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Anti-dementia drugs and hippocampal-dependent memory in rodents

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Abstract

Abnormalities in hippocampal structure and function are characteristics of early Alzheimer's disease (AD). Behavioral tests measuring hippocampal-dependent memory in rodents are often used to evaluate novel treatments for AD and other dementias. In this study, we review the effects of drugs marketed for the treatment of AD, such as the acetylcholinesterase inhibitors, donepezil, rivastigmine, galantamine and the *N*-methyl-D-aspartic acid antagonist, memantine, in rodent models of memory impairment. We also briefly describe the effects of novel treatments for cognitive impairment in rodent models of memory impairment, and discuss issues concerning the selection of the animal model and behavioral tests. Suggestions for future research are offered.

Keywords

anticholinesterases; dementia; hippocampus; memantine; memory; mouse; rat

Introduction

Among the most common features of early Alzheimer's disease (AD) is the inability to form and retain new memories, and structural abnormalities of medial temporal lobe structures, including the entorhinal cortex, perforant pathway, and hippocampus are thought to underlie such deficits. In AD, the integrity of the hippocampus is compromised by plaques, tangles and, eventually, the loss of synapses and neuron cell bodies (Alzheimer, 1907; Probst *et al.*, 1983; Bussiere *et al.*, 2002; Rekart *et al.*, 2004; West *et al.*, 2004). Moreover, in-vivo neuroimaging studies demonstrate that decreases in hippocampal volumes are a hallmark of early AD (Wang *et al.*, 2003, 2006).

The severity of deficits in verbal learning, logical memory, and visual reproduction has been correlated with decreases in hippocampal volume in AD patients (Petersen *et al.*, 2000), suggesting that hippocampal degeneration is the basis, at least in part, for the cognitive deficits of AD. Impairments in declarative memory functions have also been associated with hippocampal degeneration in a variety of animal species (Squire and Zola-Morgan, 1991). Thus, tests evaluating hippocampal-dependent memory in animal models are often used to aid in the evaluation of novel treatments for AD and other dementias. In particular, rodent models of hippocampal-dependent memory dysfunction have played an important role in anti-dementia drug development. This review will focus on rodent models of disrupted

hippocampal-based memory and the observed effects of various anti-dementia drugs on reversal of disrupted memory in these models. We will also consider issues that arise in the evaluation of the strengths and weaknesses of particular rodent models and behavioral paradigms.

Mammalian memory systems and neuroanatomical substrates

Memory systems operate both independently and in parallel with each other. In a recent review, Squire (2004) suggested a taxonomy of mammalian long-term memory systems and the brain structures thought to subserve them. Memory for procedural skills and habits were suggested to be dependent on the striatum and basal ganglia, whereas the neocortex was involved in priming and perceptual learning. Emotional responses and skeletal responses to simple classical conditioning were based on functioning of the amygdala and cerebellum, respectively, whereas non-associative learning was driven by reflex pathways. Finally, declarative memory was associated with medial temporal lobe structures, especially the hippocampus. There may be important species differences in the form of memory subserved by the hippocampus. More specifically, the function of the human hippocampus has long been associated with episodic verbal memory (Milner, 1959; Sass *et al.*, 1992), whereas the function of the rodent hippocampus has been associated with spatial navigation (Olton *et al.*, 1978; Wood and Dudchenko, 2003). These differences may, however, be more apparent than real. When selecting a behavioral paradigm for a particular species, the behavioral repertoire of the species must be considered, and differences in such repertoires may be difficult to discern from real differences in functionality.

Lesion studies in animals, especially rodents, have been the primary source of support for the hypothesis that regulation of the various types of learning and memory tasks reside in different areas of the brain. For example, delayed eyeblink conditioning has been shown to be dependent on the cerebellum (McCormick *et al.*, 1982), whereas cued conditioning has been determined to be reliant on the amygdala (Fanselow and LeDoux, 1999). The hippocampus has been shown to be particularly essential for memory tasks that require the development of configural (or contextual) rather than simple associations (Rudy and Sutherland, 1989).

The literature is replete with reports investigating the effects of anti-dementia drugs on hippocampal-dependent memory in rodents. The results of such studies, however, are sometimes equivocal or conflicted, perhaps because of methodological factors. Among these factors are (i) the experimental model utilized to induce memory impairment, (ii) the specific tests employed in the evaluation of memory-related behavior, and (iii) the drug dose and administration pattern employed in an attempt to ameliorate experimentally induced memory impairment.

Common rodent models of hippocampal-dependent memory impairment

Several different models of memory impairment have been developed and utilized for anti-dementia drug testing in rodents over the years. Among the simplest models has been the study of senescent animals. Senescent animals, however, do not typically manifest the pathological characteristics of AD or other age-related dementing illnesses, and so may not fully represent these particular disease conditions. Rather, aged animals may be more representative of the cognitive decline that accompanies 'normal' aging (Dunnett and Barth, 1991, chapter 14). Age remains, nonetheless, the most powerful predictor of AD and, other dementing illnesses, and thus, the relevance of the senescent rodent for modeling such illnesses should not be underestimated.

Administration of the muscarinic antagonist, scopolamine, is one of the most well-known models of pharmacologically induced memory impairment in rodents (Deutsch, 1971; Flood

and Cherkin, 1986; Rush and Streit, 1992). Studies using scopolamine helped form the basis for the cholinergic hypothesis of learning and memory dysfunction (Drachman and Leavitt, 1974). Other memory-impairing drugs include the nicotinic antagonist, mecamylamine, and the *N*-methyl-D-aspartic acid (NMDA) receptor antagonist, MK-801. Pharmacologic models have been very useful in the evaluation of the roles of various neurotransmitter systems in the learning and memory process, and have been especially useful for determining how anti-dementia drugs interact with cholinergic or glutamatergic systems. These types of rodent model provide a degree of predictive validity, as they have been a successful component of the drug discovery process as it is related to AD.

Lesion studies of the rodent brain, initiated by Lashley (1929), involve techniques that either physically or chemically damage specific areas of the brain to impair cognitive functioning. Studies using stereotaxic techniques to deliver electrolytic lesions have been instrumental in classifying certain learning and memory tests as dependent upon the hippocampus versus other brain regions (Sutherland *et al.*, 1983; Peinado-Manzano, 1990; McDonald and White, 1993; Mintz *et al.*, 1994). Lesion studies also have some predictive validity for the characterization of anti-dementia drugs, despite their limited construct validity in terms of the pathology of dementing diseases. These models may have a greater degree of construct validity for stroke or brain injury-related dementias.

In the last decade, significant advances in the field of molecular genetics have led to the development of transgenic mouse models of human dementias. Although no transgenic model fully mimics the human AD, several models have been developed that display one or more of the pathological features of AD, as well as deficits in cognitive functioning in general, and impairment on hippocampal-dependent tests in particular. The majority of the developed models focus on increased amyloid production in the brain. There may, however, be important differences among such transgenic models. For example, the Tg2576 mouse develops cognitive impairment in concert with the appearance of amyloid plaques at around 9 months of age (Hsiao *et al.*, 1996), whereas the PDAPP mouse has been reported to show cognitive deficits at 3 months of age, well before the appearance of plaques (8–10 months; Games *et al.*, 1995). In other reports, however, cognitive deficits are not apparent in PDAPP mice until 13 months of age. The APP23 model is currently the only model with confirmed neurodegeneration (at 14–18 months of age), and APP23 mice are also considered a model of cerebral amyloid angiopathy (Winkler *et al.*, 2001). Reports on the onset of cognitive deficits in APP23 mice vary from as early as 3 months to 18 months, whereas plaques are seen at 6 months in this model. The TgCRND8 model displays an extremely high level of A β -42 with visible plaques and cognitive deficits by 3 months of age (Chishti *et al.*, 2001). The APP/PS1 model combines two mutations reported in AD patients, and these animals show plaque deposition by 3 months of age with cognitive deficits at 15–17 months. Finally, mice that are deficient in the *APOE* gene represent an alternative transgenic model of AD-related cognitive deficits. These animals show increased atherosclerosis by 3 months (Zhang *et al.*, 1992) and display dendritic alterations by 4 months of age (Masliah *et al.*, 1995; for review of transgenic models see Higgins and Jacobsen, 2003).

At the present time, one can argue that transgenic mouse models of AD provide the most reliable face, construct, and predictive validity for evaluating new drug treatments for AD, because they reproduce the etiological basis of the human condition, often through expression of a human disease gene. Even these models, however, do not necessarily reproduce all of the pathological features of the disease (i.e. plaques, tangles and neurodegeneration). Moreover, initial attempts to design mouse models with multiple transgenes that more fully express all of the pathological characteristics of AD resulted in mice that are difficult to examine behaviorally owing to confounding gross motor dysfunction (Lewis *et al.*, 2001). Recently, a triple transgenic mouse model, 3 $\times$ TgAD, which produces plaques and tangles, has been developed

and used in behavioral studies with promising results (Billings *et al.*, 2005; Oddo *et al.*, 2006).

Issues concerning behavioral tests

Another factor in interpreting findings from rodent models of dementing illness lies in the behavioral paradigm employed to model human cognition. Many of the studies conducted in the past use varying protocols that purport to test the same cognitive construct, making comparisons between reports complicated. The importance of standardization in the field of behavioral neuroscience has recently become a topic of increased discussion (Wahlsten, 2001; Tecott and Nestler, 2004; Lewejohann *et al.*, 2006).

With the recent emphasis on translational neuroscience research, behavioral tests are being routinely included in the phenotypic characterization of transgenic animals. This is extremely beneficial for understanding the 'big picture' of genetic effects on behavior. Errors in interpretation or lack of general knowledge about the details of behavioral paradigms and the factors that can influence performance in such paradigms, however, can lead to ambiguous or conflictual findings. For example, many of the behavioral paradigms were originally developed for rats and do not work as well in mice. In contrast, differences in methodology and exploring the best way to conduct a specific test may lead to better measures of cognitive functioning in mice. Crawley (2000) provides an excellent analysis of optimal experimental protocols and designs for behavioral phenotyping of transgenic mice. In addition, the availability of commercially produced, automated equipment for behavioral testing has helped to make data collection more reliable.

In this review, we will focus on the results of studies to assess the influences of anti-dementia drugs in rodent models of AD using behavioral tests that have been established to rely on an intact, functioning hippocampus. These include spatial learning and memory and contextual fear conditioning (Aggleton *et al.*, 1986; Anagnostaras *et al.*, 1999; Petitto *et al.*, 1999; Maren and Holt, 2000; Gerlai, 2001; Clark *et al.*, 2005, Broadbent *et al.*, 2006). Spatial learning can be evaluated in several different ways, with the most popular being the Morris water maze.

The Morris water maze assesses acquisition of a hidden platform location in a pool of opaque water, with most protocols including a probe trial to evaluate retention of spatial reference memory (Morris, 1984). Spatial working memory, however, can also be measured in a water maze using alternate protocols. The Barnes maze has been considered a dry-land version of the water maze and measures the ability of an animal to locate an escape tunnel on an elevated table (Barnes, 1979). The radial arm maze (Olton and Samuelson, 1976) can assess both spatial reference and working memory depending on the protocol employed. The holeboard task is similar to the radial arm maze in that it typically requires the animal to remember the location of a food reward placed in a specific hole in the apparatus (Van der Staay *et al.*, 1990).

T-maze protocols can be used in either land-based or water-based versions and represent a simple approach to evaluating the ability of the animal to choose the correct arm based on spatial memory (Wenk, 1998). T-maze paradigms can vary considerably, in that some involve extensive training sessions or evaluate long-term retention at specific intervals, whereas others evaluate short-term spatial learning and reversal learning over a number of trials in a given session. Spontaneous alternation in a T, Y or radial arm maze has been reported to be a measure of exploratory behavior that reflects spatial working memory and is dependent upon hippocampal function (Johnson *et al.*, 1977; Gerlai, 2001; Lalonde, 2002). This procedure involves measuring the arm choice over consecutive trials or in one continuous session, based on the assumption that deficits in alternation indicate poor spatial working memory. Finally, contextual fear conditioning involves configural learning and aspects of spatial learning (Rudy and Sutherland, 1989). Typical protocols involve pairing a tone-shock presentation in a distinct

context during training and measuring freezing (or fear) in response to the context at a later time. This is a measure of classical or Pavlovian conditioning, which has been shown to be dependent upon intact hippocampal functioning, whereas freezing in response to the tone is an amygdala-dependent behavior (Phillips and LeDoux, 1992).

Issues concerning pharmacological administration

The dose, route of administration and timing of drug administration in relation to behavioral tests can influence the results obtained using various behavioral tests. Each of these pharmacological factors is important in classifying the parameters under which the drug is useful or harmful to cognitive function. This issue will not be extensively discussed in this review, but may have considerable influence on inconsistencies among findings. Physiological, neurochemical and anatomical phenotypes are also beyond the scope of this review.

Acetylcholinesterase inhibitors

The cholinergic hypothesis of AD postulates that low synaptic levels of acetylcholine (ACh) resulting from loss of cholinergic neurons in the nucleus basalis magnocellularis (NBM) lead to cognitive decline (Appel, 1981; Bartus *et al.*, 1982). Owing to this hypothesis, strategies for increasing synaptic levels of ACh have been widely explored in the development of anti-dementia drugs. One such strategy has been to block synaptic degradation of ACh through the inhibition of acetylcholinesterase (AChE). Currently, four AChE inhibitors have been approved for use in the treatment of AD; tacrine, donepezil, rivastigmine and galantamine. The use of tacrine has declined significantly because of its adverse effect on the liver (O'Brien *et al.*, 1991; Watkins *et al.*, 1994); therefore, this discussion will focus on studies involving the more commonly prescribed drugs, donepezil, rivastigmine and galantamine. Although these widely used AChE inhibitors all inhibit AChE, other variations in their pharmacodynamic profile distinguish them.

Donepezil

Donepezil is a piperidine-based, noncompetitive, reversible inhibitor of AChE with high specificity for the central versus peripheral cholinergic system. Moreover, donepezil inhibits AChE but not butyrylcholinesterase activity. Dosing parameters and the effects of donepezil in the behavioral studies discussed below are presented in Table 1.

Senescent rodents—Donepezil is the most frequently used drug in this class, and many studies have examined its effect on memory in aged rodents. Studies employing aged male Fisher 344 rats show differing results in memory improvement. Water-maze acquisition and retention was improved with a daily dose of donepezil (0.75, but not 0.375 mg/kg) beginning 4 days before testing and continuing for 15 days compared with saline-treated age-matched controls (Hernandez *et al.*, 2006). Abe *et al.* (2003) also reported significant improvement in water-maze performance (0.25 and 0.5 mg/kg). Subcutaneous administration of a comparable dose of donepezil (0.695 mg/kg/day) for 3 weeks before testing and continuing for 2 weeks resulted in no significant improvements in radial-arm-maze performance (Barnes *et al.*, 2000).

Pharmacologic impairment—In models of drug-induced memory impairment in both rats and mice, donepezil administration has been shown to be beneficial at certain doses. Doses of 0.3 and 1.0 mg/kg administered 30 min before test trials significantly decreased escape latency in water maze compared with scopolamine alone in male Sprague–Dawley rats (Chen *et al.*, 2002). Two studies of scopolamine-induced deficits in radial-arm-maze performance in rats have found that donepezil 0.6, 0.9 and 10.0 mg/kg administered before test trial improved both working and reference memory (Wang and Tang, 1998; Yamaguchi *et al.*, 2001). Improvement

in radial-arm-maze performance after scopolamine treatment was also noticed in male Wistar rats after a 0.2 mg/kg dose of donepezil (Braidia *et al.*, 1996). In contrast, Lindner *et al.* (2006) found no significant effect of donepezil on radial-arm-maze or water-maze performance with 0.1–3.0 mg/kg doses. These authors examined the influence of similar doses of donepezil on contextual memory in fear conditioning and found differing results in two studies. A dose of 1.0, but not 3.0 mg/kg improved contextual memory in one study but the opposite results were observed with these doses in the second experiment.

In studies of scopolamine-induced memory impairment in male C57 mice, donepezil at a dose of 3.0, but not 0.3 or 1.0 mg/kg, administered before testing attenuated memory deficits in the T-maze continuous alternation task (Spowart-Manning and van der Staay, 2004). Additionally, doses of 0.48, 2.4 and 7.21 μ mol/kg injected before testing attenuated decreases in spontaneous alternation in a T-maze and improved working memory in a delayed radial arm maze (Bontempi *et al.*, 2003). Csernansky *et al.* (2005), using an MK-801-induced model of memory impairment, also found improved acquisition and reversal learning in the water T-maze in a dose-dependent manner. Donepezil at doses of 0.3 and 1.0 mg/kg significantly improved contextual conditioning in that study. Spontaneous alternation in a Y-maze was also reported to be improved with doses of donepezil in mice impaired with MK-801 (Maurice *et al.*, 2006).

Lesions—Lesions of different areas of the brain induced by several methods have been used to study the effects of donepezil on deficits in hippocampal-dependent memory. Donepezil at doses of 0.3 and 1.0 mg/kg before testing improved retention performance in water maze in male Sprague–Dawley rats impaired after training by cerebral ischemia. In this study, the low dose of 0.1 mg/kg was not significant (Xu *et al.*, 2002). In addition, male Wistar rats exposed to cerebral ischemia and intracerebroventricular A β infusion showed improvement in a radial-arm-maze task with 3.0 mg/kg donepezil given acutely, before testing (Iwasaki *et al.*, 2006). Working memory performance, but not reference memory, was improved in the radial arm maze in rats with AF64A administered intracerebroventricularly to damage cholinergic neurons in the hippocampus (Cheng and Tang, 1998). In male Wistar rats with ibotenic acid lesions of the entorhinal cortex, donepezil was effective in improving acquisition in a water-maze task at doses of 0.3 and 3.0 mg/kg. Performance was better than untreated lesioned animals, but not to the level of sham controls. No effects were seen on retention in this model (Spowart-Manning and van der Staay, 2005).

Mouse models of lesion-induced memory impairment indicate male Swiss mice exposed to CO₂-induced hippocampal neurodegeneration show improvement in Y-maze spontaneous alternation with acute doses of donepezil (0.12, 0.25, 0.5 and 1.0 mg/kg) administered either before the CO₂ exposure, 1 h after exposure or 20 min before being subjected to the behavioral test (Meunier *et al.*, 2006a). These authors found a similar response in mice impaired with intracerebroventricular A β infusion (Meunier *et al.*, 2006b). Pentylentetrazol kindling, which has been shown to decrease ACh release in the hippocampus (Serra *et al.*, 1997), impaired learning in a water-maze task in male ICR mice, and donepezil treatment at a dose of 1.0 mg/kg administered before behavioral tests each day was effective in improving this deficit (Jia *et al.*, 2006).

Transgenic mice—Donepezil treatment in transgenic mouse models of AD has also been examined. Four-month-old male APP23 transgenic mice improved acquisition in water maze compared with untreated APP23 mice after donepezil administration at doses of 0.3 and 0.6 mg/kg, however, these animals did not improve to the level of wild-type controls. In addition, the low dose improved retention deficits in probe trial to the level of wild-type controls whereas the high dose had no effect. No differences were seen with treatment in wild-type animals on acquisition or retention (Van Dam *et al.*, 2005). In the Tg2576 mouse model of AD, 9-month-

old male and female mice were exposed to donepezil at doses of 0.1, 0.3 and 1.0 mg/kg daily before testing. Doses of 0.3 and 1.0 mg/kg significantly improved acquisition in the water T-maze and 0.3 mg/kg dose significantly improved contextual memory in a conditioned fear test (Dong *et al.*, 2005).

Results from studies evaluating the effects of donepezil on hippocampal-dependent memory tests generally give 'positive' results, but also suggest that dose and the paradigm used to assess memory impairment are important factors in discerning the 'efficacy' of the drug.

Rivastigmine

Rivastigmine is a carbamate-based, reversible, noncompetitive inhibitor of both AChE and butyrylcholinesterase. Its inhibitory effect is of long duration and is relatively specific to the central nervous system. Rivastigmine is approved for mild-to-moderate AD and for mild-to-moderate dementia related to Parkinson's disease. A summary of the dosing parameters and behavioral results for the following studies is presented in Table 2.

Senescent rodents—Only one study examined the effects of rivastigmine treatment on hippocampal-dependent memory in senescent animals. In this study, treatment began 3 weeks before behavioral testing in 28-month-old male F344 rats. A dose of 0.2, but not 0.1 mg/kg/day, facilitated learning in a water maze compared with age-matched controls (Ohara *et al.*, 1997a).

Pharmacologic impairment—In two studies conducted on scopolamine-induced water maze impairment in Sprague–Dawley rats, rivastigmine showed a dose-related improvement. Bejar *et al.* (1999) examined doses of 0.75, 1.5, 2.5 and 3.5 mg/kg injected before testing daily. Improvement in water-maze performance was reported at 1.5 and 2.5 mg/kg doses in male rats, whereas impairment was observed at 3.5 mg/kg dose. Wang *et al.* (2000) used both male and female rats given a dose of 0.75 mg/kg daily; greater improvement was observed in the female compared with male rats.

Lesions—Rivastigmine administration has successfully improved memory performance in lesion-induced models of memory impairment. Rivastigmine treatment in male Wistar rats with ibotenic acid lesions of the basal forebrain, at doses of 0.1 and 0.2 mg/kg, reversed deficits in water-maze performance (Ohara *et al.*, 1997b). Furthermore, acute doses of rivastigmine (0.3–1.0 mg/kg) in male Swiss mice exposed to CO₂-induced hippocampal neurodegeneration either before CO₂ or 20 min before behavioral testing reversed memory impairments in a Y-maze spontaneous alternation task (Meunier *et al.*, 2006a). These authors also found beneficial effects of rivastigmine in alternation performance in mice after intracerebroventricular A β injection (Meunier *et al.*, 2006b).

Transgenic mice—In male APP23 transgenic mice, Van Dam *et al.* (2005) showed that a low dose (0.5 mg/kg) of rivastigmine was beneficial to acquisition in water maze compared with untreated APP23 mice. High-dose rivastigmine (1.0 mg/kg) produced only slight improvements in performance compared with untreated APP23 animals. The low dose of rivastigmine also improved retention deficits in a probe trial to the level of nontransgenic animals whereas the high dose had no effect on retention. No differences in acquisition or retention were seen with rivastigmine administration in nontransgenic animals. Similarly, in ApoE-deficient mice, rivastigmine (1.5 mg/kg daily beginning 1 week before behavioral testing) improved performance in a working-memory version of the water maze in transgenic mice, with no effect on controls (Chapman *et al.*, 1998).

The effects of rivastigmine on hippocampal-dependent memory in rodent models have not been adequately studied. On the basis of the available findings, however, rivastigmine may be effective within a small range of doses. High doses, in contrast, may produce unwanted cognitive impairment.

Galantamine

Galantamine is a phenanthrene alkaloid obtained from the bulbs and flowers of the plant, *Galanthus woronowii*, and related species. It is a competitive and reversible cholinesterase inhibitor. Galantamine is also an allosteric modulator of nicotinic cholinergic receptors. The findings from the behavioral studies discussed below are summarized in Table 3.

Senescent rodents—Subchronic daily doses of galantamine (3.0 and 6.0 mg/kg) beginning 4 days before testing partially improved learning in the water maze in 22–24-month-old male F344 rats. The high dose improved retention in the probe trial compared with saline-treated age-matched controls (Hernandez *et al.*, 2006). Galantamine treatment (5.0 mg/kg) in aged male Wistar rats was beneficial in increasing spontaneous alternation in a T-maze and water-maze performance (Rispoli *et al.*, 2006). Barnes *et al.* (2000) did not, however, find significant differences in radial arm maze performance in 22-month-old male F344 rats with longer administration of galantamine (0.277 mg/kg/day) beginning 3 weeks before testing.

Galantamine treatment in 19-month-old male C57 mice at a dose of 2.0 mg/kg/day, during either training or testing, had no influence on contextual conditioning. The aged mice in this study, however, were not significantly impaired on this task relative to young mice (Gould and Feiro, 2005).

Pharmacologic impairment—The effects of galantamine on pharmacologic models of hippocampal-dependent memory impairment in rodents have not been widely studied. Fishkin *et al.* (1993) found that doses of galantamine (1.25, 2.5 or 5.0 mg/kg) attenuated scopolamine-induced deficits in memory on T-maze or water-maze tasks in rats. Male C57 mice with MK-801-induced impairments, however, showed no improvement in acquisition or reversal learning in the water T-maze or contextual conditioning with galantamine at doses of 0.25, 0.5 or 1.0 mg/kg administered before testing (Csernansky *et al.*, 2005).

Lesions—Results of galantamine administration in lesion-induced impairments on hippocampal-dependent memory tests have been encouraging. Male Wistar rats with NMDA-induced medial septal lesions show improvement in water-maze acquisition with galantamine treatment (Mulder *et al.*, 2005). Similarly, 5.0 mg/kg galantamine in rats with bilateral NBM lesions attenuated deficits in water-maze performance and spontaneous alternation in a T-maze (Rispoli *et al.*, 2006).

An acute dose of galantamine (1.0 mg/kg) before CO₂ exposure, or 20 min before behavioral testing, improved impairments in Y-maze spontaneous alternation in male Swiss mice with CO₂-induced neurodegeneration in the hippocampus, alternation was also improved with galantamine treatment in mice with intracerebroventricular A β injections (Meunier *et al.*, 2006a, b). Sweeney *et al.* (1988, 1989) conducted several studies showing that galantamine (5.0 mg/kg) in male Balb/cByJ mice with bilateral NBM lesions improves water-maze performance after acute administration, until 3.5 h after injection. They also found that although galantamine significantly improved water-maze performance in lesioned animals, it impaired performance in sham controls for up to 6 h after injection.

Transgenic mice—Van Dam *et al.* (2005) examined the effects of galantamine treatment in 4-month-old male APP23 transgenic mice. Animals were given daily injections of drugs

beginning 1 week before behavioral testing and continuing daily. Galantamine, at doses of 1.25 and 2.5 mg/kg, improved acquisition in water maze compared with untreated APP23 mice, with animals given the high dose performing almost to the level of the nontransgenic animals. Both doses improved retention deficits in the APP23 mice to the level of saline-treated nontransgenic animals, with no effects on acquisition or retention seen in the nontransgenic animals with galantamine treatment. These authors also studied the effects of galantamine in APP23 transgenic mice in a chronic delivery experiment using osmotic minipumps for total drug delivery time of 8 weeks. After a 3-week washout period, animals were tested in the water maze. Galantamine at doses of 1.3 and 2.6 mg/kg/day had no effect on acquisition in the water maze; however, the low dose significantly improved retention in a probe trial (Van Dam and De Deyn, 2006).

The effects of galantamine in rodent models of hippocampal-dependent memory disruption appear to vary based on the particular model used. Generally, positive effects were observed in transgenic and lesion models, but equivocal benefits were observed in senescent and pharmacologic models of memory impairment.

***N*-methyl-D-aspartic acid-antagonist**

Memantine

In 2003, the Food and Drug Administration approved the uncompetitive NMDA antagonist, memantine, for use in moderate-to-severe AD. Memantine is reported to have unique binding properties that allow for rapid displacement from the receptor and so avoids prolonged NMDA-receptor blockade, which can be detrimental to learning and memory (Lipton, 2006). In addition to the action of the drug at the NMDA receptor, memantine also appears to have actions as an antagonist at nicotinic receptors and at the serotonergic 5-HT₃ receptor (Buisson and Bertrand, 1998; Rammes *et al.*, 2001; Aracava *et al.*, 2005). The hypothesis behind the benefit of NMDA receptor antagonist use in AD is that amyloid induces excitotoxicity in the central nervous system and blocking the NMDA receptor will prevent excitotoxic neurodegeneration (Lipton, 2004). Although this hypothesis is a plausible explanation for neuroprotective effects observed after memantine administration, it is more difficult to relate this hypothesis to acute improvements in cognition. The specific dosing parameters used in each of the following studies and the effects of memantine on hippocampal-dependent memory tests are summarized in Table 4.

Senescent rodents—In senescent male F344 rats, chronic administration of memantine (30 mg/kg/day) in chow for 8 weeks resulted in no differences in acquisition of the water maze. There was a tendency for memantine-treated animals to have more selective search patterns in probe trials in this study (Barnes *et al.*, 1996). Acute doses of memantine (2.5, 5.0 and 10.0 mg/kg), however, had no effect on acquisition, but significantly impaired retention in adult female Sprague–Dawley rats (Creeley *et al.*, 2006).

Pharmacologic impairment—Few reports exist in the literature on the effects of memantine treatment in pharmacologic models of memory impairment. The effects of memantine on MK-801-induced impairments in radial arm maze performance were not significant (Bresink *et al.*, 1995). One study conducted by Lukyanov and Paula-Barbosa (2001) used male Wistar rats treated with ethanol for 6 months, and then with memantine for 4 weeks after ethanol withdrawal. Water-maze performance was evaluated 6 weeks after end of drug treatment. Memantine treatment improved water-maze deficits in acquisition and retention with ethanol withdrawal.

Lesions—Lesion studies with memantine are more common, perhaps owing to the hypothesized neuroprotective effects of NMDA antagonists (see above). Three studies

examining the effects of memantine on quinolinic acid lesions of the entorhinal cortex of male rats indicate that pretreatment with memantine, at doses of 20 mg/kg/day in subcutaneous osmotic minipumps, prevented lesion-induced learning and memory impairments in a T-maze and in the radial arm maze (Misztal *et al.*, 1996; Zajackowski *et al.*, 1996; Lang *et al.*, 2004). Wenk *et al.* (1994) report beneficial effects of memantine pretreatment in water-maze performance in rats with NMDA-induced NBM lesions. Memantine treatment was also shown to be effective in protecting against lesion-induced memory impairments in male F344/DuCrj rats that received bilateral injections of A β -40 and ibotenic acid into the hippocampus (Nakamura *et al.*, 2006). In a model of neuroinflammation, lipopolysaccharide infusion into the fourth ventricle has been shown to increase glutamate release and impair hippocampal-dependent memory in rats. A dose of memantine protected against cognitive deficits in water-maze performance in this study (Rosi *et al.*, 2006). Heim and Sontag (1994) also report a protective benefit of memantine against water-maze deficits at certain doses in a model of ischemia. Conversely, memantine at a dose of 30 mg/kg did not improve T-maze acquisition or retention in female Sprague–Dawley rats with impairments owing to unilateral injection of A β -40 into the hippocampus (Miguel-Hidalgo *et al.*, 2002).

Transgenic mice—A study using APP/PS1 transgenic mice treated with 30 mg/kg memantine in drinking water for 3 weeks reported improved acquisition in the water maze, whereas no effect was seen on retention (Minkeviciene *et al.*, 2004). In contrast, Van Dam *et al.* (2005) reported modest effects of a low dose (2.0 mg/kg) of memantine in male APP23 transgenic mice. Memantine, at doses of 2.0 and 10 mg/kg, was not successful in improving acquisition in water maze compared with untreated APP23 mice. The low dose improved retention deficits in probe to the level of nontransgenic controls, whereas the high dose had no effect. In addition, the high dose significantly impaired retention in nontransgenic animals compared with untreated nontransgenic animals. In a second study with APP23 mice by these authors, memantine at doses of 7.2 and 14.4 mg/kg/day was administered by implantation of osmotic minipumps. The total drug delivery time was 8 weeks, with a 3-week washout period before behavioral testing. Both doses had a tendency to improve acquisition in the water maze, with the high dose significantly improving time spent in the target quadrant in a probe trial (Van Dam and De Deyn, 2006).

Memantine appears to have beneficial effects in lesion models of memory impairment. Less consistent benefits have been observed in transgenic rodent models, and the data from other types of models is not yet adequate to make judgments about the drug's efficacy. When there are adequate data, low doses of memantine show the most consistent beneficial effects, whereas high doses may have unwanted detrimental effects on cognitive behavior.

Alternative treatments

At present, there are 34 agents in clinical trials for the treatment of AD.

Many alternative treatments are being examined based on the findings from basic biology and epidemiological studies of risk factors for developing the disease. Without being exhaustive, we include a brief discussion of treatments that have shown promise in animal models, that is amyloid targeting therapies, antioxidants and herbal supplements, anti-inflammatory agents, and cholesterol-lowering agents (see Table 5 for summary).

Amyloid targeting therapies

On the basis of the prevalence of the amyloid hypothesis in AD and the availability of transgenic animals that overexpress amyloid in the brain, treatments aimed at reducing the toxic forms of this peptide are being explored. Notably, however, the correlation between cognitive deficits and either plaque burden or levels of soluble A β are still under investigation (Koistinaho *et*

et al., 2001). Several studies have now examined hippocampal-dependent memory after A β vaccination in transgenic mouse models of AD, and have reported mostly positive results, especially with early vaccination (Janus *et al.*, 2000; Morgan *et al.*, 2000; Dodart *et al.*, 2002; Kotilinek *et al.*, 2002; Zhang *et al.*, 2003; Sigurdsson *et al.*, 2004; Hartman *et al.*, 2005; Jensen *et al.*, 2005; Asuni *et al.*, 2006; Maier *et al.*, 2006; Oddo *et al.*, 2006; Wilcock *et al.*, 2006). Chen *et al.* (2007), however, report improvements in water-maze performance only in a subset of vaccinated mice with very low amyloid levels; the benefit was not significant in all animals. In addition to vaccination, reducing amyloid levels by inhibiting either β -secretase or γ -secretase have also been examined. Comery *et al.* (2005) evaluated the effects of a γ -secretase inhibitor in Tg2576 mice and found significant improvement in contextual fear conditioning with acute administration before training. A β -secretase inhibitor was also shown to improve water-maze performance in a transgenic model after bilateral injection into the hippocampus (Singer *et al.*, 2005).

Antioxidants and herbal supplements

Oxidative stress leads to cell death through apoptosis and necrosis and may be an important factor in aging and the development of dementia. The results of some animal model experiments have suggested that antioxidant compounds may improve hippocampal-based memory. Vitamin E treatment significantly improved water-maze performance in Tg2576 mice with exposure to head trauma (Conte *et al.*, 2004). Vitamin E was also beneficial in preventing water-maze deficits in rats when administered before intracerebroventricular A β -42 infusion (Yamada *et al.*, 1999). The combination of vitamins E and C improved water-maze performance in ovariectomized female rats but had no effect on intact animals (Monteiro *et al.*, 2005). Diets high in antioxidants have also been examined and benefits in water-maze performance have been reported in aged rats given spinach, blueberry or strawberry extracts (Joseph *et al.*, 1999) and in PDAPP transgenic mice given pomegranate juice (Hartman *et al.*, 2006). In addition, the antioxidant α -lipoic acid improved deficits in contextual fear conditioning in Tg2576 mice (Quinn *et al.*, 2007).

Other alternative treatments, with mechanisms not fully understood, are being explored as treatments for dementia, such as, *Ginkgo biloba*, folic acid and curcumin. Ginkgo has proven to be effective in improving spatial memory in aged animals (Wang *et al.*, 2006) and in Tg2576 mice (Stackman *et al.*, 2003). Mixed effects, however, were seen in water-maze and radial-arm-maze performance in adult rats. Ginkgo had no effect on memory but it may have facilitated learning in this study (Shif *et al.*, 2006). Curcumin is thought to have antioxidant, anti-inflammatory, cholesterol-lowering, anticoagulant and anti-amyloid properties, and was shown to improve water-maze performance in rats with intracerebroventricular A β -42 infusions (Frautschy *et al.*, 2001). ApoE-deficient mice fed on diets lacking B vitamins were impaired in a water-maze task (Troen *et al.*, 2006), but treatment with folic acid has been less impressive, with mild benefits seen in alternation in a T-maze but no effect in water-maze performance in aged F344 rats (Lalonde *et al.*, 1993).

Anti-inflammatory agents

Neuroinflammation has also been implicated in the pathogenesis of AD, and some nonsteroidal anti-inflammatory drugs (NSAIDs) have shown efficacy in animal models of memory impairment. Sulindac in aged F344 rats attenuated age-related impairments in water radial arm maze and contextual fear conditioning (Mesches *et al.*, 2004). A second study using aged animals reported improvements in water-maze performance with chronic celecoxib treatment (Casolini *et al.*, 2002), whereas Hauss-Wegrzyniak *et al.* (1999) reported no effect of a novel NSAID, NO-flurbiprofen, on water-maze performance in aged rats but an improvement in this task in young rats impaired by intraventricular lipopolysaccharide infusion. The authors suggest that the beneficial effects of NSAIDs may be age-dependent.

Cholesterol-lowering agents

Some epidemiological studies have found positive correlations between elevated cholesterol levels and development of AD (Notkola *et al.*, 1998; Wolozin, 2002). Moreover, statins are currently being evaluated in clinical trials for AD treatments. Two studies have examined the effects of atorvastatin treatment on memory impairment owing to traumatic brain injury in both male (Lu *et al.*, 2004) and female (Qu *et al.*, 2005) rats. In both cases, modest improvements in water-maze performance were observed. Simvastatin improved water-maze performance in Tg2576 mice (Li *et al.*, 2006).

Predictive validity of rodent model results

In summary, AChE inhibitors have been shown to be only partially effective in reversing experimental deficits in hippocampal-dependent memory in rodents. These findings are in concert with the conclusions of studies evaluating human beings. A recent evaluation in collaboration with the University of Oregon Health Sciences Center published in *Consumer Reports* (March 2006) suggests that AChE inhibitors provide a significant benefit over placebo for only 10–20% of individuals with AD, and the estimated benefit of AChE inhibitors by the National Institute of Health and Clinical Excellence in the United Kingdom was considered not to be cost effective (Burns and O'Brien, 2006). Not surprisingly, AChE inhibitors are best at improving memory impairments induced by scopolamine in rodents. The results of treatment with such drugs in aged animals, or lesioned models, however, are less robust.

It is notable that cholinesterase inhibitors have also been shown to be helpful in non-AD dementias, such as dementia associated with Parkinson's disease and head trauma (Parton *et al.*, 2005; Silver *et al.*, 2006). This suggests that there may be limitations in the relevance of the extant animal models and suggests that cholinesterase inhibitors can be effective in enhancing cognition without affecting (or reversing) the underlying pathology.

The beneficial effects of memantine in animals appear modest for cognitive improvement, with the exception of memory deficits induced by excitotoxic damage. This is also consistent with reports from clinical trials in which memantine afforded only moderate benefit in patients with AD (Areosa *et al.*, 2005). Recently, the National Institute of Health and Clinical Excellence in the UK stated that memantine should not be recommended for use except as part of well-designed clinical studies (Burns and O'Brien, 2006). Even if memantine is proven to be effective in modifying the disease process, it appears to be a beneficial treatment with only modest effects on cognitive functioning.

Amyloid targeting strategies have been shown to improve cognitive functioning in transgenic models of AD, although clinical trials were halted owing to cerebral inflammation (Check, 2002). These strategies, if determined to be safe and effective, however, may have the ability to slow progression of the disease and cognitive benefits are important, but considered secondary to improving pathological conditions.

Carefully designed examinations of alternative treatments in animal models are unusual, perhaps because the development of such treatments often occurs outside of the traditional pharmaceutical industry. Nonetheless, evaluations of the anti-dementia properties of such agents in animal models of dementia are still needed. These studies also highlight the influence of diet or environmental factors on hippocampal-dependent memory. Although none of these treatments to date appears to hold the cure for AD, research into the mechanisms for hormonal, nutritional and oxidative stress influences on memory impairment is likely to offer important insights into disease mechanisms in the future.

Directions for future research

Dementia is multifactorial. Uncovering the mechanisms involved in the progression and development of AD and other dementias has led to the realization that several factors, genetic and environmental, influence its development and progression. We have made remarkable gains in our understanding of dementias, especially AD, in the last decade; however, there is still much left to understand. Animal models are an invaluable tool for characterizing the mechanisms underlying disease and exploring possible therapeutic approaches.

Overcoming limitations of current animal models

Combining information from complementary animal models should provide a fuller understanding of the potential benefits of a new anti-dementia drug. Using the animal model most relevant to the pathophysiology of the target disease would seem to produce the most reliable results. Examining, however, the effect of the treatment in a second model, one that is not intuitively related to the treatment mechanism or disease state, would provide information about the generalizability of any drug effects.

Notably, the majority of animal model studies of anti-dementia drugs used exclusively male animals. Certainly, epidemiological studies indicate that females are no less likely (and perhaps more likely) to develop AD (Fratiglioni *et al.*, 1997; Swanwick and Lawlor, 1999). Reasons may include longer life expectancy, or the disappearance of the protective benefit of estrogen after menopause and may exacerbate cognitive decline and confound AD diagnosis. From an investigator's standpoint, using male animals eliminates the interactions with fluctuating female hormones that influence memory, but it also limits the findings to a single sex. More studies clarifying gender differences in the drug treatment of dementia are needed.

Standardized behavioral test battery

In addition to the animal model, the behavioral measure utilized to assess memory is important in evaluating the effects of anti-dementia drugs. In behavioral assessments of memory, one aims to avoid inducing variables, such as stress, to the paradigm that may result in behavior unrelated to the memory type the investigator is attempting to assess. Methods for avoiding confounding data by using improper behavioral testing methods are discussed by Gerlai and Clayton (1999) and extensively by Crawley (2000).

Screening for nonmemory-related behaviors, such as anxiety or sensorimotor deficits, is important for elucidating phenotypical factors, especially in transgenic mouse models that may influence performance on memory tests without necessarily being directly affected by the treatment. It has been proposed by several investigators that a standard behavioral screen that includes measures of neurological function, general activity and cognitive functioning should be used when evaluating the effects of agents on animal models (discussed in Hrabé de Angelis *et al.*, 2006). Potential treatments for neuropsychiatric disorders have the possibility of interfering with a wide variety of behaviors. Thus, it would also be helpful to characterize a range of central-nervous-system-related behaviors to be certain that the putative treatment is effective in changing the behavior of interest without introducing unwanted behavioral alterations.

Importance of behavioral studies in animals for the development of anti-dementia drugs

Why are behavioral models important for studying of the mechanisms of dementia and the putative effects of novel anti-dementia drugs? We can attempt to reduce disease processes to the molecular level, the molecular changes observed *in vitro* need to be correlated with interpretable changes in function. In the case of AD and other dementias, we need reliable measures of memory to assess fully the effects of novel drugs as treatments for the disease.

A key intermediate step in determining whether a novel treatment will work in human patients is to determine whether or not memory is improved in a relevant animal model. If, however, a drug-induced change in a biological variable does not produce a corresponding change in behavior, it could be the result of improper methodology. The studies discussed in this review demonstrate the progress that has been made in understanding the anatomical and physiological mechanisms underlying memory, and their relevance to human dementias. Continuing improvements in the validity of the available animal models to test novel drugs should improve our ability to discover and develop new treatments for AD and other dementias.

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Table 1

Donepezil

Model	Animal	Dose (mg/kg)	Effect	Parameters	Behavioral Test	Reference
Senscent	Rat (male Fisher 344)	0.375	NS	Daily injection (i.p.) 4 days before testing to 15 days during testing	WM	Hernandez <i>et al.</i> (2006)
	Rat (male F344)	0.75	+ A&R	Osmotic minipump (s.c.) 3 weeks before testing through 2 weeks during testing	RAM	Barnes <i>et al.</i> (2000)
		0.695	NS			
	Rat (male F344)	0.25	+	Acute administration (p.o.) 60 min before testing daily	WM	Abe <i>et al.</i> (2003)
	Mouse (male C57)	0.5	+	Acute administration (s.c.) 20 min before testing daily	RAM TSA	Bontempi <i>et al.</i> (2003)
		0.12	NS (RAM & TSA)			
		0.24	+ (RAM) NS (TSA)			
		0.48	NS (RAM) + (TSA)			
		0.96	+ (RAM) NS (TSA)			
		1.92	NS (RAM & TSA)			
Pharmacologic Scopolamine	Rat (male SD)	0.1	+ A	Daily injection (i.p.) 30 min before testing	WM	Chen <i>et al.</i> (2002)
		0.3	+ A&R			
		1.0	+ A&R			
	Rat (male SD)	0.3	NS	Acute administration (p.o.) before test trial	RAM	Wang and Tang (1998)
		0.6	+			
		0.9	+			
	Rat (male Wistar)	1.2	NS	Acute administration (p.o.) 120 min before test trial	RAM	Braidia <i>et al.</i> (1996)
		0.12	NS			
		0.18	NS			
		0.25	+			
		0.5	NS			

Model	Animal	Dose (mg/kg)	Effect	Parameters	Behavioral Test	Reference
MK-801	Rat (male SD)	0.01	NS	Acute administration (p.o.) 60 min before test trial	RAM	Yamaguchi <i>et al.</i> (2001)
		0.1	NS			
		1.0	NS			
		10	+			
	Rat (male SD)	0.1	NS (RAM)	Daily administration (i.p.) 30 min before testing	RAM (0.1,0.3,1.0)	Lindner <i>et al.</i> (2006)
		0.3	NS (RAM)		WM (2.0,3.0)	
		1.0	+ con NS (RAM)		CF (1.0,3.0)	
		2.0	NS (WM)			
	Mouse (male C57)	3.0	+ con NS (WM)			
		3.0	+	Acute administration (i.p.) 20 min before testing	TSA	Spowart-Manning and van der Staay (2004)
		1.2	NS	Acute administration (s.c.) 20 min before testing	TSA	Bontempi <i>et al.</i> (2003)
	Mouse (male C57)	2.4	+			
		7.21	+			
		14.42	NS			
		21.64	NS			
Lesion	Cerebral Ischemia	0.1	+ A&REV	Daily administration (i.p.) 20 min before testing	Water T	Csemansky <i>et al.</i> (2005)
		0.3	+ A&REV + con		CF	
		1.0	+ A&REV + con			
		0.12	+	Acute injection (i.p.) before testing	YSA	Maurice <i>et al.</i> (2006)
		0.25	+			
		0.5	+			
		1.0	+			
		0.1	NS	Trained in task before CI, DON administered before test trial	WM	Xu <i>et al.</i> (2002)
		0.3	+			
		1.0	+			

Model	Animal	Dose (mg/kg)	Effect	Parameters	Behavioral Test	Reference
CI + A β infusion	Rat (male Wistar)	3.0	+	Acute administration (p.o.) 60 min before testing	RAM	Iwasaki <i>et al.</i> (2006)
Ibotenic Acid (EC)	Rat (male Wistar)	0.3	+ A	Acute administration (p.o.) 30 min before testing daily	WM	Spowart-Manning and van der Staay (2005)
AF64A (ICV)	Rat (male SD)	1.0	NS	ICV injection after training, beh testing beginning 3 weeks post surgery. Administration (p.o.) 30 min before testing	RAM	Cheng and Tang (1998)
		3.0	+ A			
		0.6	NS			
		1.0	+			
CO ₂	Mouse (male Swiss)	2.0	+	Administration (i.p.) either 1 h prior to CO ₂ , 1 h post CO ₂ or 20 min before testing	YSA	Meunier <i>et al.</i> (2006a)
		3.0	NS			
		0.12	NS			
		0.25	+			
A β infusion	Mouse (male Swiss)	0.5	+	Administration (i.p.) before testing. Beh testing 7 days after ICV injection	YSA	Meunier <i>et al.</i> (2006b)
		1.0	+			
		0.12	NS			
		0.25	NS			
PTZ kindling	Mouse (male ICR)	0.5	+	Daily (p.o.) 60 min before testing	WM	Jia <i>et al.</i> (2006)
		1.0	+			
		1.0	+			
		0.3	+ A&R			
Transgenic	APP23 (male 4 months)	0.3	+ A	Daily administration (i.p.) 30 min before testing, beginning 1 week before testing	WM	Van Dam <i>et al.</i> (2005)
		0.6	NS			
		0.1	+ A + con			
		0.3	+ A (NS con)			
Tg2576 (male and female 9 months)	Tg2576 (male and female 9 months)	1.0	NS	Daily injection (i.p.) before testing	Water T and CF	Dong <i>et al.</i> (2005)
		0.1	+			

Model	Animal	Dose (mg/kg)	Effect	Parameters	Behavioral Test	Reference
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Summary of studies evaluating effects of donepezil treatment in tests of hippocampal-based memory.

+, significant improvement; Beh, behavioral; CF, conditioned fear; CI, cerebral ischemia; con, contextual memory; EC, entorhinal cortex; ICV, intracerebroventricular; i.p., intraperitoneally; NS, no significant differences; p.o., orally; (A, acquisition; R, retention; when distinctions were made in report); RAM, radial arm maze; REV, reversal learning; s.c., subcutaneously; SD, Sprague-Dawley; TSA, T-maze spontaneous alternation; WM, water maze; YSA, Y-maze spontaneous alternation.

Table 2

Rivastigmine

Model	Animal	Dose (mg/kg)	Effect	Parameters	Behavioral test	Reference
Senescent	Rat (male Fisher 344)	0.1	NS	Daily administration (p.o.) 3 weeks before testing	WM	Ohara <i>et al.</i> (1997a)
		0.2	+			
Pharmacologic						
Scopolamine	Rat (male SD)	0.75	NS	Daily injection (i.p.) 30 min before testing	WM	Bejar <i>et al.</i> (1999)
		1.5	+			
		2.5	+			
		3.5	—			
	Rat (male and female SD)	0.75	+	Daily injection (i.p.) before testing	WM	Wang <i>et al.</i> (2000)
MK-801	Mouse (male Swiss)	0.3	+	Injection (i.p.) 30 min before testing	TSA	Maurice <i>et al.</i> (2006)
		1.0	+			
Lesion						
Ibotenic acid (BF)	Rat (male Wistar)	0.1	+	Daily before testing (p.o.)	WM	Ohara <i>et al.</i> (1997b)
		0.2	+			
CO ₂	Mouse (male Swiss)	0.3	NS	Administration either 1 h before CO ₂ , 1 h after CO ₂ or 20 min before testing	YSA	Meunier <i>et al.</i> (2006a)
		1.0	+			
ICV Aβ	Mouse (male Swiss)	0.3	NS	Administration (i.p.) before testing, 7 days after ICV injection	YSA	Meunier <i>et al.</i> (2006b)
		1.0	+			
Experimental Allergic Encephalomyelitis (EAE)	Rat	0.5	+ R	Daily in chow beginning on day of immunization and continuing through behavioral testing, which began 90 days later	WM	D'Intino <i>et al.</i> (2005)
Transgenic	APP23 (male 4mos)	0.5	+ A&R	Daily injections (i.p.) beginning 1 week before testing	WM	Van Dam <i>et al.</i> (2005)
		1.0	+ A			
	<i>ApoE</i> deficient	1.5	+	Daily (i.p.) beginning 1 week before testing	WM	Chapman <i>et al.</i> (1998)

Summary of studies evaluating effects of rivastigmine treatment in tests of hippocampal-based memory.

–, significant impairment; +, significant improvement; A, acquisition; BF, basal forebrain; i.p., intraperitoneal; NS, no significant differences; p.o., orally; R, retention; s.c., subcutaneously; SD, Sprague-Dawley; TSA, T-maze spontaneous alternation; WM, water maze; YSA, Y-maze spontaneous alternation.

Table 3

Galantamine

Model	Animal	Dose (mg/kg)	Effect	Parameters	Behavioral test	Reference
Senescent	Rat (male Fisher 344)	3.0	+ A	Daily administration beginning 4 days before testing	WM	Hernandez <i>et al.</i> (2006)
		6.0	+ A&R			
	Rat (male Wistar)	5.0	+	Daily injection (i.p.) before testing	WM	Rispoli <i>et al.</i> (2006)
Pharmacologic						
	Rat (male Fisher 344)	0.277	NS	Osmotic minipump beginning 3 weeks prior to testing	TSA	Barnes <i>et al.</i> (2000)
	Mouse (male C57)	2.0	NS	Daily injection (i.p.) before testing	CF	Gould and Feiro (2005)
Scopolamine						
	Rat	1.25	+	Daily injection (i.p.) 30 min before testing	Tmaze	Fishkin <i>et al.</i> (1993)
		2.5	+		WM	
MK-801						
	Mouse (male C57)	0.25	NS	Daily injection (i.p.) before testing	Water T	Csemansky <i>et al.</i> (2005)
		0.5	NS		CF	
Lesion						
		1.0	NS			
	Rat (male Wistar)	1.0	+ A	1st injection 1 h after lesion, maintained for 7 days at twice daily (i.p.) injections.	WM	Mulder <i>et al.</i> (2005)
CO ₂						
	Mouse (male Swiss)	3.0	+ A			
		0.3	NS	Administration either 1 h before CO ₂ , 1 h post CO ₂ or 20 min before testing	YSA	Meunier <i>et al.</i> (2006a)
ICV Aβ						
	Mouse (male Swiss)	1.0	+			
		0.3	NS	Administration (i.p.) before testing, 7 days after ICV injection	YSA	Meunier <i>et al.</i> (2006b)
NBM						
		1.0	+			
	Rat (male Wistar)	5.0	+	Daily injection (i.p.) before testing	WM TSA	Rispoli <i>et al.</i> (2006)
NBM						
	Mouse (male BALB)	5.0	+	Acute administration (i.p.) before testing	WM	Sweeney <i>et al.</i> (1988, 1989)

Model	Animal	Dose (mg/kg)	Effect	Parameters	Behavioral test	Reference
Transgenic	APP23 (male 4 months)	1.25	+ A&R	Daily administration (i.p.) beginning 1 week before testing	WM	Van Dam <i>et al.</i> (2005)
		2.5	+ A&R			
	APP23 (male 4 months)	1.3	+ R	8-week administration through osmotic minipumps, beh testing began after 3-week washout	WM	Van Dam and De Deyn (2006)
		2.6	NS			

Summary of studies evaluating effects of galantamine treatment in tests of hippocampal-based memory.

+, significant improvement; A, acquisition; Beh, behavioral; CF, conditioned fear; EC, entorhinal cortex; H, hippocampus; i.p., intraperitoneal; ICV, intracerebroventricular; NBM, nucleus basalis magnocellularis; NS, no significant differences; p.o., orally; R, retention; RAM, radial arm maze; TSA, T-maze spontaneous alternation; WM, water maze; YSA, Y-maze spontaneous alternation.

Table 4

Memantine

Model	Animal	Dose (mg/kg)	Effect	Parameters	Behavioral test	Reference
Senescent	Rat (male F344)	30	NS	Daily in chow	WM	Barnes <i>et al.</i> (1996)
Pharmacologic	Rat (female SD)	2.5	NS	Acute administration before test trial	Holeboard	Creeley <i>et al.</i> (2006)
		5.0	-R			
		10.0	-R			
	Rat (male Wistar)	20 mg/kg loading dose, then 1.0 mg/kg every 12 h	+ A&R	Daily for 4 weeks after ethanol withdrawal, beh testing began after 6-week washout	WM	Lukoyanov and Paula-Barbosa (2001)
MK-801	Rat (male SD)	30	NS	Daily in chow	RAM	Bresink <i>et al.</i> (1995)
Lesion						
Quinolinic acid (EC)	Rat (male SD)	20	+	Osmotic minipumps s.c. daily beginning before lesion	Tmaze	Miszal <i>et al.</i> (1996)
Ibotenic acid (H) + A β -40	Rat (male F344/DuCrj)	5	NS	Osmotic minipumps daily beginning 1 day before infusion and continuing for 6 weeks	RAM	Zajackowski <i>et al.</i> (1996)
		10	+ A&R			
		20	+ A&R			
A β -40 (H)	Rat (female SD)	30	NS	Osmotic minipumps daily beginning 2 days before infusion	Tmaze	Miguel-Hidalgo <i>et al.</i> (2002)
Lipopolysaccharide (LPS) infusion	Rat (male F344)	10	+	Osmotic minipumps beginning during infusion, beh testing began third week after surgery	WM	Rosi <i>et al.</i> (2006)
Quinolinic acid (EC)	Rat (male SD)	20	+	Osmotic minipumps 7–13 days after lesion, 4 days before beh test	RAM	Lang <i>et al.</i> (2004)
Carotid artery occlusion	Rat (male Han-Wistar)	5	+	Injection before 24 min occlusion (beh test at 8–10 weeks after surgery)	WM	Heim and Sontag (1994)

Model	Animal	Dose (mg/kg)	Effect	Parameters	Behavioral test	Reference
NMDA (NBM)	Rat (male Long-Evans)	10	NS	Injection before 60 min occlusion (beh test at 6 months after surgery)	WM	Wenk <i>et al.</i> (1994)
		20	NS			
		30	+			
Transgenic	APP23 (male 4 mos)	30	+	Injection (i.p.) 30 before and 5 h after lesion	Tmaze	Van Dam <i>et al.</i> (2005)
		2.0	+ R	Daily administration beginning 1 week before testing	WM	
	APP23 (male 4 mos)	10.0	NS	8 week administration through osmotic minipumps, beh testing began after 3-week washout	WM	Van Dam and Deyn (2006)
		7.2	NS			
	APP/PS1	14.4	+ R	Daily in drinking water for 3 weeks	WM	Minkeviciene <i>et al.</i> (2004)
		30	+ A			

Summary of studies evaluating effects of memantine treatment in tests of hippocampal-based memory.

+, significant improvement; Beh, behavioral; CV, intracerebroventricular; EC, entorhinal cortex; H, hippocampus; i.p., intraperitoneal; NBM, nucleus basalis magnocellularis; NS, no significant differences; (R, retention; A, acquisition, as indicated when distinctions were reported), p.o., orally RAM, radial arm maze; s.c., subcutaneous; WM, water maze.

Table 5

Alternative treatment strategies

Treatment category	Animal/model	Treatment	Effect	Parameters	Behavioral test	Reference
Amyloid targeting	APP/PS1	A β vaccine		Initial injection (sc) at 7.5 months, second injection 2 weeks later, then maintained monthly	Water RAM	Morgan <i>et al.</i> (2000)
		Age 7–11 months	NS			
		Age 7–15 months	+			
	TgCRND8	A β vaccine	+	Injections at 6, 8, 12, 16 and 20 weeks	WM	Janus <i>et al.</i> (2000)
	PDAPP	A β vaccine	+	One injection (i.p.) 24 h before testing	Holeboard	Dodart <i>et al.</i> (2002)
	Tg2576	A β vaccine	+	Four injections during testing, beginning after baseline WM	WM	Kotilinek <i>et al.</i> (2002)
	PDAPP	A β vaccine		Administration via several routes (p.o., intramuscular, and intranasal) beginning at 1 or 12 months of age	WM	Zhang <i>et al.</i> (2003)
		Age 1–13 months	+			
		Age 12–17 months	+			
	PDAPP	A β vaccine	+	Weekly injection (i.p.) beginning at 17–19 months old	WM	Hartman <i>et al.</i> (2005)
	APP/PS1	A β vaccine	+ WM	Monthly injections beginning at 2 months	WM	Jensen <i>et al.</i> (2005)
		Age 2–5 months			Water RAM	
		Age 2–15 months	NS (Water RAM, Barnes, or YSA) + WM (A) + Water RAM			
		γ -secretase inhibitor (DAPT)	NS (Barnes, YSA) +	Acute administration	CF	Conery <i>et al.</i> (2005)
	Tg2576					

Treatment category	Animal/model	Treatment	Effect	Parameters	Behavioral test	Reference
Antioxidants and herbal supplement	hAPP	β -secretase inhibitor	+	(p.o.) 3 h before training Bilateral injection into hippocampus 4 weeks before testing	WM	Singer <i>et al.</i> (2005)
	hAPP	A β vaccine	+ A	Two doses on first day of testing (intranasal administration)	WM	Maier <i>et al.</i> (2006)
	Tg2576	A β vaccine	+	Weekly injections (i.p.) beginning at 20 months	Water RAM	Wilcock <i>et al.</i> (2006)
	Tg2576	A β vaccine		Initial injection at 11 or 19 months, second injection 2 weeks later, then maintained monthly	RAM	Asuni <i>et al.</i> (2006)
	3 $\times$ TgAD	Age 11–24 months Age 19–24 months A β vaccine	+ NS	Acute injection beginning 3 days before testing Chronic beginning 2 months before testing	TSA	Oddo <i>et al.</i> (2006)
	PDAPP	Chronic A β vaccine	+ NS (overall)	Monthly injections beginning at 7 or 11 months of age.	WM	Chen <i>et al.</i> (2007)
	Tg2576 + head trauma	Vitamin E	+	Administration in chow beginning 1 month before TBI (at 12 months of age). Beh testing began 8 weeks after injury	WM	Conte <i>et al.</i> (2004)
	Rat/ICV A β -42	Vitamin E	+(WM) NS (YSA)	Vitamin E or idebenone administered (p.o.) beginning 3 days before AB infusion	WM	Yamada <i>et al.</i> (1999)
		Idebenone	+(WM, YSA)		YSA	

Treatment category	Animal/model	Treatment	Effect	Parameters	Behavioral test	Reference
	Rat (OVX female)	Vitamin E and C	+	Daily injection (i.p.) beginning 7 days after surgery and continuing for 30 days	WM	Monteiro <i>et al.</i> (2005)
	Rat/senescent	High antiox diet	+	Administration in chow for 8 weeks before testing	WM	Joseph <i>et al.</i> (1999)
	PDAPP	Pomegranate juice	+	In drinking water beginning at 6 months and continuing through testing to 12.5 months of age	WM	Hartman <i>et al.</i> (2006)
	Tg2576	ALA	+	Administration in chow beginning at 10 months, behavioral testing beginning at 16 months of age.	CF	Quinn <i>et al.</i> (2007)
	Rat/senescent	<i>Ginkgo biloba</i>	+	In chow beginning 30 days before testing	WM	Wang <i>et al.</i> (2006)
	Tg2576	<i>Ginkgo biloba</i>	+	Daily administration (p.o.) of 70 mg/kg beginning at 8 months continuing for 6 months	WM	Stackman <i>et al.</i> (2003)
	Rat	<i>Ginkgo biloba</i>	NS	Daily administration (p.o.) of 10, 20, or 40 mg/kg	WM	Shif <i>et al.</i> (2006)
	Rat/ICV A β -42	Curcumin	+	Administration in chow beginning 2 months before A β infusion	RAM	Frautschy <i>et al.</i> (2001)
	Rat/senescent	Folic acid	+	Injection (i.p.) every 2 days for 32 days	TSA	Lalonde <i>et al.</i> (1993)
	Rat/senescent	Sulindac	NS		WM	
Anti-inflammatory	Rat/senescent		+	Administration for 2 months before training	WM	Mesches <i>et al.</i> (2004)

Treatment category	Animal/model	Treatment	Effect	Parameters	Behavioral test	Reference
Cholesterol-lowering	Rat/senescent	Celecoxib	+	Oral administration 2 × /day for 4 months	CF	Casolini <i>et al.</i> (2002)
	Rat/senescent Rat/ICV LPS	NFP	NS	Daily (sc) injection	WM	Hauss-Wegrzyniak 1999
	Rat (male)/TBI	Atorvastatin	+	Oral administration for 7 days beginning 1 day after TBI	WM	Lu <i>et al.</i> (2004)
	Rat (female)/TBI	Atorvastatin	+	Oral administration for 7 days beginning 1 day after TBI	WM	Qu <i>et al.</i> (2005)
	Tg2576	Simvastatin	+	In chow for 3 months before testing, beginning at 11 months of age	WM	Li <i>et al.</i> (2006)

Summary of studies evaluating effects of alternative treatments in tests of hippocampal-based memory.

+, significant improvement; Beh, behavioral; CF, conditioned fear; i.p., intraperitoneal; ICV, intracerebroventricular; NS, no significant differences; (R, retention; A, acquisition, when distinctions were made in report); RAM, radial arm maze; s.c., subcutaneous; TBI, traumatic brain injury; TSA, T-maze spontaneous alternation; WM, water maze; YSA, Y-maze spontaneous alternation.