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The Effects of Cholesterol on Learning and Memory

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Abstract

Cholesterol is vital to normal brain function including learning and memory but that involvement is as complex as the synthesis, metabolism and excretion of cholesterol itself. Dietary cholesterol influences learning tasks from water maze to fear conditioning even though cholesterol does not cross the blood brain barrier. Excess cholesterol has many consequences including peripheral pathology that can signal brain via cholesterol metabolites, proinflammatory mediators and antioxidant processes. Manipulations of cholesterol within the central nervous system through genetic, pharmacological, or metabolic means circumvent the blood brain barrier and affect learning and memory but often in animals already otherwise compromised. The human literature is no less complex. Cholesterol reduction using statins improves memory in some cases but not others. There is also controversy over statin use to alleviate memory problems in Alzheimer's disease. Correlations of cholesterol and cognitive function are mixed and association studies find some genetic polymorphisms are related to cognitive function but others are not. In sum, the field is in flux with a number of seemingly contradictory results and many complexities. Nevertheless, understanding cholesterol effects on learning and memory is too important to ignore.

Keywords

Alzheimer's disease; apolipoprotein E; ATP binding cassette transporters; cholesterol-fed rabbit; classical conditioning; eyeblink conditioning; fear conditioning; low-density lipoprotein receptors; statins; water maze; 24S-hydroxcholesterol

The Effects of Cholesterol on Learning and Memory

Cholesterol is ubiquitous in the central nervous system (CNS) and vital to normal brain function including signaling, synaptic plasticity, and learning and memory. Cholesterol is so important to brain function that it is generated independently of cholesterol metabolism in the rest of the body and is sequestered from the body by the blood brain barrier (BBB). A large number of studies pioneered by Dietschy and Turley among others have confirmed that systemic cholesterol levels do not influence cholesterol in the CNS (Dietschy, 2009; Dietschy and Turley, 2001; Dietschy and Turley, 2004). Given the importance of cholesterol to normal brain

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function, the current review will focus on the role of cholesterol in one of the most important functions of the brain – learning and memory.

Cholesterol Metabolism

Cholesterol metabolism in the CNS has a number of features in common with cholesterol metabolism in the rest of the body. In both locations, acetyl-CoA is converted to 3-hydrox-3-methylglutaryl-CoA (HMG-CoA) which is converted in a rate-limiting step to mevalonate by the enzyme HMG-CoA reductase. Mevalonate is then converted to squalene which is converted to lanosterol, which, through a series of 19 additional steps, is finally converted to cholesterol. In the adult CNS, cholesterol is synthesized almost exclusively in glial cells – astrocytes and, to a lesser extent, oligodendrocytes – with only a small amount of cholesterol synthesized in neurons. As a result of the critical role played by cholesterol in CNS function, cholesterol synthesis, metabolism, and excretion are all tightly regulated.

The major players in cholesterol synthesis, metabolism, and excretion and hence the major areas of interest in studying the effects of cholesterol on learning and memory include cholesterol itself, the enzyme HMG-CoA reductase, the cholesterol transport protein apolipoprotein E (ApoE), the adenosine triphosphate (ATP) binding cassette (ABC) transporter proteins A1 and G1 (ABCA1, ABCG1), the low-density lipoprotein receptor (LDLR) and LDLR-related protein (LRP), the oxysterols 24S-hydroxycholesterol and 27-hydroxycholesterol to which cholesterol is converted in the brain and body, respectively, and the liver X-activated receptors (LXRs) for which oxysterols are ligands and that induce expression of ApoE and ABCA1 genes (Benarroch, 2008).

CNS cholesterol represents almost 25% of the body's total unesterified cholesterol and the majority (~70%) is found in the myelin sheath with the rest found in glial and neuronal membranes (Dietschy, 2009; Dietschy and Turley, 2001). Although a great deal of cholesterol is synthesized by neurons in the developing brain, synthesis is greatly reduced in the adult brain and takes place in glial cells (Goritz *et al.*, 2006; Pfrieger, 2002). Cholesterol synthesis begins in the endoplasmic reticulum of astrocytes and involves HMG-CoA reductase which is regulated by cholesterol's inhibition of sterol-regulated element binding protein (SREBP) that binds to the sterol-regulated element-1 of the HMG-CoA reductase gene in the nucleus to modify gene expression (Benarroch, 2008; Martins *et al*., 2009). Cholesterol in astrocytes is bound to ApoE and transported into the cerebrospinal fluid (CSF) via the ABCA1 transporter protein and taken up by neurons via the low-density lipoprotein receptor. The genes for both ApoE and ABCA1 are controlled by Liver × receptors and as such are important regulators of cholesterol synthesis. Liver × receptors, in turn, are activated by the cholesterol metabolite 24S-hydroxycholesterol and to a lesser extent by 27-hydroxycholesterol (Bjorkhem, 2009). Cholesterol in the CNS is converted to 24S-hydroxycholesterol by the enzyme 24S-hydroxylase (CYP24A1, a member of the cytochrome P450 family) and can cross the BBB to be excreted from the brain (Bjorkhem *et al*., 2009; Russell *et al*., 2009). Cholesterol in the rest of the body can be converted to 27-hydroxycholesterol by 27-hydroxylase (CYP27A1) and cross the BBB into the CNS (Heverin *et al*., 2005) to act as a ligand at specific receptors (e.g., LXR) and regulate enzymatic activity.

Learning and Memory Paradigms

Human tests

Assessment of learning and memory in humans, typically described more broadly as the measurement of cognitive function, consists of administering standardized tests designed to quantify intelligence, assess list learning and recall, determine comprehension, and probe different forms of procedural and episodic memory (Baldwin and Farias, 2009; Jacova *et al*.,

2007; McDowell and Kristjansson, 1996). The number and type of test batteries designed to test cognitive function continues to grow with as many as 18 different batteries designed to be administered by computer (Wild *et al*., 2008). In some cases, learning and memory can be assessed with components of more global intelligence tests including the Working Memory Index of the Wechsler Adult Intelligence Scale (WAIS) or, in clinical settings, the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog). In other cases, standardized tests have been specifically designed to measure cognitive impairment including the widely used Mini Mental Status Exam (MMSE). The MMSE is a brief instrument used to screen for dementia that is scored on a 30-point scale and tests orientation, registration, attention and calculation, recall, and language and practice. Scores have age and education norms with a score of less than 24 generally considered to be abnormal and indicative of mild cognitive impairment with decreasing scores considered to index increasing severity of impairment.

Animal tests

The vast majority of experiments that have examined the effects of cholesterol on animal learning and memory have used a relatively small number of behavioral paradigms including the water maze and radial-arm maze, cued and contextual fear conditioning, passive and active avoidance, and eyeblink conditioning.

Water maze

The water maze is a spatial navigation task also known as the Morris water maze (Morris, 1984) that assesses spatial learning and memory by allowing a mouse or rat to swim in a pool of opaque water in which an escape platform has been placed. In the cued or visible platform version, the platform is positioned above the water or its position just below the water is indicated by a flag or other proximal cue. In the hidden-platform version of the task, the platform is submerged and spatial cues are placed beyond the maze so that the subject must navigate to the platform using these spatial cues. In addition to assessing learning of and memory for a specific cue (e.g., the flag), the visible platform version of the task can assess whether sensory and motor abilities have been compromised by a treatment or condition. For example, a transgenic mouse may not be able to find the platform because it cannot swim as well as wild-type controls or cannot see the flag.

Learning the water maze task is usually assessed over a number of trials and measured as the time taken and the distance swum to the platform after the rodent is released from different positions around the edge of the pool. Memory for the task is assessed on days after training by allowing the rat or mouse to search for a platform that has been removed and measuring the time spent in the quadrant where the platform used to be, the number of times it crosses the position of the platform, and the time spent in the other quadrants of the pool.

Radial arm maze

The radial arm maze usually consists of a central start box from which radiate as many as twelve but usually eight identical runways (arms) with a goal box at the end of each arm where food or water can be left as a reward. The start box has a gate to each of the arms that can be closed limiting the number of arms to which the subject has access. In some paradigms the characteristics of the arms can modified so that they may be a different color, enclosed or provided with a different texture. Each arm contains photo beams that determine entry and may be used to determine speed. Runways entered and time to traverse the runway can also be assessed by an observer who should be "blind" to the experimental condition of the animals.

Fear conditioning

Cued fear conditioning involves the delivery of a brief foot shock through an electrified floor grid that is signaled by a cue such as a 30-second tone or light. Contextual fear conditioning involves the delivery of a brief foot shock that takes place in a different, usually novel environment. Cued and contextual fear conditioning may be combined within the same chamber. The rodent response to foot shock is freezing and increased heart rate. These two responses and particularly freezing have become standard indices of what is hypothesized to be fear of the cue or the context with which the foot shock has been paired.

Passive and active avoidance

Like fear conditioning, active and passive avoidance tasks involve a brief foot shock delivered through an electrified floor grid to a mouse or rat in a specific location. However, in avoidance tasks, the rodent must either move from the location where it has experienced the shock (active avoidance) or not enter that location (passive avoidance). An important aspect in both tasks is that rodents normally prefer a dark location over a brightly lit one and the foot shock usually occurs in the dark location. To avoid foot shock, a rat or mouse must either leave the dark side of the enclosure for the brightly lit side (active) or stay in the brightly lit side and not enter the dark side (passive). The day following active avoidance training, the latency with which a rodent leaves the previously shocked location is measured. The day following passive avoidance training the latency to enter the previously shocked dark location is measured. In some cases, a rat or mouse may never enter the dark location and an upper latency cut-off value is assigned (Crawley, 2000; Lu *et al*., 2009).

Eyeblink conditioning

Classical or Pavlovian conditioning of the eyeblink was originally developed in the early part of the 20th century and modeled after Pavlov's studies with dogs pairing an innocuous or neutral stimulus such as a bell with a significant event such as food (Pavlov, 1927). In the case of eyeblink or eyelid conditioning, the neutral stimulus is typically a brief tone or flashing light and the significant event is a puff of air to the eye that elicits reflex closure of the eyelids. With repeated pairings of the tone and air puff, subjects soon begin to close their eyes before the puff reaches the cornea providing evidence that an association between the two has been formed. Eyeblink conditioning is most commonly conducted with rabbits (Gormezano *et al*., 1983) or rats (Schmajuk and Christiansen, 1990; Skelton, 1988).

Each of the foregoing behavioral paradigms and procedures has been used to assess the effects of dietary, genetic and pharmacological manipulations of cholesterol, cholesterol synthesis and cholesterol metabolism on animal learning and memory. In the case of the effects of cholesterol on human learning and memory, dietary and pharmacological manipulations as well as genetic differences have been assessed almost exclusively by psychological testing including intelligence tests, cognitive testing including tests of recall, cognitive impairment and dementia, and epidemiological analysis.

Cholesterol

Human Studies

There is a significant body of evidence that high cholesterol levels may be detrimental to human learning and memory. A significant number of studies show that elevated serum cholesterol is a risk factor for mild cognitive impairment (Foster, 2006; Kivipelto *et al*., 2001; Näslund *et al*., 2000; Solomon *et al*., 2007; Yaffe *et al*., 2002) and dementia (Solomon *et al*., 2009b; Whitmer *et al*., 2005) and that cholesterol levels are correlated with measures of intelligence (Atzmon *et al*., 2002; Muldoon *et al*., 1997; Reitan and Shipley, 1963; van Exel *et al*., 2002; Yaffe *et al*., 2002) except in the very elderly (Solomon *et al*., 2009a; West *et al*., 2008). Low

HDL cholesterol has been correlated with deficits and declines in memory in midlife (Singh-Manoux *et al*., 2008). A study of cholesterol synthesis showed the level of the cholesterol precursors lanosterol and lathosterol are correlated with low memory performance as subjects age (Teunissen *et al*., 2003). Epidemiological evidence also suggests a strong relationship between cholesterol levels and Alzheimer's disease - a disease noted for its severe decline in learning and memory (Canevari and Clark, 2007; Evans *et al*., 2000; Hartmann, 2001; Jarvik *et al*., 1995; Ledesma and Dotti, 2006; Lesser *et al*., 2009; Notkola *et al*., 1998; Simons *et al*., 2001; Sjogren *et al*., 2006; Stewart *et al*., 2001).

There are other human studies, however, showing that increased cholesterol improves learning and memory. For example, high cognitive functioning is correlated with high cholesterol (Elias *et al*., 2005; Panza *et al*., 2006) and cholesterol may protect against cognitive decline especially in the elderly (Mielke *et al*., 2005; Panza *et al*., 2006; van den Kommer *et al*., 2009; West *et al*., 2008). A factor that is in some dispute is the relationship between LDL and HDL and improved memory. West and colleagues have shown that better memory functioning is associated with higher total and LDL cholesterol levels in the very elderly whereas Atzmon and coworkers have suggested that only higher HDL levels are correlated with better cognitive function in the very elderly (Atzmon *et al*., 2002; West *et al*., 2008).

Taken together, the human data suggest that there is a relationship between cholesterol levels and adult learning and memory. This relationship appears to change as a function of age with cholesterol having its most detrimental effects in middle age and it's most beneficial or protective effects in the very old. Interestingly, a recent study by Perry and colleagues found that there was no association between cognitive measures and serum cholesterol concentrations among the young (Perry *et al*., 2009).

Animal studies

Manipulations of cholesterol in animals have shown a number of different relationships between cholesterol and memory. For example, decreasing cholesterol in aged animals improves learning and memory for tasks such as the water maze (Kessler *et al*., 1986; Yehuda *et al*., 1998; Yehuda and Carasso, 1993). Feeding mice a 2% cholesterol diet for eight weeks may result in deficits in working memory in the water maze (Thirumangalakudi *et al*., 2008) but not always (Li *et al*., 2003). Feeding middle-aged rats a diet high in cholesterol andfat for eight weeks also resulted in deficits in working memory in the water maze (Granholm *et al*., 2008). Rats, mice and rabbits given calcium channel blockers that reduce the esterification of cholesterol and increase the hydrolysis of existing cholesterol esters (Nayler, 1999; Schachter, 1997) demonstrate improvements in a number of learning and memory paradigms including passive avoidance (Quartermain *et al*., 2001), water maze (Kane and Robinson, 1999; Quartermain *et al*., 2001), and eyeblink conditioning in rats and rabbits (Deyo *et al*., 1989; Kane and Robinson, 1999; Quartermain, 2000; Woodruff-Pak *et al*., 1997).

Elevating cholesterol in young DBA/2 mice improves performance in the water maze - a task normally impaired in this mutant (Miller and Wehner, 1994; Upchurch and Wehner, 1988). Dufour and colleagues showed feeding adult rats 2% cholesterol enhances water maze learning (Dufour *et al*., 2006). This effect was replicated by Micale and colleagues who also showed the enhancement in water maze learning could be reversed by blocking steroid synthesis (Micale *et al*., 2008). Animals that are either deficient in cholesterol or have cholesterol synthesis blocked have problems with learning and memory in the water maze (Endo *et al*., 1996; Voikar *et al*., 2002) and during classical conditioning of the rat eyeblink (Endo *et al*., 1996; O'Brien *et al*., 2002; Voikar *et al*., 2002; Xu *et al*., 1998). The learning deficits in eyeblink conditioning induced by impaired cholesterol synthesis were reversed by feeding rats cholesterol (Xu *et al*., 1998).

In a series of rabbit eyelid conditioning experiments we have documented the effects of feeding cholesterol on both learning and memory. Prompted by Sparks' original observation that cholesterol-fed rabbits developed elevated levels of neuronal beta amyloid (Sparks *et al*., 1994), we were surprised to find that rabbits fed cholesterol for eight weeks showed improved trace classical conditioning and reflex facilitation of the NMR (Schreurs *et al*., 2003) and that these facilitating effects of cholesterol were a function of the concentration (Schreurs *et al*., 2007b) and duration of the cholesterol diet (Schreurs *et al*., 2007a). These facilitating effects were generalized beyond NMR conditioning because an eight-week, 2% cholesterol diet also facilitated rabbit heart rate conditioning – an index of conditioned fear (Schreurs *et al*., 2007c). It wasn't until beta amyloid plaques were induced by adding 0.12 PPM copper to the drinking water given cholesterol-fed rabbits that learning suffered and rabbits performed more poorly than normal chow-fed controls (Sparks and Schreurs, 2003). Woodruff-Pak and her colleagues have shown that this cholesterol and copper-induced deficit in rabbit eyelid conditioning can be reversed by the administration of galantamine – an acetylcholinesterase inhibitor used to treat Alzheimer's disease.

More recently, we have examined the effects of a 2% cholesterol diet on memory of NMR conditioning and found that an eight-week cholesterol diet following ten days of paired classical conditioning debilitated the rabbits' ability to remember the association formed eight weeks earlier (Darwish *et al*., 2010). This effect occurred in the absence of detectable diet-induced changes in the cholesterol content of the brain which is consistent with the finds of Diestchy and Turley (2004). Surprisingly, there was a significantly higher level of cholesterol in the hippocampus and forebrain of rabbits given classical conditioning relative to unpaired controls regardless of their diet, suggesting that cholesterol levels in the brain can change as a function of experience (Dufour *et al*., 2006; Koudinov and Koudinova, 2001) as well as experience being able to change as a function of cholesterol.

Peripheral effects of cholesterol

The interesting question that is raised by the effects of cholesterol on learning and memory turns upon the inability of dietary cholesterol to cross the BBB into the CNS. The peripheral effects of feeding rabbits cholesterol are atherosclerosis, inflammation, and liver toxicity. As a result of elevated cholesterol, the liver produces increased lipoproteins rich in cholesterol esters that stay in the bloodstream and lead to atherosclerotic lesions. High levels of LDL trigger the endothelial cell expression of adherence molecules that mediate attachment of monocytes and lymphocytes to the rabbit artery wall that then migrate into the wall and result in fatty streaks (Jessup *et al*., 2004; Rader and Daugherty, 2008). Oxidized LDL in the artery wall accumulates in macrophages that have differentiated from monocytes and develop into foam cells. Other macrophages are activated by proinflammatory cytokines in the artery wall and release more proinflammatory mediators including reactive oxygen and nitrogen species, interleukin-1β, and tumor necrosis factor alpha (Hansson *et al*., 2008).

There is a body of literature documenting the effects of proinflammatory mediators including tumor necrosis factor alpha and interleukin-1β on synaptic plasticity (Di Filippo *et al*., 2008; Pickering and O'Connor, 2007) and membrane excitability (Schafers and Sorkin, 2008; Viviani *et al*., 2007). Moreover, systemic injection of the inflammatory cytokine interleukin- acquisition of classically conditioned eyeblink responses in rats (Servatius and Beck, 2003). Although there is evidence that these peripheral inflammatory mediators are transported across the BBB (Banks, 2005), breaches of the BBB including those produced by a high cholesterol diet (Chen *et al*., 2008; Sparks *et al*., 2000) may increase the influence of these mediators in the brain. Cholesterol in the rabbit induces hepatotoxicity by activating hepatic stellate cells, producing fibrosis, fat deposition and ballooning degeneration leading to focal necrosis, inflammatory reactions and lipogranuloma (Kainuma *et al*., 2006). Antioxidant activity of

glutathione peroxidase and catalase decrease significantly in the cholesterol-fed rabbit liver giving rise to increased oxidation and formation of lipid peroxidation and oxysterols (Mahfouz and Kummerow, 2000).

Given the above, our ability to understand the mechanisms by which cholesterol influences learning and memory may turn upon its peripheral as well as central effects. For example, there is strong evidence that human cognitive impairment is correlated with the extent of cholesterol-induced atherosclerosis both in peripheral arterial disease (Rafnsson *et al*., 2009) and in carotid atherosclerosis (Romero *et al*., 2009). Regardless of the source of mediators thought to influence learning and memory, learning and memory are functions of the CNS and it is the CNS that must be reached by these mediators before they can have an effect.

Central effects of cholesterol

The central effects of feeding a cholesterol diet to rabbits have been explored by a number of investigators including Sparks and his colleagues who have examined microglia (Xue *et al*., 2007) and the role of copper in beta amyloid accumulation and clearance (Sparks *et al*., 2002b; Sparks, 2004; Sparks, 2007; Sparks *et al*., 2007) and Ghribi and his co-workers who have focused on the relationship between cholesterol and beta amyloid (Ghribi *et al*., 2006a; Ghribi *et al*., 2006b; Jaya Prasanthi *et al*., 2008; Sharma *et al*., 2008). The most consistent central effect of feeding rabbits cholesterol is the accumulation of intracellular beta amyloid – a finding first reported by Sparks (Sparks *et al*., 1994) and replicated in a number of different laboratories (Beach, 2008; Ghribi *et al*., 2006b; Ronald *et al*., 2009; Woodruff-Pak *et al*., 2007; Wu *et al*., 2003; Zatta *et al*., 2002).

There is a very large body of data implicating cholesterol in the deposition of beta amyloid, and thus, in Alzheimer's disease (Canevari and Clark, 2007; Hirsch-Reinshagen and Wellington, 2007; Ledesma and Dotti, 2006; Reid *et al*., 2007; Sparks, 2007) but see (Elder *et al*., 2007). Although a detailed analysis of this literature is beyond the scope of the current review, it is important to note that the relationship between cholesterol and beta amyloid is complex (Bales, 2010; Grimm *et al*., 2007; Hartmann, 2001; Kirsch *et al*., 2003; Ledesma and Dotti, 2006; Lukiw *et al*., 2005; Martins *et al*., 2009; McLaurin *et al*., 2003; Panza *et al*., 2006; Raffai and Weisgraber, 2003; Roher *et al*., 1999; Sjogren *et al*., 2006; Wood *et al*., 2007; Yanagisawa, 2002) and may involve a number of factors including: (1) the dependence of beta and gamma secretase on cholesterol to cleave the amyloid precursor protein (APP) (Frears *et al*., 1999; Wahrle *et al*., 2002), (2) the connection between apoE and Alzheimer's disease (Esler *et al*., 2002; Hartmann, 2001; Hoshino *et al*., 2002; Jarvik *et al*., 1995; Notkola *et al*., 1998), (3) a cholesterol-induced overproduction of beta amyloid which blocks cholesterol trafficking and leads to neurodegeneration (Liu *et al*., 1998; Yao and Papadopoulos, 2002), and (4) the role ApoE plays in calcium homeostasis (Hartmann *et al*., 1994; Veinbergs *et al*., 2002). There is also evidence that beta amyloid may affect cholesterol (Hartmann, 2006). It should be noted that there are many who argue that beta amyloid has important normal physiological functions (Grimm *et al*., 2007; Pearson and Peers, 2006; Wegiel *et al*., 2007) that take place throughout life (Wegiel *et al*., 2007) and it is only when there is an imbalance in beta amyloid production or clearance that it becomes toxic (Pearson and Peers, 2006; Sparks, 2007).

A growing body of evidence, particularly from cell culture systems and transgenic rodents, indicates it is the oligomeric form of beta amyloid that is important for its toxic effects and its effects on learning and memory (Billings *et al*., 2005; Billings *et al*., 2007; Dineley *et al*., 2002; Lesne *et al*., 2006; Ma *et al*., 2007; Morgan, 2003; Shankar *et al*., 2008). The initial debate about the relative effects of soluble versus insoluble beta amyloid (Despande *et al*., 2006; Gouras *et al*., 2005; Haass and Selkoe, 2007; Kayed *et al*., 2003; Zerbinatti *et al*., 2004) has given way to a more recent discussion of the oligomeric form of beta amyloid with

higher soluble oligomers being more toxic and having greater effects on synaptic plasticity than monomers or dimers (Chafekar *et al*., 2008; Lacor *et al*., 2007; LaFerla *et al*., 2007; Shankar *et al*., 2007; Shankar *et al*., 2008; Walsh and Selkoe, 2007). However, Shankar et al. (2008) have shown that soluble beta amyloid dimers obtained from AD patients disrupted memory for passive avoidance in rats. Finally, it should be noted that despite the considerable body of evidence implicating beta amyloid in Alzheimer's disease there is a significant minority who have argued that it is not all clear that beta amyloid is the cause of the disease (Joseph *et al*., 2001; Obrenovich *et al*., 2002; Pearson and Peers, 2006; Robakis, 2010; Robinson and Bishop, 2002; Savory *et al*., 2002).

Statins

One of the major strategies for treating high cholesterol and the cardiovascular disease that results is to interfere with the rate limiting step in cholesterol synthesis by inhibiting HMG-CoA reductase using statins – HMG-CoA reductase inhibitors. Statins have been very successful in lowering cholesterol and have been found to have a number of additional benefits including improved endothelial function, decreased oxidative stress, decreased inflammation, and improved immune responses (Jasinska *et al*., 2007; Liao and Laufs, 2005). As a result, it is difficult to determine whether statins' effects on learning and memory are dependent on their effects on lowering cholesterol or on their non-cholesterol pleiotropic effects (Gotto Jr. and Farmer, 2001; Jasinska *et al*., 2007; Liao and Laufs, 2005).

Human studies

There is some evidence, although controversial, that lowering cholesterol levels with statins may reduce the rate of cognitive decline in Alzheimer's disease patients (Arvanitakis *et al*., 2008; Haag *et al*., 2009; Hoglund *et al*., 2005; Hoyer and Riederer, 2007; Solomon and Kivipelto, 2009; Sparks *et al*., 2006; Zandi *et al*., 2005). These studies were prompted by earlier reports that statins lowered the risk of developing dementia (Jick *et al*., 2000; Wolozin *et al*., 2000). This area of research has been reviewed recently by McGuinness and colleagues for the Cochrane Database and they found there was no significant evidence that statins either helped or hindered cognition in Alzheimer's patients. This is important because there is an older literature of case reports and clinical trials suggesting that statins may have a negative impact on cognition (Evans and Golomb, 2009; Muldoon *et al*., 2000). Given these mixed results of statin effects on cognition in Alzheimer's disease patients, some have suggested it might be useful to parse the data in terms of whether or not statins in cross the BBB (Fassbender *et al*., 2002; Haag *et al*., 2009; Sparks *et al*., 2002a; Thelen *et al*., 2006). Interestingly, Haag et al. (2009) recently reported that statins reduced the risk of Alzheimer's disease regardless of whether or not they crossed the BBB. Nevertheless, in the most recent international, multicenter, double-blind, randomized, parallel-group study with 640 patients, Feldman and associates reported no clinical benefit of atorvastatin as a treatment for mild or moderate Alzheimer's disease (Feldman *et al*., 2010).

In contrast to studies with dementia patients, there is some evidence that statins may aid cognition in non-demented subjects. For example, a study by Parale and colleagues shows that statins improve cognitive function in non-demented patients over controls (Parale *et al*., 2006). In another study, Bernick and co-workers found that statin use slightly reduced the rate of cognitive decline in a group of normal subjects aged over 65 compared to matched non-treated controls (Bernick *et al*., 2005). Although the preponderance of demented-patient evidence suggests no strong positive or negative effects of statins on learning and memory, the data from non-demented subjects suggest that others may benefit. It could be argued that by the time dementia is advanced, there is so much pathology that statins can no longer be of benefit. To emphasize this point, Sparks and colleagues found that taking statins reduced the

incidence of cognitive decline for those at risk for but not showing signs of Alzheimer's disease (Sparks *et al*., 2008).

Animal studies

A number of animal studies have shown statins can facilitate learning and memory in rodents (Li *et al*., 2006; Lu *et al*., 2007). Li et al. (2006) showed that simvastatin was able to improve acquisition of the water maze task but had no effect on the visible platform version of the task suggesting statins affect learning without affecting sensory or motor function. Lu et al. (2007) demonstrated that rats suffering traumatic brain injury spent more time in the platform quadrant following water maze training if given simvastatin or atorvastatin compared to saline controls. Rats given simvastatin, a statin that crosses the BBB, did better than rats given atorvastatin, a statin that does not cross the BBB. There was no comparison of the effects of the statins on water maze performance in the absence of brain jury. In another water maze experiment, Koladiya and colleagues found that statins were able to reduce L-methione-induced vascular dementia that caused deficits in both acquisition and retention of the water maze task (Koladiya *et al*., 2008). However, both learning and memory in rats given the statins alone were no better than in controls.

Apolipoprotein E

ApoE is a glycoprotein secreted by glia that forms part of a lipoprotein particle that transports cholesterol through the CNS particularly to neurons. ApoE may also be involved in other transport functions particularly the clearance of beta amyloid. There is a significant body of literature showing that learning and memory in both human and non-human subjects is affected by the expression and specific allelic isoforms of ApoE (E2, E3, and E4). In Alzheimer's disease patients, the ApoE4 allele is over-represented and the ApoE3 allele is under-represented (Martins *et al*., 2009) suggesting the former is a risk factor for the disease whereas the latter may be protective. The suggestion that there is an increased susceptibility for developing Alzheimer's disease associated with the ApoE4 allele has been firmly established (Brouwers *et al*., 2008; Chen *et al*., 2002; Deary *et al*., 2002; Mayeux *et al*., 2001; Poirier, 2005; Sparks, 1997).

Human studies

Despite the strong association between ApoE genotype and Alzheimer's disease, the evidence for the effects of ApoE on normal human learning and memory has been less clear. A number of early studies found that there was an association between ApoE genotype and cognition in middle-aged adults (Deary *et al*., 2002; Dik *et al*., 2001; Flory *et al*., 2000; Juva *et al*., 2000; Mayeux *et al*., 2001; Wilson *et al*., 2002) whereas other studies found no such relationship in the elderly (Small *et al*., 2000) or very elderly (Salo *et al*., 2002). More recent studies indicate that the effects of ApoE genotype on cognitive function may be affected by cholesterol levels (de Frias *et al*., 2007) but even when cognitive test results are adjusted for total cholesterol, the ApoE4 allele still has a significant negative effect (Liu *et al*., 2008). The interaction between ApoE allele and cholesterol levels points to the complexity of trying to examine a single aspect of cholesterol's effects on learning and memory in isolation. This becomes particularly important for ApoE because it is involved not only in cholesterol transport but in beta amyloid aggregation and clearance, and may be involved in tau phosphorylation, synaptic plasticity and neuroinflammation (Kim *et al*., 2009).

Animal studies

Unlike human studies where ApoE cannot be manipulated, animal studies have examined the effects of ApoE insertion and deletion in transgenic mice as well as infusion of ApoE directly into rat brain to determine the effects of ApoE on learning and memory. Although some

consistency has now emerged, it should be noted that, like the human studies, there are contradictory findings on the effects of ApoE on learning and memory in mice (Lominska *et al*., 2001) and that some of these differences may be due to strain and gender issues – a theme that appears to pervade research with transgenic mice (Arndt and Surjo, 2001; Brooks *et al*., 2004; van der Staay and Steckler, 2001). In a comprehensive study by Hartman and co-workers, ApoE knockout mice were engineered to have the human isoforms of ApoE3 or ApoE4 expressed in astrocytes and these mice were compared to ApoE knockout mice and wild type controls on a range of behavioral tasks (Hartman *et al*., 2001). Hartman and colleagues reported that all the ApoE mice were more reactive than the wild type mice on sensory/motor tasks including their startle response to a loud noise. However, ApoE mice showed no differences in water maze acquisition or retention. It was only when mice were tested in the radial arm maze that significant differences began to emerge in the acquisition of the task with ApoE4 mice needing more days to reach criterion and committing more errors than any other group. In contrast to the Hartman et al. (2001) water maze data, other groups have shown that ApoE deletions (Veinbergs *et al*., 2000) and human ApoE4 insertions (Bour *et al*., 2008) have deleterious effects on water maze performance. Importantly, the study by Bour et al. (2008) as well as an earlier study by the same group (Grootendorst *et al*., 2005) showed that there was some gender specificity to the effects of ApoE4 insertion on learning and memory with female mice showing poor water maze performance and retention whereas males where no worse than wild-type controls. Interestingly, there is one study that shows spatial maze learning – at least in the radial arm maze – is dependent on the age and background strain of the ApoE deficient mice (Lominska *et al*., 2001). Specifically, it wasn't until six months of age that ApoE deficient mice on a C57Bl/6 background failed to show learning. One of the most recent ApoE experiments involved delivery of ApoE peptides directly into the hippocampus of rats rather than manipulation of gene expression in mice (Eddins *et al*., 2009). Eddins and colleagues found that infusion of segments of the ApoE protein into the ventral hippocampus produced impairment in the radial arm maze that persisted for several weeks after the infusion.

As in the case of statins, ApoE appears to be involved in a number of functions other than its direct effects on cholesterol. As mentioned above, ApoE has been implicated strongly in beta amyloid deposition and clearance with ApoE4 being less effective in clearing beta amyloid than ApoE2 or ApoE3 (Martins *et al*., 2009). Double transgenic mice that express both human beta amyloid and ApoE have provided evidence of the isoform-dependent effects of ApoE on beta amyloid accumulation (Bales, 2010). In a recent review, Kim et al. (2009) describe additional roles for ApoE including involvement in neurotoxicity, tau phosphorylation, neuroinflammation, cerebrovascular function and brain metabolism. The role of ApoE in learning and memory is further complicated because it is regulated by the ABCA1 and because it plays a role as a ligand for the low density lipoprotein receptor.

ATP Binding Cassette Transporters

Although 13 of 48 ATP binding cassette transporters are active in the CNS, only ABCA1 and ABCG1 have been examined for their role in learning and memory. The cholesterol transporter ABCA1 is a crucial regulator of ApoE and with the genetic loss of ABCA1 there is a significant increase in beta amyloid in the CNS (Kim *et al*., 2008).

Human studies

Reynolds and co-workers have conducted targeted genetic association analyses of ABCA1 and Alzheimer's disease and found there to be a highly significant relationship between the two, implicating ABCA1 in dementia (Reynolds *et al*., 2009). Akram and colleagues recently found that there was a significant positive correlation between ABCA1 mRNA expression and dementia severity and that this differential expression was also reflected at the protein level (Akram *et al*., 2010).

The ATP binding cassette transporter ABCG1 is also important for cholesterol transport but there is considerable debate about whether or not it has a role in beta amyloid production with some suggesting it may even have a protective function (Kim *et al*., 2008). However, there is at least one study showing that ABCG1 is associated with Alzheimer's disease (Wollmer *et al*., 2007).

Animal studies

In the only ABCA1 animal study to date, Lefterov et al. (2009) reported that the memory deficits shown by an Alzheimer's disease transgenic mouse model (aged APP transgenic mice) in water maze acquisition and retention were exacerbated by a deficiency in ABCA1. Importantly, they found that mice deficient in ABCA1 without the APP mutation performed as well as wild-type controls (Lefterov *et al*., 2009).

There are two studies of learning and memory in transgenic mice over-expressing ABCG1 from different groups and both failed to find any effects of ABCG1 on water maze acquisition or retention (Burgess *et al*., 2008; Parkinson *et al*., 2009). Perhaps like ABCA1, ABCG1 may only have an effect when learning and memory are already compromised as in the human studies of dementia and the Lefterov et al. (2009) study of APP transgenic mice.

Low-Density Lipoprotein Receptors

The LDLR family is comprised of at least nine members, two of which – the low-density lipoprotein receptor and low-density lipoprotein receptor-related protein (LRP) – have been examined for a role in Alzheimer's disease (Deane *et al*., 2009) and in mouse learning and memory (Qiu *et al*., 2006).

Human studies

There have been a number of studies of the association between members of the LDLR family and Alzheimer's disease in humans and they have yielded conflicting results. Despite a number of studies finding no association between the LDLR gene polymorphism rs5925 and Alzheimer's disease (Bertram *et al*., 2007; Rodriguez *et al*., 2006), one study has found that a different polymorphism (rs688) may be related to Alzheimer's disease – at least in men (Zou *et al*., 2008). With the exception of one study where there was a genetic association between LRP and Alzheimer's disease in a sample of Chinese patients (Zhou *et al*., 2008), other studies have found no significant association between LRP polymorphisms and Alzheimer's disease (Bahia *et al*., 2008; Sagare *et al*., 2007) or learning and memory during aging in non-demented subjects (Reynolds *et al*., 2006). However, LRP has been shown to transport beta amyloid from the brain across the BBB and is lower in the serum of Alzheimer's patients than controls (Sagare *et al*., 2007).

Animal studies

Studies of the effects of the LDLR family on murine learning and memory can be divided into those that employ genetic deletion of LDLR (Cao *et al*., 2006; Mulder *et al*., 2004; Thirumangalakudi *et al*., 2008) and, because deletion of LRP is a lethal mutation, those that manipulate LRP either by over-expression (Zerbinatti *et al*., 2004), administration of an antagonist (Harris-White *et al*., 2004), or reduced expression using antisense (Jaeger *et al*., 2010).

Cao and colleagues showed that cross-breeding LDLR-deficient mice with Tg2576 mice produced animals that at 10 months of age were hypercholesterolemic, had increased cerebral beta amyloid deposits and were impaired in water maze learning and retention compared to Tg2576 mice in which LDLRs were intact. Importantly, single transgenic mice deficient in

LDLRs also became hypercholesterolemic but showed no deficits in water maze performance compared to control mice not deficient in LDLRs (Cao *et al*., 2006). These latter results are in contrast to an earlier study by Mulder et al. (2004) who found that compared to mice with LDLRs, LDLR-deficient mice had impaired memory for the location of a hidden platform in the water maze task. Differences between these two studies have been attributed to gender and background strain differences (Cao *et al*., 2006). However, it should be noted that, like any genetic manipulation, there is the potential for unwanted side effects. In this case, LDLR-deficient mice suffer from higher blood pressure and heart rate than controls (Mulder *et al*., 2004). Thirumangalakudi et al. (2008) also found memory impairment in LDLR-deficient mice compared to controls but in this case it was in retention of the radial-arm version of the water maze. In this task, hidden platforms are placed at the end of four of eight maze arms and the animal must locate a platform by swimming down the arms of the maze. Once a platform is found, it is removed and the animal must find another of the remaining platforms. Memory is assessed later in terms of the number of entries into arms that previously contained a platform (correct) and those that never contained a platform (error). The background strain for this latter study was the same as that in the Cao et al. (2006) study (C57BL/6) but the gender was not specified.

In a study of LRP, Zerbinatti et al. (2004) reported that over-expression of the LRP receptor in mice also over-expressing the amyloid precursor protein induced an increase in soluble beta amyloid as a function of age and resulted in poorer acquisition of the water maze task in both young and old mice. In a second LRP study, Harris-White and colleagues showed that receptor-associated protein (RAP), an LRP antagonist, attenuated the cellular targeting of beta amyloid induced by transforming growth factor and prevented deficits in water maze memory retention (Harris-White *et al*., 2004). Interestingly, as in a number of other cases where administration of a treatment to controls has no effect, administration of the RAP by itself did not significantly alter water maze memory scores compared to saline controls. In a third study, Sagare and colleagues chronically treated APP transgenic mice with LRP-IV – a major binding domain of LRP that binds beta amyloid with high affinity – and found treated mice performed better in a novel object recognition task than vehicle-treated APP mice (Sagare *et al*., 2007). Finally, Jaeger et al. (2009) used LRP mRNA antisense infusion into the brain to decrease the level of LRP and found impaired active avoidance and object recognition compared to animals infused with scrambled antisense. Unlike the Zerbianatti, Harris-White, and Sagare studies, the study by Jaeger and colleagues did not manipulate beta amyloid but did find it was increased in the brain and decreased crossing the BBB out of the CNS.

Liver × Receptors

LXRs are key transcription regulators of carbohydrate and lipid metabolism and are abundant throughout the body and brain. LXRs act as cholesterol and cholesterol metabolite sensors and regulate the expression of ABCA1 as well as ABCG1 and induce ApoE secretion. The importance of LXRs as system sterol sensors has led to the identification and testing of LXR agonists in a number of rodent models (Baranowski, 2008).

Human studies

There are no human studies of the effects of LXR on learning and memory.

Animal studies

Three different transgenic mouse studies have reported improvements in learning and memory following use of the LXR agonists TO901317 (Riddell *et al*., 2007; Vanmierlo *et al*., 2009) and GW3965 (Jiang *et al*., 2008). Riddell et al. (2007) showed that seven days of orally administered, brain penetrant TO0901317 lowered the level of beta amyloid in the

hippocampus and improved memory of contextual fear conditioning in young APP transgenic mice (Tg2576) compared to wild-type controls. Similarly, Jiang et al. (2008) showed that six days of orally administered GW3965 to aged Tg2576 mice lowered the level of beta amyloid in the hippocampus and improved memory of contextual fear conditioning. The drug did not affect wild-type controls. Vanmierlo et al. (2009) found that extended administration of TO0901317 in the food of aged double transgenic APP-Presenilin (APP/PS) mice for six to nine weeks did not change beta amyloid plaque levels but did restore impaired object recognition memory. Object recognition involves exposing mice to two novel objects that can be explored and then, after a delay, presenting one of the now familiar objects with another novel object and allowing the mice to explore the two objects again. Mice that remember the familiar object will spend more time exploring the novel object. These improvements in learning and memory occurred against a backdrop of increased brain cholesterol precursor and decreased cholesterol metabolite levels (Vanmierlo *et al*., 2009) and elevated brain ApoE and ABCA1 levels (Jiang *et al*., 2008; Riddell *et al*., 2007). Clearly, LXR agonists have multiple CNS effects on key components of the cholesterol metabolic pathway. What remains to be determined is the causal connection between this multiplicity of effects and learning and memory. This is particularly important because as noted above, manipulation of ApoE or ABCA1 in wild-type controls has no effect on learning and memory.

Cholesterol Metabolites

Cholesterol is not degraded within the brain and cannot cross the BBB. However, cholesterol must be excreted and this is accomplished when cholesterol is converted into the brain-specific cholesterol metabolite 24S-hydroxcholesterol by the enzyme 24S-hydroxlase (Bjorkhem, 2002). In the periphery, systemic cholesterol is metabolized within the body to one of a number of products including the metabolite 27-hydroxycholesterol which can cross the BBB and enter the CNS (Heverin *et al*., 2005). The role of cholesterol metabolites in learning and memory in humans have been explored by measuring levels of 24S- and 27-hydoxycholesterol in serum and the cerebrospinal fluid (Kolsch *et al*., 2004; Papassotiropoulos *et al*., 2002; van den Kommer *et al*., 2009) and by identifying genetic polymorphisms related to cognitive impairment and Alzheimer's disease (Fernandez del Pozo *et al*., 2006; Fu *et al*., 2009; Papassotiropoulos *et al*., 2005). Animal studies of the effects of cholesterol metabolites on learning and memory have included knockout mice lacking 24-hydroxylase (Kotti *et al*., 2006), infusion of 24-hydroxycholesterol into the brain (Zhao *et al*., 2009) and manipulation of the CYP46A1 gene that encodes the enzyme cholesterol 24-hydroxylase (Hudry *et al*., 2009).

Human studies

Lutjohann and colleagues have reported a series of studies in which they measured the cholesterol metabolites 24S- and 27-hydroxycholesterol in demented patients and controls. In one study they found that levels of 24S-hydroxycholesterol in the cerebrospinal fluid of Alzheimer's patients and those with mild cognitive impairment were higher than in subjects without cognitive impairment (Papassotiropoulos *et al*., 2002). In a second study, Heverin et al. (2005) found increased post mortem levels of 27-hydroxcholesterol in the brains Alzheimer's patients compared to controls. In a third study, cholesterol-corrected levels of both 24S- and 27-hydroxycholesterol were significantly reduced in the plasma of demented versus non-demented subjects and depressed patients (Kolsch *et al*., 2004). This relationship did not hold in a longitudinal study of cognitive decline in normal subjects between the ages of 55 and 85 where only the ratio between cholesterol and 27-hydroxycholesterol in carriers of the ApoE4 allele was a predictor of worsening cognitive function (van den Kommer *et al*., 2009). The variability in these data may be attributable, in part, to the very small quantities of these metabolites and the difficulty in measuring them. It is also interesting that what appear to be

consistent findings *in vitro* have been less consistent *in vivo* suggesting that there are complex interactions among and between many of the steps in the synthesis and metabolism of cholesterol in the CNS (Bjorkhem, 2009; Russell *et al*., 2009).

A number of genetic association studies have found polymorphisms of the 24S-hydroxylase gene CYP46A1 in patients with mild cognitive impairment and Alzheimer's disease. Papassotiropoulos et al. (2005) reported that a cluster of cholesterol-related genes including a single nucleotide polymorphism of CYP46A1 (rs754203) contributed to the risk for Alzheimer's disease. Fernandez del Pozo and her colleagues examined the effect of the polymorphic site rs754203 on mild cognitive impairment and Alzheimer's disease in patients with the ApoE3 or ApoE4 allele (Fernandez del Pozo *et al*., 2006). They found that the polymorphism increased the risk of Alzheimer's disease in those with the ApoE3 form but not in those with the ApoE4 form. A number of polymorphisms of the CYP46A1 gene including rs754203 were examined in older Chinese subjects who were stratified into cognitively intact, mild, moderate, and severely demented using the Chinese versions of the MMSE and ADAS-cog (Fu *et al*., 2009). Fu et al. found at a 2-year follow up that subjects who deteriorated to dementia were more likely to carry the polymorphic site rs754203 or rs3742376 of the 24-hydroxylase gene than those that did not.

Animal studies

Kotti and her colleagues found that transgenic mice lacking 24-hydroxylase failed to learning the water maze task compared to wild-type controls (Kotti *et al*., 2006). These mice were also significantly worse than wild-type controls in both cued and contextual fear conditioning. Importantly, the 24-hydroxlase-deficient mice not only failed to synthesize or accumulate 24S-hydroxycholesterol, they show a 50% decrease in cholesterol synthesis in the brain. Zhao and co-workers showed that ten days after three infusions of 24S-hydroxycholesterol into the rat lateral ventricle, animals trained and tested in the water maze were found to have longer escape latencies, travel further and spend less time in the target quadrant than saline-injected and sham controls (Zhao *et al*., 2009). Importantly, the 24S-hydroxycholesterol infusions were found to be neurotoxic because they resulted in hippocampal lesions and significant numbers of apoptotic cells (Zhao *et al*., 2009). These neurotoxic effects were avoided by Hudry and her coworkers by using an adeno-associated virus encoding human CYP46A1 to increase 24S-hydroxycholesterol content in the cortex and hippocampus of APP/PS transgenic mice (Hudry *et al*., 2009). These investigators found that over-expression of CYP46A1 improved the cognitive deficits in APP/PS mice both in terms of the acquisition and retention of the water maze compared to APP/PS mice injected with a mutated version of the adeno-associated virus that did not over-express CYP46A1. They also found that mice over-expressing CYP46A1 had reduced levels of beta amyloid production and amyloid deposits compared to APP/PS control mice.

The differences between the various cholesterol metabolite studies that have been conducted in human and animal learning and memory attest to the complications that can arise when manipulating a complex metabolic pathway. For example, the 24-hydoxylase knock out study by Kotti et al. (2006) altered not only 24S-hydroxycholseterol but cholesterol synthesis itself. The reduction in cholesterol synthesis was compensated for by a decrease in HMG-CoA reductase activity as a result of negative feedback by cholesterol and, as a result, overall CNS cholesterol levels were unchanged (Kotti *et al*., 2006). Thus, 24S-hydroxycholesterol is not only a metabolite of cholesterol, it is also a involved in cholesterol synthesis because it regulates gene expression that maintains cholesterol homeostasis. Specifically, 24S-hydroxycholesterol can up-regulate ApoE via LXR (as well as ABCA1 and ABCG1) and increase ApoE-mediated cholesterol efflux from cells (Martins *et al*., 2009).

Conclusion

There is a large body of data showing that cholesterol is involved in learning and memory but the nature of that involvement appears to be as complex as the synthesis, metabolism and homeostasis of cholesterol itself. In some cases, there have been opposite behavioral results from the same transgenic manipulation only to find that the discrepancies may be attributable to strain or gender differences. We have examined data showing that dietary cholesterol can influence a diverse number of learning tasks from water maze to eyelid and fear conditioning even though cholesterol added to the diet does not cross the BBB. Manipulations of cholesterol within the CNS that circumvent the BBB through genetic, pharmacological, or metabolic measures have also produced a range of results but often in animals that have already been otherwise compromised. The same manipulations in normal controls have sometimes been found to be ineffective. The human cholesterol literature is no less complex. Reductions in cholesterol levels using statins having been found to be effective in improving learning and memory in some cases but not in others. Similarly, there is a great deal of controversy over whether statins can help alleviate the problems with learning and memory found in Alzheimer's disease. Correlations of cholesterol levels with cognitive function have been found to be positive, negative, or to have no relationship at all. Association studies of cholesterol and cognition have found some genetic polymorphisms to be related to cognitive functions whereas others have not.

What is clear from all of these experiments is that cholesterol is critical to learning and memory and disturbances in cholesterol levels, synthesis or metabolism have significant consequences. These disturbances appear to have a range of direct and indirect effects. Although dietary cholesterol does not cross the BBB we have seen that there are a range of consequences of increasing cholesterol including significant peripheral pathology that may signal the brain along a number of different pathways including cholesterol metabolites, pro-inflammatory mediators and antioxidant processes. In cases where attempts have been made to model the complexity of these myriad effects, results have been difficult to interpret. Although a powerful tool in understanding the role of cholesterol, transgenic mouse models have significant short comings in terms of unlooked for side-effects and strain and gender issues. Finally, it seems clear that understanding the effects of cholesterol on learning and memory, although challenging, is too important to ignore.

Reference List

Akram A, Schmeidler J, Kastel P, Hof PR, Haroutunian V. Increased expression of cholesterol transporter ABCA1 is highly correlated with severity of dementia in AD hippocampus. Brain Res 2010;1318:167–177. [PubMed: 20079340]

Arndt SS, Surjo D. Methods for behavioural phenotyping of mouse mutants. How to keep the overview. Behav. Brain Res 2001;125:39–42. [PubMed: 11682091]

Arvanitakis Z, Schneider JA, Wilson RS, Bienias JL, Kelly JF, Evans DA, Bennett DA. Statins, incident Alzheimer disease, change in cognitive function, and neuropathology. Neurology 2008;70:1795–1802. [PubMed: 18199831]

Atzmon G, Gabriely I, Griener W, Davidson D, Schechter C, Brazilai N. Plasma HDL levels highly correlate with cognitive function in exceptional longevity. Journal of Gerontology Series A, Biological Sciences and Medical Sciences 2002;57A:M712–M715.

Bahia VS, Kok F, Marie SN, Shinjo S, Caramelli P, Nitrini R. Polymorphisms of APOE and LRP genes in Brazilian individuals with Alzheimer disease. Alzheimer's Disease and Associated Disorders 2008;22:61–65.

Baldwin S, Farias ST. Neuropsychological assessment in the diagnosis of Alzheimer's disease. Current Protocols in Neuroscience 2009;49:10.3.1–10.3.8.

Bales KR. Brain lipid metabolism, apolipoprotein E and the pathophysiology of Alzheimer's disease. Neuropharmacology 2010:xxx. In press.

Banks WA. Blood-brain barrier transport of cytokines: a mechanism for neuropathology. Curr. Pharm. Des 2005;11:973–984. [PubMed: 15777248]

Baranowski M. Biological role of liver × receptors. J. Physiol. Pharmacol 2008;59(Suppl 7):31–55. [PubMed: 19258656]

Beach TG. Physiologic origins of age-related β-amyloid deposition. Neurodegenerative Diseases 2008;5:143–145. [PubMed: 18322373]

Benarroch EE. Brain cholesterol metabolism and neurologic disease. Neurology 2008;71:1368–1373. [PubMed: 18936430]

Bernick C, Katz R, Smith NL, Rapp S, Bhadelia R, Carlson M, Kuller LH. Statins and cognitive function in the elderly. Neurology 2005;65:1388–1394. [PubMed: 16275825]

Bertram L, Hsiao M, MCQueen MB, Parkinson M, Mullin K, Blacker D, Tanzi RE. The LDLR locus in Alzheimer's disease: a family-based study and meta-analysis of case-control data. Neurobiol. Aging 2007;18:e18–e21.

Billings LM, Green KN, McGaugh JL, LaFerla FM. Learning decreases Aβ*56 and tau pathology and ameliorates behavioral decline in 3xTg-AD mice. J. Neurosci 2007;27:751–761. [PubMed: 17251414]

Billings LM, Oddo S, Green KN, McGaugh JL, LeFerla FM. Intraneuronal Aβcauses the onset of early Alzheimer's disease-related cognitive deficits in transgenic mice. Neuron 2005;45:675–688. [PubMed: 15748844]

Bjorkhem I. Do oxysterols control cholesterol homeostasis? The Journal of Clinical Investigation 2002;110:725–730. [PubMed: 12235099]

Bjorkhem I. Are side-chain oxidized oxysterols regulators also in vivo? J. Lipid Res 2009;50:S213–S218. [PubMed: 18952574]

Bjorkhem I, Cedazo-Minguez A, Leoni V, Meaney S. Oxysterols and neurodegenerative disorders. Mol. Aspects Med 2009;30:171–179. [PubMed: 19248803]

Bour A, Grootendorst J, Vogel E, Kelche C, Dodart J-C, Bales K, Moreau PH, Sullivan PM, Mathis C. Middle-aged human apoE4 targeted-replacement mice show retention deficits on a wide range of spatial memory tasks. Behav. Brain Res 2008;193:174–182. [PubMed: 18572260]

Brooks SP, Pask T, Jones L, Dunnett SB. Behavioural profiles of inbred mouse strains used as transgenic backgrounds. I: motor tests. Genes, Brain and Behavior 2004;3:206–215.

Brouwers N, Sleegers K, Van Broeckhoven C. Molecular genetics of Alzheimer's disease: an update. Ann. Med 2008;18:1–22.

Burgess BL, Parkinson PF, Racke MM, Hirsch-Reinshagen V, Fan J, Wong C, Stukas S, Theroux L, Chan JY, Donkin J, Wilkinson A, Balik D, Christie B, Poirier J, Lutjohann D, DeMattos RB, Wellington CL. ABCG1 influences the brain cholesterol biosynthetic pathway but does not affect amyloid precursor protein or apolipoprotein E metabolism in vivo. J. Lipid Res 2008;49:1254–1267. [PubMed: 18314463]

Canevari L, Clark JB. Alzheimer's disease and cholesterol: the fat connection. Neurochem. Res 2007;32:739–750. [PubMed: 17191138]

Cao D, Fukuchi K, Wan H, Kim H, Li L. Lack of LDL receptor aggravates learning deficits and amyloid deposits in Alzheimer transgenic mice. Neurobiol. Aging 2006;27:1632–1643. [PubMed: 16236385]

Carlsson CM, Gleason CE, Hess TM, Moreland KA, Blazel HM, Koscik RL, Schreiber NTN, Johnson SC, Atwood CS, Puglielli L, Hermann BP, McBride PE, Stein JH, Sager MA, Asthana S. Effects of simvastatin on cerebrospinal fluid biomarkers and cognition in middle-aged adults at risk for Alzheimer's disease. Journal of Alzheimer's Disease 2008;13:187–192.

Carlsson CM, Nondahl DM, Klein BE, McBride PE, Sager MA, Schubert CR, Klein R, Cruickshanks KJ. increased atherogenic lipoproteins are associated with cognitive impairment: effects of statins and subclinical atherosclerosis. Alzheimer's Disease and Associated Disorders 2009;23:11–17.

Chafekar SM, Baas F, Scheper W. Oligomer-specific aβtoxicity in cell models is mediated by selective uptake. Biochim. Biophys. Acta 2008;1782:523–531. [PubMed: 18602001]

Chen JC, Edwards CL, Vidyarthi S, Pitchumoni S, Trabizi S, Barboriak D, Charles HC, Doriaswamy PM. Learning and recall in subjects at genetic risk for Alzheimer's disease. Journal of Neuropsychiatry and Clinical Neuroscience 2002;14:58–63.

Chen X, Gawryluk JW, Wagener JF, Ghribi O, Geiger JD. Caffeine blocks disruption of the blood brain barrier in a rabbit model of Alzheimer's disease. Journal of Neuroinflammation 2008;5:1–14. [PubMed: 18171484]

Crawley, JN. Behavioral phenotyping of transgenic and knockout mice. Wiley-Liss; New York: 2000. What's wrong with my mouse?.

Darwish DS, Wang D, Konat GW, Schreurs BG. Dietary cholesterol impairs memory and memory increases brain cholesterol and sulfatide levels. Behav. Neurosci 2010;124:115–123. [PubMed: 20141286]

de Frias CM, Bunce D, Wahlin A, Adolfsson R, Sleegers K, Cruts M, Van Broeckhoven C, Nilsson L-G. Cholesterol and triglycerides moderate the effect of apolipoprotein E on memory functioning in older adults. Journal of Gerentology: Psychological Sciences 2007;62B:P112–P118.

Deane R, Bell RD, Sagare A, Zlokovic BV. Clearance of amyloid-βacross the blood-brain barrier: implications for therapies in Alzheimer's disease. CNS & Neurological Disorder - Drug Targets 2009;8:16–30.

Deary IJ, Whiteman MC, Pattie A, Starr JM, Hayward C, Wright AF, Carothers A, Whalley LJ. Cognitive change and the APOE ε4 allele. Nature 2002;418:932. [PubMed: 12198535]

Despande A, Mina E, Glabe C, Busciglio J. Different conformations of amyloid βinduce toxicity by distinct mechanisms in human cortical neurons. J. Neurosci 2006;26:6011–6018. [PubMed: 16738244]

Deyo RA, Straube KT, Disterhoft JF. Nimodipine facilitates associative learning in aging rabbits. Science 1989;243:809–811. [PubMed: 2916127]

Di Filippo M, Sarchielli P, Picconi B, Calabresi P. Neuroinflammation and synaptic plasticity: theoretical basis for a movel, immune-centred, therapeutic approach to neurological disorders. Trends Pharmacol. Sci 2008;29:402–412. [PubMed: 18617277]

Dietschy JM. Central nervous system: cholesterol turnover, brain development and neurodegeneration. Biol. Chem 2009;390:287–293. [PubMed: 19166320]

Dietschy JM, Turley SD. Cholesterol metabolism in the brain. Curr. Opin. Lipidol 2001;12:105–112. [PubMed: 11264981]

Dietschy JM, Turley SD. Cholesterol metabolism in the central nervous system during early development and in the mature animal. J. Lipid Res 2004;45:1375–1397. [PubMed: 15254070]

Dik MG, Jonker C, Comijs HC, Bouter LM, Twisk JWR, van Kamp GJ, Deeg DJH. Memory complaints and APOE-ε4 accelerate cognitive decline in cognitively normal elderly. Neurology 2001;57:2217–2222. [PubMed: 11756600]

Dineley KT, Xia X, Bui D, Sweatt JD, Zheng H. Accelerated plaque accumulation, associative learning deficits, and up-regulation of α7 nicotinic receptor protein in transgenic mice co-expressing mutant human presenilin 1 and amyloid precursor proteins. J. Biol. Chem 2002;277:22768–22780. [PubMed: 11912199]

Dufour F, Liu Q-Y, Gusev P, Alkon DL, Atzori M. Cholesterol-enriched diet affects spatial learning and synaptic function in hippocampal synapses. Brain Res 2006;1103:88–98. [PubMed: 16814755]

Eddins D, Klein RC, Yakel JL, Levin ED. Hippocampal infusion of apolipoprotein E peptides induce long-lasting cognitive impairment. Brain Res. Bull 2009;79:111–115. [PubMed: 19185602]

Elder GA, Cho JY, English DF, Franciosi S, Schmeidler J, Sosa M.A. Gama, De Gasperi R, Fisher EA, Mathews PM, Haroutunian V, Buxbaum JD. Elevated plasma cholesterol does not affect brain Aβin mice lacking the low-density lipoprotein receptor. J. Neurochem 2007;102:1220–1231. [PubMed: 17472705]

Elias PK, Elias MF, D'Agostino RB, Sullivan LM, Wolf PA. Serum cholesterol and cognitive performance in the Framingham heart study. Psychosom. Med 2005;67:24–30. [PubMed: 15673620]

Endo Y, Nishimura J-I, Kimura F. Impairment of maze learning in rats following long-term glucocorticoid treatments. Neurosci. Lett 1996;203:199–202. [PubMed: 8742027]

Esler WP, Marshall JR, Stimson ER, Ghilardi JR, Vinters HV, Mantyh PW, Maggio JE. Apolipoprotein E affects amyloid formation but not amyloid growth *in vitro*: mechanistic implications for ApoE4 enhanced amyloid burden and risk for Alzheimer's disease. Amyloid: Journal of Protein Folding Disorders 2002;9:1–12.

Evans MA, Golomb BA. Statin-associated adverse cognitive effects: survey results from 171 patients. Pharmacotherapy 2009;29:800–811. [PubMed: 19558254]

Evans RM, Emsley CL, Gao S, Sahota A, Hall KS, Farlow MR, Hendrie H. Serum cholesterol, *APOE* genotype, and the risk of Alzheimer's disease: a population-based study of African Americans. Neurology 2000;54:240–242. [PubMed: 10636159]

Fassbender K, Stroick M, Bertsch T, Ragaschke A, Kuehl S, Walter S, Walter J, Brechtel K, Muehlhauser F, von Bergmann K, Lutjohann D. Effects of statins on human cerebral cholesterol metabolism and secretion of Alzheimer amyloid peptide. Neurology 2002;59:1257–1258. [PubMed: 12391360]

Feldman HH, Doody RS, Kivipelto M, Sparks DL, Waters DD, Jones RW, Schwam E, Schindler R, Hey-Hadavi J, DeMicco DA, Breazna A. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. Neurology 2010;74:956–964. [PubMed: 20200346]

Fernandez del Pozo V, Alvarez Alvarez M, Fernandez Martinez M, Galados Alcelay L, Gomez Busto F, Pena JA, Alfonso-Snachez MA, Zarranz Imirizaldu JJ, de Pancordo MM. Polymorphism in the cholesterol 24S-hydroxylase gene (CYP46A1) associated with the APOEpsilon3 allele increases the risk of Alzheimer's disease and of mild cognitive impairment progressing to Alzheimer's disease. Dement. Geriatr. Cogn. Disord 2006;21:81–87. [PubMed: 16340204]

Flory JD, Manuck SB, Ferrell RE, Ryan CM, Muldoon MF. Memory performance and the apolipoprotein E polymorphism in a community sample of middle-aged adults. American Journal of Medical Genetics (Neuropsychiatric Genetics) 2000;96:707–711. [PubMed: 11121165]

Foster TC. Biological markers of age-related memory deficits. Treatment of senescent physiology. CNS Drugs 2006;20:153–166. [PubMed: 16478290]

Frears ER, Stephens DJ, Walters CE, Davies H, Austen BM. The role of cholesterol in the biosynthesis of β-amyloid. NeuroReport 1999;10:1699–1705. [PubMed: 10501560]

Fu BY, Ma SL, Tang NL, Tam CW, Lui VW, Chiu HF, Lam LC. Cholesterol 24-hydroxylase (CYP46A1) polymorphisms are associated with faster cognitive deterioration in Chinese older persons: a two-year follow up study. Int. J. Geriatr. Psychiatry 2009;24:921–926. [PubMed: 19212968]

Ghribi O, Golovko MY, Larsen B, Schrag M, Murphy EJ. Deposition of iron and β-amyloid plaques is associated with cortical cellular damage in rabbits fed with long-term cholesterol-enriched diets. J. Neurochem 2006a;99:438–449. [PubMed: 17029598]

Ghribi O, Larsen B, Schrag M, Herman MM. High cholesterol content in neurons increases BACE, β-amyloid, and phosphorylated tau levels in rabbit hippocampus. Exp. Neurol 2006b;200:460–467. [PubMed: 16696972]

Goritz C, Mauch DH, Pfrieger FW. Multiple mechanisms mediate cholesterol-induced synaptogenesis in a CNS neuron. Mol. Cell. Neurosci 2006;29:190–201. [PubMed: 15911344]

Gormezano, I.; Kehoe, EJ.; Marshall, BS. Twenty years of classical conditioning research with the rabbit. In: Sprague, JM., editor. Progress in psychobiology and physiological psychology. Academic Press; New York: 1983. p. 197-275.

Gotto AM Jr. Farmer JA. Pleiotropic effects of statins: do they matter? Curr. Opin. Lipidol 2001;12:391–394. [PubMed: 11507323]

Gouras GK, Almeida CG, Takahashi RH. Intraneuronal Aβaccummulation and origin of plaques in Alzheimer's disease. Neurobiol. Aging 2005;26:1235–1244. [PubMed: 16023263]

Granholm A-C, Bimonte-Nelson HA, Moore AB, Nelson ME, Freeman LR, Sambamurti K. Effects of a saturated fat and high cholesterol diet on memory and hippocampal morphology in middle-aged rats. Journal of Alzheimer's Disease 2008;14:133–145.

Grimm MOW, Grimm HS, Hartmann T. Amyloid beta as a regulator of lipid homeostasis. Trends in Molecular Medicine 2007;13:337–344. [PubMed: 17644432]

Grootendorst J, Bours A, Vogel E, Kelche C, Sullivan PM, Dodart J-C, Bales K, Mathis C. Human apoE targeted replacement mouse lines: h-apoE4 and h-apoE3 mice differ on spatial memory performance and avoidance behavior. Behav. Brain Res 2005;159:1–14. [PubMed: 15794991]

Haag MDH, Hofman A, Koudstaal PJ, Stricker BHC, Breteler MMB. Statins as associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam study. J. Neurol. Neurosurg. Psychiatry 2009;80:13–17. [PubMed: 18931004]

Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β-peptide. Nature Reviews Molecular Cell Biology 2007;8:101–112.

Hansson GK, Robertson A-KL, Soderberg-Naucler C. Inflammation and atherosclerosis. Annual Review of Pathology: Mechanisms of Disease 2008;1:297–329.

Harris-White ME, Balverde Z, Lim GP, Kim P, Miller SA, Hammer H, Galasko D, Frautschy SA. Role of LRP in TGFbeta2-mediated neuronal uptake of Abeta and effects on memory. J. Neurosci. Res 2004;77:217–228. [PubMed: 15211588]

Hartman RE, Wozniak DF, Nardi A, Olney JW, Sartorius L, Holtzman DM. Behavioral phenotyping of GFAP-ApoE3 and -ApoE4 transgenic mice: ApoE4 mice show profound working memory impairments in the absence of Alzheimer's-like neuropathology. Exp. Neurol 2001;170:326–344. [PubMed: 11476599]

Hartmann H, Eckert A, Muller W. Apolipoprotein E and cholesterol affect neuronal calcium signalling: the possible relationship to β-neurotoxicity. Biochem. Biophys. Res. Commun 1994;200:1185–1192. [PubMed: 8185566]

Hartmann T. Cholesterol, Aβand Alzheimer's disease. Trends Neurosci 2001;11:S45–S48. [PubMed: 11881745]

Hartmann T. Role of amyloid precursor protein, amyloid-βand γ-secretase in cholesterol maintenance. Neurodegenerative Diseases 2006;3:305–311. [PubMed: 17047372]

Heverin M, Meaney S, Lutjohann D, Diczfalusy U, Wahren J, Bjorkhem I. Crossing the barrier: net flux of 27-hydroxycholesterol into the human brain. J. Lipid Res 2005;46:1047–1052. [PubMed: 15741649]

Hirsch-Reinshagen V, Wellington CL. Cholesterol metabolism, apolipoprotein E, adenosine triphosphate-binding cassette transporters, and Alzheimer's disease. Curr. Opin. Lipidol 2007;18:325–332. [PubMed: 17495608]

Hoglund K, Thelen KM, Syversen S, Sjogren M, von Bergmann K, Wallin A, Vanmechelen E, Vanderstichele H, Lutjohann D, Blennow K. The effect of simvastatin treatment on the amyloid precursor protein and brain cholesterol metabolism in patients with Alzheimer's disease. Dement. Geriatr. Cogn. Disord 2005;19:256–265. [PubMed: 15785028]

Hoshino T, Kamino K, Matsumoto M. Gene dose effect of the *APOE*-ε4 allele on plasma HDL cholesterol level in patients with Alzheimer's disease. Neurobiol. Aging 2002;23:41–45. [PubMed: 11755017]

Hoyer S, Riederer P. Alzheimer disease - no traget for statin treatment. A mini review. Neurochem. Res 2007;32:695–706. [PubMed: 17063393]

Hudry E, Van Dam D, Kulik W, De Deyn PP, Stet FS, Ahouansou O, Benraiss A, Delacourte A, Bougneres P, Aubourg P, Cartier N. Adeno-associated virus gene therapy with cholesterol 24-hydroxylase reduces the amyloid pathology before or after onset of amyloid plaques in mouse models of Alzheimer's disease. Molecular Therapy 2009;18:44–53. [PubMed: 19654569]

Jacova C, Kertesz A, Blair M, Fisk JD, Feldman HH. Neuropsychological testing and assessment of dementia. Alzheimer's & Dementia 2007;3:299–317.

Jaeger LB, Dohgu S, Hwang MC, Farr SA, Murphy MP, Fleegal-Demotta MA, Lynch JL, Robinson SM, Niehoff ML, Johnson SN, Kumar VB, Banks WA. Testing the neurovascular hypothesis of Alzheimer's disease: LRP-1 antisense reduces blood-brain barrier clearance, increases brain levels of amyloid-beta protein, and impairs cognition. Journal of Alzheimer's Disease 2010;17:553–570.

Jarvik GP, Wijsman EM, Kukull WA, Schellenberg GD, Yu C, Larson EB. Interactions of apolipoprotein E genotype, total cholesterol level, age, and sex in prediction of Alzheimer's disease. Neurology 1995;45:1092–1096. [PubMed: 7783869]

Jasinska M, Owczarek J, Orszulak-Michalak D. Statins: a new insight into their mechanisms of action and consequent pleiotropic effects. Pharmacological Reports 2007;59:483–499. [PubMed: 18048949]

Jaya Prasanthi RP, Schommer E, Thomasson S, Thompson A, Feist G, Ghribi O. Regulation of β-amyloid levels in the brain of cholesterol-fed rabbit, a model system for sporadic Alzheimer's disease. Mech. Ageing Dev 2008;29:649–655. [PubMed: 18845178]

Jessup W, Kritharides L, Stocker R. Lipid peroxidation in atherogenesis: an overview. Biochem. Soc. Trans 2004;32:134–138. [PubMed: 14748732]

Jiang Q, Lee CYD, Mandrekar S, Wilkinson B, Cramer P, Zelcer N, Mann K, Lamb B, Wilson TM, Collins JL, Richardson JC, Smith JD, Comery TA, Riddell D, Holtzman DM, Tontonoz P, Landreth

GE. ApoE promotes the proteolytic degradation of Aβ. Neuron 2008;58:681–693. [PubMed: 18549781]

Jick H, Zornberg GL, Jick SS, Seshardi S, Drachman DA. Statins and the risk of dementia. Lancet 2000;356:1627–1631. [PubMed: 11089820]

Joseph J, Shukitt-Hale B, Denisova NA, Martin A, Perry G, Smith MA. Copernicus revisited: amyloid beta in Alzheimer's disease. Neurobiol. Aging 2001;22:131–146. [PubMed: 11164287]

Juva K, Verkkoniemi A, Viramo P, Polvikoski T, Kainulainen K, Kontula K, Sulkava R. Apolipoprotein E, cognitive function, and dementia in a general population aged 85 years and over. Int. Psychogeriatr 2000;12:379–387. [PubMed: 11081958]

Kainuma M, Fujimoto M, Sekiya N, Tsuneyama K, Cheng C, Takano Y, Tersawa K, Shimada Y. Cholesterol-fed rabbit as a unique model of nonalcoholic, nonobese, non-insulin-resistant fatty liver disease with characteristic fibrosis. J. Gastroenterol 2006;41:971–980. [PubMed: 17096066]

Kane KA, Robinson GB. Effect of chronic nimodipine on spatial learning and on long-term potentiation. Behav. Brain Res 1999;98:95–101. [PubMed: 10210526]

Kayed R, Head E, Thompson JL, McIntire TM, Milton SC, Cotman CW, Glabe CG. Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science 2003;300:486–489. [PubMed: 12702875]

Kessler AR, Kessler B, Yehuda S. In vivo modulation of brain cholesterol level and learning performance by a novel plant lipid: indication of interactions between hippocampal-cortical cholesterol and learning. Life Sci 1986;38:1185–1192. [PubMed: 3959749]

Kim J-H, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. Neuron 2009;63:287–303. [PubMed: 19679070]

Kim KW, Youn JC, Jhoo JH, Lee DY, Lee KU, Lee JH, Woo JI. Apolipoprotein E ε4 Allele is not associated with the cognitive impairment in community-dwelling normal elderly individuals. Int. J. Geriatr. Psychiatry 2002;17:635–640. [PubMed: 12112161]

Kim WS, Weickert CS, Garner B. Role of ATP-binding cassette transporters in brain lipid transport and neurological disease. J. Neurochem 2008;104:1145–1166. [PubMed: 17973979]

Kirsch C, Eckert GP, Koudinov AR, Muller WE. Brain cholesterol, statins and Alzheimer's disease. Pharmacopsychiatry 2003;36:S113–S119. [PubMed: 14574624]

Kivipelto M, Helkala E-L, Hanninen T, Laakso MP, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and late-life mild cognitive impairment: a population-based study. Neurology 2001;56:1683–1689. [PubMed: 11425934]

Koladiya RU, Jaggi AS, Singh N, Sharma BK. Ameliorative role of atorvastatin and pitavastatin in L-methionine induced vascular dementia in rats. BMC Pharmacolgy 2008;9:8–14.

Kolsch H, Heun R, Kerksiek A, Bergmann KV, Maier W, Lutjohann D. Altered levels of plasma 24S- and 27-hydroxycholesterol in demented patients. Neurosci. Lett 2004;368:303–308. [PubMed: 15364416]

Kotti TJ, Ramirez DMO, Pfeiffer BE, Huber KM, Russell DW. Brain cholesterol turnover required for geranylgeraniol production and learning in mice. Proceedings of the National Academy of Sciences, USA 2006;103:3869–3874.

Koudinov AR, Koudinova NV. Essential role of cholesterol in synaptic plasticity and neuronal degeneration. FASEB J 2001;15:1858–1860. [PubMed: 11481254]

Lacor PN, Buniel MC, Furlow PW, Clemente AS, Velasco PT, Wood M, Viola KL, Klein WL. Aβoligomer-induced aberrations in synapse composition, shape, and density provide a molecular basis for loss of connectivity in Alzheimer's disease. J. Neurosci 2007;27:796–807. [PubMed: 17251419]

LaFerla FM, Green KN, Oddo S. Intracellular amyloid-βin Alzheimer's disease. Nature Reviews Neuroscience 2007;8:499–509.

Ledesma MD, Dotti CG. Amyloid excess in Alzheimer's disease: what is cholesterol to be blamed for? FEBS Lett 2006;580:5525–5532. [PubMed: 16814780]

Lefterov I, Fitz NF, Cronican A, Lefterov P, Staufenbiel M, Koldamova R. Memory deficits in APP23/Abca1+/− mice correlate with the level of Abeta oligomers. ASN Neuro 2009;1:xxx.

Lesne S, Koh MT, Kotilinek L, Kayed R, Glabe CG, Yang A, Gallagher M, Ashe KH. A specific amyloid-βprotein assembly in the brain impairs memory. Nature 2006;440:352–357. [PubMed: 16541076]

Lesser GT, Haroutunian V, Purohit DP, Beeri MS, Schmeidler J, Honkanen L, Neufeld R, Libow L. Serum lipid levels are related to Alzheimer's pathology in nursing home residents. Dement. Geriatr. Cogn. Disord 2009;27:42–49. [PubMed: 19129700]

Li L, Cao D, Garber DW, Kim H, Fukuchi K. Association of aortic atherosclerosis with cerebral β-amyloidosis and learning deficits in a mouse model of Alzheimer's disease. Am. J. Pathol 2003;163:2155–2164. [PubMed: 14633589]

Li L, Cao D, Kim H, Lester R, Fukuchi K. Simvastatin enhances learning and memory independent of amyloid load in mice. Ann. Neurol 2006;60:729–739. [PubMed: 17192930]

Liao JK, Laufs U. Pleiotropic effects of statins. Annu. Rev. Pharmacol. Toxicol 2005;45:89–118. [PubMed: 15822172]

Liu F, Pardo LM, Schuur M, Sanchez-Juan P, Isaacs A, Sleegers K, de Koning I, Zorkoltseva IV, Axenovich TI, Wittman JCM, Janssens ACJW, van Sweiten JC, Aulchenko YS, Oostra BA, Van Duijn CM. The apolipoprotein E gene and its age-specific effects on cognitive function. Neurobiol. Aging 2008;xx:xxx.

Liu Y, Peterson DA, Schubert D. Amyloid βpeptide alters intracellular vesicle trafficking and cholesterol homeostasis. Proceedings of the National Academy of Sciences, USA 1998;95:13266–13271.

Lominska C, Levin JA, Wang J, Sikes J, Kao C, Smith JD. Apolipoprotein E deficiency effects on learning in mice are dependent upon the background strain. Behav. Brain Res 2001;120:23–34. [PubMed: 11173082]

Lu D, Qu C, Goussev A, Jiang H, Lu C, Schallert T, Mahmood A, Chen J, Chopp M. Statins increase neurogenesis in the dentate gyrus, reduce delayed neuronal death in the hippocampal CA3 region, and improve spatial learning in rat after traumatic brain injury. J. Neurotrauma 2007;24:1132–1146. [PubMed: 17610353]

Lu J, Wu D-M, Zheng Y-L, Sun D-X, Hu B, Shan Q, Zhang Z-F, Fan S-H. Trace amounts of copper exacerbate beta amyloid-induced neurotoxicity in the cholesterol-fed mice through TNF-mediated inflammatory pathway. Brain. Behav. Immun 2009;23:193–203. [PubMed: 18835350]

Lukiw WJ, Pappolla M, Pelaez RP, Bazan NG. Alzheimer's disease - a dysfunction in cholesterol and lipid metabolism. Cell. Mol. Neurobiol 2005;25:475–483. [PubMed: 16075376]

Ma H, Lesne S, Kotilinek L, Steidl-Nicols JV, Sherman M, Younkin L, Younkin S, Forster C, Sergeant N, Delacourte A, Vassar R, Citron M, Kofuji P, Boland LM, Ashe KH. Involvment of β-site APP cleaving emzyme 1 (BACE1) in amyloid precusor protein-mediated enhancement of memory and activity-dependent synaptic plasticity. Proceedings of the National Academy of Sciences 2007;104:8167–8172.

Mahfouz MM, Kummerow FA. Cholesterol-rich diets have different effects on lipid peroxidation, cholesterol oxides, and antioxidant enzymes in rats and rabbits. Journal of Nutritional Biochemistry 2000;11:293–302. [PubMed: 10876104]

Martins IJ, Berger T, Sharman MJ, Verdile G, Fuller SJ, Marins RN. Cholesterol metabolism and transport in the pathogenesis of Alzheimer's disease. J. Neurochem 2009;111:1275–1308. [PubMed: 20050287]

Masse I, Bordet R, Deplanque D, Al Khedr A, Richard F, Libersa C, Pasquier F. Lipid lowering agents are associated with a slower cognitive decline in Alzheimer's disease. Journal of Neurology Neurosurgery and Psychiatry 2005;76:1624–1629.

Mayeux R, Small SA, Tang M-X, Tycko B, Stern Y. Memory performance in healthy elderly without Alzheimer's disease: effects of time and apolipoprotein-E. Neurobiol. Aging 2001;22:683–689. [PubMed: 11445269]

McDowell, I.; Kristjansson, E. Mental status testing. In: McDowell, I.; Newell, C., editors. Measuring health: a guide to rating scales and questionnaires. Oxford University Press; New York: 1996. p. 287-334.

McLaurin J, Darabie AA, Morrison MR. Cholesterol, a modulator of membrane-associated aβ-fibrillogenesis. Pharmacopsychiatry 2003;36:S130–S135. [PubMed: 14574627]

Micale V, Scapagnini G, Colombrita C, Mazzola C, Alkon DL, Drago F. Behavioral effects of dietary cholesterol in rats tested in experimental models of mild stress and cognition tasks. Eur. Neuropsychopharmacol 2008;18:462–471. [PubMed: 18222653]

Mielke MM, Zandi PP, Sjogren M, Gustafson D, Ostling S, Steen B, Skoog I. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology 2005;64:1689–1695. [PubMed: 15911792]

Miller S, Wehner JM. Cholesterol treatment facilitates spatial learning performance in DBA/2Ibg mice. Pharmacology Biochemistry and Behavior 1994;49:257–261.

Morgan D. Learning and memory deficits in APP transgenic mouse models of amyloid deposition. Neurochem. Res 2003;28:1029–1034. [PubMed: 12737527]

Morris R. Developments of a water-maze procedure for studying spatial learning in the rat. J. Neurosci. Methods 1984;11:47–60. [PubMed: 6471907]

Mulder M, Jansen PJ, Janssen BJ, van de Berg WD, van der Boom H, Havekes LM, de Kloet RE, Ramaekers FC, Blokland A. Low-density lipoprotein receptor-knockout mice display impaired spatial memory associated with a decreased synaptic density in the hippocampus. Neurobiol. Dis 2004;16:212–219. [PubMed: 15207278]

Muldoon MF, Barger SD, Ryan CM, Flory JD, Lehoczky JP, Matthews KA, Manuck SB. Effects of lovastatin on cognitive function and psychological well-being. Am. J. Med 2000;108:538–547. [PubMed: 10806282]

Muldoon MF, Ryan CM, Matthews KA, Manuck SB. Serum cholesterol and intellectual performance. Psychosom. Med 1997;59:382–387. [PubMed: 9251158]

Näslund J, Haroutunian V, Mohs R, Davis KL, Davies P, Greengard P, Buxbaum JD. Correlation between elevated levels of amyloid β-peptide in the brain and cognitive decline. JAMA 2000;283:1571–1577. [PubMed: 10735393]

Nayler WG. Review of preclinical data of calcium channel blockers and atherosclerosis. J. Cardiovasc. Pharmacol 1999;33:S7–S-11. [PubMed: 10071257]

Notkola I-L, Sulkava R, Pekkanen J, Erkinjunti T, Ehnholm C, Kivinen P, Tuomilehto J, Nissinen A. Serum total cholesterol, apolipoprotein Eε4 allele, and Alzheimer's disease. Neuroepidemiology 1998;17:14–20. [PubMed: 9549720]

O'Brien WT, Xu G, Batta A, Tint GS, Salen G, Dyer CA, Kendler A, Servatius RJ. Developmental sensitivity of associative learning to cholesterol synthesis inhibitors. Behav. Brain Res 2002;129:141–152. [PubMed: 11809505]

Obrenovich ME, Joseph JA, Atwood CS, Perry G, Smith MA. Amyloid-β: a (life) preserver for the brain. Neurobiol. Aging 2002;23:1097–1099. [PubMed: 12470809]

Panza F, D'Introno A, Colacicco AM, Capurso C, Pichichero G, Capurso SA, Capurso A, Solfrizzi V. Lipid metabolism in cognitive decline and dementia. Brain Research Reviews 2006;51:275–292. [PubMed: 16410024]

Papassotiropoulos A, Lutjohann D, Bagli M, Locatelli S, Jessen F, Buschfort R, Ptok U, Bjorkhem I, von Bergmann K, Heun R. 24S-hydroxycholesterol in cerebrospinal fluid is elevated in early stages of dementia. J. Psychiatr. Res 2002;36:27–32. [PubMed: 11755458]

Papassotiropoulos A, Wollmer MA, Tsolaki M, Brunner F, Molyva D, Lutjohann D, Nitsch R, Hock C. A cluster of cholesterol-related genes confers susceptibility for Alzheimer's disease. J. Clin. Psychiatry 2005;66:940–947. [PubMed: 16013913]

Parale GP, Baheti NN, Kulkarni PM, Panchal NV. Effects of atorvastatin on higher functions. Eur. J. Clin. Pharmacol 2006;62:259–265. [PubMed: 16489473]

Parkinson PF, Kannangara TS, Eadie BD, Burgess BL, Wellington CL, Christie BR. Cognition, learning behaviour and hippocampal synaptic plasticity are not disrupted in mice over-expressing the cholesterol transporter ABCG1. Lipids in Health and Disease 2009;8:xxx.

Pavlov, IP. Conditioned reflexes: An investigation of the physiological activity of the cerebral cortex. Anrep, GV., translator. Oxford University Press; London: 1927.

Pearson HA, Peers C. Physiological roles for amyloid βpeptides. J. Physiol. (Lond) 2006;575:5–10. [PubMed: 16809372]

Perry LA, Stigger CB, Ainsworth BE, Zhang J. No association between cognitive acheivements, academic performance and serum cholesterol concentrations among school-aged children. Nutritional Neuroscience 2009;12:160–166. [PubMed: 19622240]

Pfrieger FW. Outsourcing in the brain: do neurons depend on cholesterol delivery by astrocytes? BioEssays 2002;25:72–78. [PubMed: 12508285]

Pickering M, O'Connor JJ. Pro-inflammatory cytokines and their effects in the dentate gyrus. Prog. Brain Res 2007;163:339–354. [PubMed: 17765728]

Poirier J. Apolipoprotein E, cholesterol transport and synthesis in sporadic Alzheimer's disease. Neurobiol. Aging 2005;26:355–361. [PubMed: 15639314]

Qiu S, Korwek KM, Weeber EJ. A fresh look at an ancient family: emerging roles for low density lipoprotein receptors in synaptic plasticity and memory formation. Neurobiol. Learn. Mem 2006;85:16–29. [PubMed: 16198608]

Quartermain D. Chronic administration of the Ca^{2+} channel blocker amlodipine facilitates learning and memory in mice. Eur. J. Pharmacol 2000;399:57–63. [PubMed: 10876023]

Quartermain D, deSoria VG, Kwan A. Calcium channel antagonists enhance retention of passive avoidance and maze learning in mice. Neurobiol. Learn. Mem 2001;75:77–90. [PubMed: 11124048]

Rader DJ, Daugherty A. Translating molecular discoveries into new therapies for atherosclerosis. Nature 2008;451:904–913. [PubMed: 18288179]

Raffai RL, Weisgraber KH. Cholesterol: from heart attacks to Alzheimer's disease. J. Lipid Res 2003;44:1423–1430. [PubMed: 12837845]

Rafnsson SB, Deary IJ, Fowkes FG. Peripheral arterial disease and cognitive function. Vasc. Med 2009;14:51–61. [PubMed: 19144780]

Reid PC, Urano Y, Kodama T, Hamakubo T. Alzheimer's disease: cholesterol, membrane rafts, isoprenoids and statins. Journal of Cellular and Molecular Medicine 2007;11:383–392. [PubMed: 17635634]

Reitan RM, Shipley RE. The relationship of serum cholesterol changes to psychological abilities. J. Gerontol 1963;18:350–357. [PubMed: 14071815]

Reynolds CA, Hong M-G, Eriksson UK, Blennow K, Bennet AM, Johansson B, Malmburg B, Berg S, Wiklund F, Gatz M, Pedersen NL, Prince JA. A survey of ABCA1 sequence variation confirms association with dementia. Hum. Mutat 2009;30:1–7. [PubMed: 18566966]

Reynolds CA, Prince JA, Feuk L, Brookes AJ, Gatz M, Pedersen NL. Longitudinal memory performance during normal aging: twin association models of APOE and other Alzheimer candidate genes. Behav. Genet 2006;36:185–194. [PubMed: 16402284]

Riddell DR, Zhou H, Comery TA, Kouranova E, Lo CF, Warwick HK, Ring RH, Kirksey Y, Aschmies S, Xu J, Kubek K, Hirst WD, Gonzales C, Chen Y, Murphy E, Leonard S, Vasylyev D, Oganesian A, Martone RL, Pangalos MN, Reinhart PH, Jacobsen JS. The LXR agonist TO901317 selectively lowers hippocampal Aβ42 and improves memory in the Tg2576 mouse model of Alzheimer's disease. Mol. Cell. Neurosci 2007;34:621–628. [PubMed: 17336088]

Robakis NK. Are Aβand Its derivatives causative agents or innocent bystanders in AD? Neurodegenerative Diseases 2010;7:32–37. [PubMed: 20160455]

Robinson SR, Bishop GM. Aβas a bioflocculant: implications for the amyloid hypothesis of Alzheimer's disease. Neurobiol. Aging 2002;23:1051–1072. [PubMed: 12470802]

Rodriguez E, Mateo I, Llorca J, Sanchez-Quintana C, Infante J, Berciano J, Combarros O. No association between low density lipoprotein receptor genetic variants and Alzheimer's disease risk. American Journal of Medical Genetics (Neuropsychiatric Genetics) 2006;141B:541–543.

Roher AE, Kuo Y-M, Kokjohn KM, Emmerling MR, Gracon S. Amyloid and lipids in the pathology of Alzheimer disease. Amyloid: Journal of Protein Folding Disorders 1999;6:136–145.

Romero JR, Beiser A, Seshardi S, Benjamin J, Polak JF, Vasan RS, Au R, DeCarli C, Wolf PA. Carotid artery atherosclerosis, MRI indices of brain ischemia, aging, and cognitive impairment: the Framingham study. Stroke 2009;40:1590–1596. [PubMed: 19265054]

Ronald JA, Chen Y, Bernas L, Kizler HH, Rogers KA, Hegele RA, Rutt BK. Clinical field-strength MRI of amyloid plaques induced by low-level cholesterol feeding in rabbits. Brain 2009;132:1346–1354. [PubMed: 19293239]

Russell DW, Halford RW, Ramirez DMO, Shah R, Kotti T. Cholesterol 24-hydroxylase: an enzyme of cholesterol turnover in the brain. Annu. Rev. Biochem 2009;78:1017–1040. [PubMed: 19489738]

Sagare A, Deane R, Bell RD, Johnson B, Hamm K, Pendu R, Marky A, Lenting PJ, Wu Z, Zarcone T, Goate A, Mayo K, Perlmutter D, Coma M, Zhong Z, Zlokovic BV. Clearance of amyloid-βby circulating lipoprotein receptors. Nat. Med 2007;13:1029–1031. [PubMed: 17694066]

Salo A, Ylikoski R, Verkkoniemi A, Polvikoski T, Juva K, Rastas S, Kontula K, Kainulainen K, Niinisto L, Notkola I-L, Sulkava R. Does apolipoprotein E influence learning and memory in the nondemented oldest old? Int. Psychogeriatr 2002;13:451–459. [PubMed: 12003251]

Savory J, Ghribi O, Herman MM. Is amyloid β-peptide neurotoxic or neuroprotective and what is its role in the binding of metal ions? Neurobiol. Aging 2002;23:1089–1092. [PubMed: 12470807]

Schachter M. Calcium antagonists and atherosclerosis. Int. J. Cardiol 1997;62:S9–S15. [PubMed: 9488190]

Schafers M, Sorkin L. Effects of cytokines on neuronal excitability. Neurosci. Lett 2008;437:188–193. [PubMed: 18420346]

Schmajuk NA, Christiansen BA. Eyeblink conditioning in rats. Physiology & Behavior 1990;48:755–758. [PubMed: 2082376]

Schreurs BG, Smith-Bell CA, Darwish DS, Stankovic G, Sparks DL. Classical conditioning of the rabbit's nictitating membrane response is a function of the duration of dietary cholesterol. Nutritional Neuroscience 2007a;10:159–168. [PubMed: 18019398]

Schreurs BG, Smith-Bell CA, Darwish DS, Stankovic G, Sparks DL. High dietary cholesterol facilitates classical conditioning of the rabbit's nictitating membrane response. Nutritional Neuroscience 2007b;10:31–43. [PubMed: 17539481]

Schreurs BG, Smith-Bell CA, Darwish DS, Wang D, Burhans L, Gonzales-Joekes J, Deci S, Stankovic G, Sparks DL. Cholesterol enhances classical conditioning of the rabbit heart rate response. Behav. Brain Res 2007c;181:52–63. [PubMed: 17466388]

Schreurs BG, Smith-Bell CA, Lochhead J, Sparks DL. Cholesterol modifies classical conditioning of the rabbit (*Oryctolagus cuniculus*) nictitating membrane response. Behav. Neurosci 2003;117:1220–1232. [PubMed: 14674842]

Servatius RJ, Beck KD. Facilitated acquisition of the classically conditioned eyeblink response in male rats after systemic IL-1β. Integr. Physiol. Behav. Sci 2003;38:169–178. [PubMed: 15070080]

Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, Sabatini BL. Natural oligomers of the Alzheimer amyloid-βprotein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. J. Neurosci 2007;27:2866–2875. [PubMed: 17360908]

Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, Brett FM, Farrell MA, Rowan MJ, Lemere CA, Regan CM, Walsh DM, Sabatini BL, Selkoe DJ. Amyloid-βprotein dimers isolated directly from Alzheimer's brains impairs synaptic plasticity and memory. Nat. Med 2008;14:837–842. [PubMed: 18568035]

Sharma S, Prasanthi J, Schommer E, Feist G, Ghribi O. Hypercholesterolemia-induced Aβaccumulation in rabbit brain is associated with alteration in IGF-1 signaling. Neurobiol. Dis 2008;32:426–432. [PubMed: 18775495]

Simons M, Keller P, Dichgans J, Schulz JB. Cholesterol and Alzheimer's disease: Is there a link? Neurology 2001;57:1089–1093. [PubMed: 11571339]

Singh-Manoux A, Gimeno D, Kivimaki M, Brunner E, Marmot MG. Low HDL cholesterol is a risk factor for deficit and decline in memory in midlife: the Whitehall II study. Arteriosclerosis, Thrombosis and Vascular Biology 2008;28:1556–1562.

Sjogren M, Mielke M, Gustafson D, Zandi P, Skoog I. Cholesterol and Alzheimer's disease - is there a relation? Mech. Ageing Dev 2006;127:138–147.

Skelton RW. Bilateral cerebellar lesions disrupt conditioned eyelid responses in unrestrained rats. Behav. Neurosci 1988;102:586–590. [PubMed: 3166733]

Small BJ, Graves AB, McEvoy CL, Crawford FC, Mullan M, Mortimer JA. Is ApoE-ε4 a risk factor for cognitive impairment in normal aging? Neurology 2000;54:2082–2088. [PubMed: 10851367]

Solomon A, Kareholt I, Ngandu T, Winblad B, Nissinen A, Tuomilehto J, Soininen H, Kivipelto M. Serum cholesterol changes after midlife and late-life cognition. Neurology 2007;68:751–756. [PubMed: 17339582]

Solomon A, Kareholt I, Ngandu T, Wolozin B, MacDonald SWS, Winblad B, Nissinen A, Tuomilehto J, Soininen H, Kivipelto M. Serum cholesterol, statins and cognition in non-demented elderly. Neurobiol. Aging 2009a;30:1006–1009. [PubMed: 18022292]

Solomon A, Kivipelto M. Cholesterol-modifying strategies for Alzheimer's disease. Expert Reviews in Neurotherapeutics 2009;9:695–709.

Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. Dement. Geriatr. Cogn. Disord 2009b; 28:75–80. [PubMed: 19648749]

Sparks DL. Coronary artery disease, hypertension, ApoE and cholesterol: a link to Alzheimer's disease. Annals New York Academy of Sciences 1997;826:128–146.

Sparks DL. Cholesterol, copper, and accumulation of thioflavine s-reactive Alzheimer's-like amyloid βin rabbit brain. J. Mol. Neurosci 2004;24:97–104. [PubMed: 15314257]

Sparks DL. Cholesterol metabolism and brain amyloidosis: evidence for a role of copper in the clearance of Aβthrough the liver. Current Alzheimer Research 2007;4:165–169. [PubMed: 17430242]

Sparks DL, Connor DJ, Browne PJ, Lopez JE, Sabbagh MN. HMG-CoA reductase inhibitors (statins) in the treatment of Alzheimer's disease and why it would be ill-advised to use one that crosses the blood-brain barrier. Journal of Nutrition, Health and Aging 2002a;6:324–331.

Sparks DL, Connor DJ, Sabbagh MN, Petersen RB, Lopez J, Browne P. Circulating cholesterol levels, apolipoprotein E genotype and dementia severity influence the benefit of atorvastatin treatment in Alzheimer's disease: results of the Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial. Acta Neurol. Scand 2006;114:s3–s7.

Sparks DL, Kryscio RJ, Sabbagh MN, Connor DJ, Sparks LM, Liebsack C. Reduced risk of incident AD with elective statin use in a clinical trial cohort. Current Alzheimer Research 2008;5:416–421. [PubMed: 18690839]

Sparks DL, Kuo Y-M, Roher AE, Martin TA, Lukas RJ. Alterations of Alzheimer's disease in the cholesterol-fed rabbit, including vascular inflammation. Preliminary observations. Annals New York Academy of Sciences 2000;903:335–344.

Sparks DL, Lochhead J, Horstman D, Wagoner T, Martin T. Water quality has a pronounced effect on cholesterol-induced accumulation of Alzheimer amyloid (aβ) in rabbit brain. Journal of Alzheimer's Disease 2002b;4:523–529.

Sparks DL, Martin T, Stankovic G, Waggoner T, Van Adel R. Influence of water quality on cholesterol induced systemic pathology. The Journal of Nutrition, Health & Aging 2007;11:189–193.

Sparks DL, Scheff SW, Hunsaker JC III, Liu H, Landers T, Gross DR. Induction of Alzheimer-like β-amyloid immunoreactivity in the brains of rabbits with dietary cholesterol. Exp. Neurol 1994;126:88–94. [PubMed: 8157129]

Sparks DL, Schreurs BG. Trace amounts of copper in water induce β-amyloid plaques and learning deficits in a rabbit model of Alzheimer's disease. Proceedings of the National Academy of Sciences, USA 2003;100:11065–11069.

Stewart R, Russ C, Richards M, Brayne C, Lovestone S, Mann A. Apolipoprotein E genotype, vascular risk and early cognitive impairment in an African Caribbean population. Dement. Geriatr. Cogn. Disord 2001;12:251–256. [PubMed: 11351136]

Teunissen CE, de Vente J, von Bergmann K, Bosma H, Van Boxtel MPJ, De Bruijn C, Jolles J, Steinbusch HWM, Lutjohann D. Serum cholesterol, precursors and metabolites and cognitive performance in an aging population. Neurobiol. Aging 2003;24:147–155. [PubMed: 12493560]

Thelen KM, Laaksonen R, Paiva H, Lehtimaki T, Lutjohann D. High-dose statin treatment does not alter plasma marker for brain cholesterol metabolism in patients with moderately elevated plasma cholesterol levels. J. Clin. Pharmacol 2006;46:812–816. [PubMed: 16809807]

Thirumangalakudi L, Prakasam A, Zhang R, Bimonte-Nelson HA, Sambamurti K, Kindy MS, Bhat NR. High cholesterol-induced neuroinflammation and amyloid precursor protein processing correlate with the loss of working memory in mice. J. Neurochem 2008;106:475–485. [PubMed: 18410513]

Upchurch M, Wehner JM. DBA/2Ibg mice are incapable of cholinergically-based learning in the Morris water maze. Pharmacology Biochemistry & Behavior 1988;29:325–329.

van den Kommer TN, Dik MG, Comijs HC, Fassbender K, Lutjohann D, Jonker C. Total cholesterol and oxysterols: early markers for cognitive decline in elderly? Neurobiol. Aging 2009;30:534–545. [PubMed: 17888546]

van der Staay FJ, Steckler T. Behavioral phenotyping of mouse mutants. Behav. Brain Res 2001;125:3–12. [PubMed: 11682087]

van Exel E, de Craen AJM, Gussekloo J, Houx P, Bootsma-van der Weil A, Macfarlane PW, Blauw GJ, Westendorp RGJ. Association between high-density lipoprotein and cognitive impairment in the oldest old. Ann. Neurol 2002;51:716–721. [PubMed: 12112077]

Vanmierlo T, Rutten K, Dederen J, Bloks VW, van Vark-van der Zee LC, Kuipers F, Kiliaan A, Blokland A, Sijbrands EJG, Steinbusch H, Prickaerts J, Lutjohann D, Mulder M. Liver × receptor activation restores memory in aged AD mice without reducing amyloid. Neurobiol. Aging. 2009 In press.

Veinbergs I, Everson A, Sagara Y, Masliah E. Neurotoxic effects of apolipoprotein E4 are mediated via dysregulation of calcium homeostasis. J. Neurosci. Res 2002;67:379–387. [PubMed: 11813243]

Veinbergs I, Mallory M, Sagara Y, Masliah E. Vitamin E supplementation prevents spatial learning deficits and dendritic alterations in aged apolipoprotein E-deficient mice. Eur. J. Neurosci 2000;12:4541–4546. [PubMed: 11122365]

Viviani B, Gardoni F, Marinovich M. Cytokines and neuronal ion channels in health and disease. Int. Rev. Neurobiol 2007;82:247–263. [PubMed: 17678965]

Voikar V, Rauvala H, Ikonen E. Cognitive deficit and development of motor impairment in a mouse model of Niemann-Pick type C disease. Behav. Brain Res 2002;132:1–10. [PubMed: 11853852]

Wahrle S, Das P, Nyborg AC, McLendon C, Shoji M, Kawarabayashi T, Younkin LH, Younkin SG, Golde TE. Cholesterol-dependent γ-secretase activity in buoyant cholesterol-rich membrane microdomains. Neurobiol. Dis 2002;9:11–23. [PubMed: 11848681]

Walsh DM, Selkoe DJ. Aβoligomers - a decade of discovery. J. Neurochem 2007;101:1172–1184. [PubMed: 17286590]

Wegiel J, Kuchna I, Nowicki K, Frackowiak J, Mazur-Kolecka B, Imaki H, Wegiel J, Mehta PD, Silverman WP, Reisberg B, deLeon M, Wisniewski T, Pirttilla T, Frey H, Lehtimaki T, Kivimaki T, Visser FE, Kamphorst W, Potempska A, Bolton D, Currie JR, Miller DL. Intraneuronal Aβimmunoreactivity is not a predictor of brain amyloidosis-βor neurofibrillary degeneration. Acta Neuropathol. (Berl) 2007;113:389–402. [PubMed: 17237937]

West R, Beeri MS, Schmeidler J, Hannigan CM, Angelo G, Grossman HT, Rosendorff C, Silverman JM. Better memory functioning associated with higher total and low-density lipoprotein cholesterol levels in very elderly subjects without the apolipoprotein e4 allele. Am. J. Geriatr. Psychiatry 2008;16:781–785. [PubMed: 18757771]

Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005;64:277–281. [PubMed: 15668425]

Wild K, Howieson D, Webbe F, Seeyle A, Kaye J. Status of computerized cognitive testing in aging: a systematic review. Alzheimer's & Dementia 2008;4:428–437.

Wilson RS, Schnieder JA, Barnes LL, Beckett LA, Aggarwal NT, Cochran EJ, Berry-Kravis E, Bach J, Fox JH, Evans DA, Bennett DA. The apolipoprotein E ε4 allele and decline in different cognitive systems during a 6-year period. Arch. Neurol 2002;59:1154–1160. [PubMed: 12117364]

Wollmer MA, Sleegers K, Ingelsson M, Zekanowski C, Brouwers N, Maruszak A, Brunner F, Huynh KD, Kilander L, Brudin RM, Hedlund M, Giedraitis V, Glaser A, Engelsborghs S, De Deyn PP, Kapaki E, Tsolaki M, Daniilidou M, Molyva D, Paraskevas GP, Thal DR, Barcikowska M, Kuznicki J, Lannfelt L, Van Broeckhoven C, Nitsch RM, Hock C, Papassotiropoulos A. Association study of cholesterol-related genes in Alzheimer's disease. Neurogenetics 2007;8:179–188. [PubMed: 17387528]

Wolozin B, Kellman W, Celesia GC, Siegel G. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. Arch. Neurol 2000;57:1439–1443. [PubMed: 11030795]

Wood, WG.; Igbavboa, U.; Eckert, GP.; Muller, WE. Cholesterol - a Janus-faced molecule in the central nervous system. In: Reith, NEA., editor. Handbook of Neurochemistry and Molecular Neurobiology: Neural Membrane and Transport. Springer; New York: 2007. p. 152-171.

Woodruff-Pak DS, Agelan A, Del Valle L. A rabbit model of Alzheimer's disease: valid at neuropathological, cognitive, and therapeutic levels. Journal of Alzheimer's Disease 2007;11:371–383.

Woodruff-Pak DS, Chi J, Li Y-T, Pak MH, Fanelli RJ. Nimodipine ameliorates impaired eyeblink classical conditioning in order rabbits in the long-delay paradigm. Neurobiol. Aging 1997;18:641–649. [PubMed: 9461062]

Wu C-W, Liao P-C, Lin C, Kuo C-J, Chen S-T, Cehn H-I, Kuo Y-M. Brain region-dependent increases in β-amyloid and apolipoprotein E levels in hypercholesterolemic rabbits. J. Neural Transm 2003;110:641–649. [PubMed: 12768359]

Xu G, Servatius RJ, Shefer S, Tint GS, O'Brien WT, Batta AK, Salen G. Relationship between abnormal cholesterol synthesis and retarded learning in rats. Metabolism 1998;47:878–882. [PubMed: 9667239]

Xue Q-S, Sparks DL, Streit WJ. Microglial activation in the hippocampus of hypercholesterolemic rabbits occurs independent of increased amyloid production. Journal of Neuroinflammation 2007;4:20–30. [PubMed: 17718905]

Yaffe K, Barret-Connor E, Lin F, Grady D. Serum lipoprotein levels, statin use, and cognitive function in older women. Arch. Neurol 2002;59:378–384. [PubMed: 11890840]

Yanagisawa K. Cholesterol and pathological processes in Alzheimer's disease. J. Neurosci. Res 2002;70:361–366. [PubMed: 12391598]

Yao Z-X, Papadopoulos V. Function of β-amyloid in cholesterol transport: a lead to neurotoxicity. FASEB J 2002;16:1677–1679. [PubMed: 12206998]

Yehuda S, Carasso RL. Modulation of learning, pain thresholds, and thermoregulation in the rat by preparations of free purified α-linolenic and linoleic acids: determination of the optimal ω3-to-ω6 ratio. Proceedings of the National Academy of Sciences, USA 1993;90:10345–10349.

Yehuda S, Rabinovitz S, Motofsky DI. Modulation of learning and neuronal membrane composition in the rat by essential fatty acid preparation: time-course analysis. Neurochem. Res 1998;23:627–634. [PubMed: 9566600]

Zandi PP, Sparks DL, Khachaturian AS, Tschanz JT, Norton M, Steinberg M, Wesl-Bohmer KA, Breitner JCS, Cache County Investigators. Do statins reduce risk of incident dementia and Alzheimer's disease? Arch. Gen. Psychiatry 2005;62:217–224. [PubMed: 15699299]

Zatta P, Zambenedetti P, Stella MP, Licastro F. Astrocytosis, microgliosis, metallothionein-I-II and amyloid expression in high cholesterol-fed rabbits. Journal of Alzheimer's Disease 2002;4:1–9.

Zerbinatti CV, Wozniak DF, Cirrito J, Cam JA, Osaka H, Bales KR, Zhuo M, Paul SM, Holtzman DM, Bu G. Increased soluble amyloid-βpeptide and memory deficits in amyloid model mice overexpressing the low-density lipoprotein receptor-related protein. Proceedings of the National Academy of Sciences, USA 2004;101:1075–1080.

Zhao S, Liao W, Xu N, Xu H, Yu C, Liu X, Li C. Polar metabolite of cholesterol induces rat cognitive dysfunctions. Neuroscience 2009;164:398–403. [PubMed: 19699274]

Zhou Y-T, Zhang Z-X, Chan P, He X-M, Tang M-N, Wu C-B, Hong Z. Genetic association between low-density lipoprotein receptor-related protein gene polymorphisms and Alzheimer's disease in Chinese Han population. Neurosci. Lett 2008;444:109–111. [PubMed: 18706476]

Zou F, Gopalraj RK, Lok J, Zhu H, Ling IF, Simpson JF, Tucker HM, Kelly JF, Younkin SG, Dickson DW, Petersen RC, Graff-Radford NR, Bennet DA, Crook JE, Younkin SG, Estus S. Sex-dependent association of a common low-density lipoprotein receptor polymorphism with RNA splicing efficiency in the brain and Alzheimer's disease. Hum. Mol. Genet 2008;17:929–935. [PubMed: 18065781]

Table 1

Effects of Cholesterol Manipulations in Humans

Variable	Measure	Change	References
Serum cholesterol level	Intelligence	Correlation	(Atzmon *et al*., 2002; Muldoon *et al*., 1997; Reitan and Shipley, 1963; van Exel *et al*., 2002; Yaffe *et al*., 2002)
Elevated serum cholesterol	Cognitive function	Correlation	(Elias *et al*., 2005; Panza *et al*., 2006)
	Dementia	Increase	(Solomon *et al*., 2009b; Whitmer *et al*., 2005)
	Alzheimer's disease	Increase	(Canevari and Clark, 2007; Evans *et al*., 2000; Hartmann, 2001; Jarvik *et al*., 1995; Ledesma and Dotti, 2006; Lesser *et al*., 2009; Notkola *et al*., 1998; Simons *et al*., 2001; Sjogren *et al*., 2006; Stewart *et al*., 2001)
	Cognitive decline	Decrease	(Mielke *et al*., 2005; Panza *et al*., 2006; van den Kommer *et al*., 2009; West *et al*., 2008)
Decreased serum cholesterol (Statin therapy)	Alzheimer's disease	No change	(Arvanitakis *et al*., 2008; Carlsson *et al*., 2009; Feldman *et al*., 2010)
		Decrease	(Masse *et al*., 2005; Sparks *et al*., 2008)
	Dementia	Decrease	(Jick *et al*., 2000)
	Cognition	Increase	(Carlsson *et al*., 2008; Solomon *et al*., 2009a)
		Decrease	(Evans and Golomb, 2009)
		No change	(Muldoon *et al*., 2000)
Apolipoprotein E (ApoE4)	Alzheimer's disease	Increase	(Brouwers *et al*., 2008; Chen *et al*., 2002; Deary *et al*., 2002; Mayeux *et al*., 2001; Poirier, 2005; Sparks, 1997)
	Cognition	Decrease	(Deary *et al*., 2002; Dik *et al*., 2001; Flory *et al*., 2000; Juva *et al*., 2000; Liu *et al*., 2008; Mayeux *et al*., 2001; Wilson *et al*., 2002)
		No change	(Kim *et al*., 2002; Salo *et al*., 2002; Small *et al*., 2000)
Apolipoprotein E (ApoE3)		Increase	(Martins *et al*., 2009)
ATP Binding cassette – ABCA1	Alzheimer's disease	Correlation	(Akram *et al*., 2010; Reynolds *et al*., 2009)
– ABCG1	Alzheimer's disease	Correlation	(Wollmer *et al*., 2007)
Low-density Lipoprotein Receptors (Gene polymorphism)	Alzheimer'sdisease	No association	(Bahia *et al*., 2008; Bertram *et al*., 2007; Rodriguez *et al*., 2006; Sagare *et al*., 2007)
	Alzheimer's disease	Association	(Zhou *et al*., 2008)
	Cognition	No association	(Reynolds *et al*., 2006)
Cholesterol metabolites (24S-hydroxycholesterol)	Alzheimer's disease	Increase (in brain)	(Papassotiropoulos *et al*., 2002)
	Dementia	Decrease (in plasma)	(Kolsch *et al*., 2004)
(27-hydroxycholesterol)	Alzheimer's disease	Increase (in brain)	(Heverin *et al*., 2005)
Cholesterol metabolites (Gene polymorphism)	Alzheimer's disease	Association	(Fernandez del Pozo *et al*., 2006; Papassotiropoulos *et al*., 2005)
	Dementia	Association	(Fu *et al*., 2009)

Table 2

Effects of Cholesterol Manipulations in Animals

Variable	Measure	Change	References
Elevated serum cholesterol	Water maze learning	Increase	(Dufour *et al*., 2006; Micale *et al*., 2008; Miller and Wehner, 1994; Upchurch and Wehner, 1988)
		Decrease	(Granholm *et al*., 2008; Thirumangalakudi *et al*., 2008)
	Eyeblink conditioning acquisition	Increase	(Schreurs *et al*., 2003; Schreurs *et al*., 2007a; Schreurs *et al*., 2007b)
	Eyeblink conditioning memory	Decrease	(Darwish *et al*., 2010)
Elevated cholesterol + copper		Decrease	(Sparks and Schreurs, 2003; Woodruff-Pak *et al*., 2007)
Decreased serum cholesterol	Water maze learning	Increase	(Kane and Robinson, 1999; Kessler *et al*., 1986; Quartermain *et al*., 2001; Yehuda *et al*., 1998; Yehuda and Carasso, 1993)
	Eyeblink conditioning	Increase	(Endo *et al*., 1996; O'Brien *et al*., 2002; Voikar *et al*., 2002; Xu *et al*., 1998)
	Passive avoidance	Increase	(Quartermain *et al*., 2001)
Statin treatment	Water maze learning and zmemory	Increase	(Li *et al*., 2006; Lu *et al*., 2007)
		No change	(Koladiya *et al*., 2008)
Apolipoprotein E (ApoE4)	Water maze	Decrease	(Bour *et al*., 2008; Grootendorst *et al*., 2005; Veinbergs *et al*., 2000)
	Water maze	No change	(Hartman *et al*., 2001)
	Radial arm maze	Decrease	(Eddins *et al*., 2009; Hartman *et al*., 2001; Lominska *et al*., 2001)
ATP Binding cassette – ABCA1	Water maze	No change	(Lefterov *et al*., 2009)
– ABCG1	Water maze	No change	(Burgess *et al*., 2008; Parkinson *et al*., 2009)
Low-density Lipoprotein Receptors	Water maze	Decrease	(Mulder *et al*., 2004)
		No change	(Cao *et al*., 2006)
	Water radial arm maze	Decrease	(Thirumangalakudi *et al*., 2008)
	Active avoidance	Decrease	(Jaeger *et al*., 2010)
LRP + amyloid precursor protein	Water maze	Decrease	(Harris-White *et al*., 2004; Zerbinatti *et al*., 2004)
Liver × receptor agonist	Fear conditioning	Increase	(Jiang *et al*., 2008; Riddell *et al*., 2007)
	Object recognition	Increase	(Vanmierlo *et al*., 2009)
Cholesterol metabolites (24S-hydroxycholesterol)	Water maze	Decrease	(Hudry *et al*., 2009; Kotti *et al*., 2006; Zhao *et al*., 2009)