Review

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, pro-inflammatory 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.

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Contents

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, 2004). Given the importance of cholesterol to normal brain function, the current review will focus on the role of cholesterol in one of the most important functions of the brain—learning and memory.

1. 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 X receptors and as such are important regulators of cholesterol synthesis. Liver X 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.

2. 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 trans-

genic 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 s 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).

Summary: 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.

3. Cholesterol

3.1. 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) (Table 1) .

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).

3.2. 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

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's disease	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)

a diet high in cholesterol and fat 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) (Table 2).

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 was not 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

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 memory	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 X receptor agonist	Fear conditioning	Increase	(Jiang et al., 2008; Riddell et al., 2007)
	Object recognition	Increase	(Vanmierlo et al., in press)
Cholesterol metabolites (24S-hydroxycholesterol)	Water maze	Decrease	(Hudry et al., 2009; Kotti et al., 2006; Zhao et al., 2009)

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 Dietschy 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.

3.3. 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-1β facilitates 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.

3.4. 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, 2007; Sparks, 2004, 2007) and Ghribi and his co-workers who have focused on the relationship between cholesterol and beta amyloid (Ghribi et al., 2006a,b; 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, in press; 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, 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, 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).

4. 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 and Farmer, 2001; Jasinska et al., 2007; Liao and Laufs, 2005).

4.1. 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 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).

4.2. 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.

5. 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).

5.1. 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).

5.2. 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 was not 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, in press). 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.

6. 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).

6.1. 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).

6.2. 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.

7. 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).

7.1. 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).

7.2. 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. (2010) 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.

8. Liver X 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).

8.1. Human studies

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

8.2. 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., in press) 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. (in press) 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., in press) 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.

9. 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).

9.1. 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.

9.2. 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).

10. 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.

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