drugs, mGluR2/3 agonists, somatostatin receptor ligands, estrogen receptor ligands, D2 agonists, calcium channel modulators (e.g., MEM 1003 and nimodipine), adrenergic compounds (e.g., nicergoline), opioid antagonists (e.g., naloxone) and GABA-related compounds.

9. Animal models and their translational value

In the last several years there has been a growing concern over the discrepancies between preclinical results in AD-related animal models and clinical evaluations of novel AD-related compounds (Carlsson, 2008). A more general concern over the translation of preclinical results to clinical trial data is now evident in multiple health-related disciplines (see Lowenstein and Castro, 2008; Simon, 2008). It is clear that new and more rigorous efforts to develop animal models that meet the demands of face, construct, and predictive validity be undertaken so that preclinical endeavors become more translational. It is also our opinion that specific batteries of behavioral tasks that more closely map onto the domains of cognition that are evaluated in clinical trials be developed and that some type of composite score approach to the animal tests be created that is analogous to those used in clinical studies (e.g., Mini-Mental Status Exam) so that an "overall" drug effect on cognition can be estimated. It is also very important that the full results of failed clinical trials be published in peer reviewed journals (a practice that is uncommon at present) so that the human and animal data can be carefully compared. Currently, such clinical trial results are often found only in abstract form or as summary data in reviews or lay publications, a practice that often makes it difficult for the science community to understand the reason for the so called "failure" of an investigational new drug (see review, McArthur et al., 2010).

10. Summary and conclusions

Given the rapid growth of our elderly population and their concerns about memory loss and dementia it is incumbent on the scientific community to develop more effective pro-cognitive drugs. As diagnostic criteria for memory disorders evolve, the demand for pro-cognitive therapeutic agents is likely to move beyond AD and dementia to include MCI and potentially even less severe forms of memory decline. While there are a considerable number of compounds in various stages of preclinical development as pro-cognitive agents, due to the complexity of human cognition (and illness like AD that devastate cognition), the development of compounds that are both safe and effective (with sustained pro-cognitive effects over time) will likely require the diligent efforts of academia and private industry and the full armamentarium of a variety of scientific methods. Such methods include modern drug discovery techniques (e.g., molecular modeling, combinatorial chemistry, and high throughout biological assays), the latest advances in molecular biology and transgenics, and more traditional research methods such as medicinal chemistry, behavioral neuroscience, and classical pharmacology.

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