A lipid-leakage model for Alzheimer's Disease

Jonathan D'Arcy Rudge [1]

[1] School of Biological Sciences, University of Reading, Reading, Berkshire, United Kingdom

Corresponding Author: Jonathan Rudge [1]

Email address: jon_rudge@btinternet.com

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Abstract

This paper describes a potential new explanation for Alzheimer's disease (AD), referred to here as the lipid leakage model. It proposes that AD is caused by the influx of lipids following the breakdown of the blood brain barrier (BBB).

The model argues that a principle role of the BBB is to protect the brain from external lipid access. When the BBB is damaged, it allows a mass influx of free fatty acids (FFAs) and lipid-rich lipoproteins to the brain, which in turn causes neurodegeneration, amyloidosis, tau tangles and other AD characteristics.

The model also argues that, whilst β-amyloid causes neurodegeneration, as is widely argued, its principal role in the disease lies in damaging the BBB. It is the external lipids, entering as a consequence, that are the primary drivers of neurodegeneration in AD, especially FFAs, which stimulate microglia-driven neuroinflammation, inhibit neurogenesis and cause endosomal-lysosomal abnormalities, all characteristic of AD. In most cases amyloidosis and tau tangle formation lie downstream of these lipids and are in many ways as much symptomatic of the disease as causative.

In support of this, it is argued that the pattern of damage caused by the influx of FFAs into the brain is likely to resemble the neurodegeneration seen in alcohol-related brain damage (ARBD), a disease that shows many similarities to AD, including the areas of the brain it affects. The fact

that anterograde amnesia is far more pronounced in AD than ARBD results from the greater hydrophobicity of FFAs, in an anaesthesia-related manner.

Keywords: *Lipids, Alzheimer's, alcohol-related brain damage, blood-brain barrier, β-amyloid, tau tangles, amyloidosis, neurodegeneration, neurogenesis, ethanol, anaesthesia*

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1 Introduction

Alzheimer's disease is a neurodegenerative disorder first described by the German physician Lois Alzheimer in 1907. It is a form of dementia characterised by the extensive death of brain cells and associated with widespread plaques and strongly staining fibrils.

Whilst these same characteristics, including the distinctive deposits now known as amyloid plaques and tau tangles, are individually seen in other forms of neurodegeneration, their occurrence together appears to be unique to AD. AD has emerged as the most common dementia, accounting for over half of all dementias, with an especially high prevalence amongst over-85 year-olds in the developed world (OECD, 2013). Yet, despite more than a century having elapsed since AD's first discovery, and, in spite of the extensive suffering and financial costs caused by the disease, only limited progress has been made in understanding its aetiology, with an effective treatment yet to be developed.

This has not been for lack of trying. Amongst a number of promising explanations the cholinergic hypothesis, which emerged in the 1980s, sought to explain the disease in terms of reduced synthesis of acetylcholine (ACh) (Contestabile, 2011). But, whilst substantial evidence points to AD-associated deficits in the cholinergic projection system of the brain (Contestabile, 2011), animal studies indicate that cholinergic damage causes only moderate cognitive deficits

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(Parent & Baxter, 2004), and attempts to increase ACh levels with drugs, including acetylcholinesterase inhibitors, do not significantly slow disease progression (Contestabile, 2011) (Frölich, 2002).

In the 1990s an alternative model emerged, the amyloid cascade hypothesis, which postulated that beta-amyloid (Aβ), a proteolytic product of amyloid precursor protein (APP), is the fundamental cause of the disease (Pimplikar, 2009). This is still the dominant model for explaining AD, backed by a substantial body of evidence, not least the fact that Aβ is the main component of amyloid plaques (Pimplikar, 2009). Moreover, in inherited forms of the disease, collectively referred to as familial AD (FAD), a number of genes related to normal APP processing have been found to be abnormal (Wu et al., 2012). Similarly, people with Down's syndrome (DS) who possess an extra copy of chromosome 21, on which APP resides, typically go on to develop a form of dementia largely indistinguishable from AD (Nieuwenhuis-Mark, 2009). Any model of AD needs to take into account these facts.

However, the amyloid cascade hypothesis is not without problems of its own, not least the fact that a number of studies have shown a poor correlation between amyloid plaque distribution and disease progression (Pimplikar, 2009) (Bowman & Quinn, 2008) (Terry et al., 1991). In some instances high plaque levels are completely unassociated with dementia (Aizenstein H et al., 2008). And twenty years since the hypothesis was first raised, treatments aimed at preventing or eliminating amyloid plaques have yet to show any significant benefits in preventing dementia (Pimplikar, 2009) (Sperling et al., 2011).

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Most studies of AD, proposing Aβ as the causative agent, assume that the Aβ found in cerebral plaques must originate within the brain. However, this has recently come into question, with doubts being raised as to whether cerebral production of Aβ is significantly elevated in individuals with non-inherited, late-onset forms of AD (LOAD) (Takechi et al., 2010a) (Cummings et al., 1998).

This has led some researchers to propose that the Aβ deposits may originate from outside the brain (Takechi et al., 2010a) (Deane et al., 2009). However, the size of the Aβ protein prevents it travelling across the BBB unaided (Deane et al., 2009). Thus, entry of the Aβ protein into the brain requires either that specific transporter proteins are available to carry it across, or that the BBB is disrupted in some way. Whilst such transporters do exist there are also others that transport Aβ in the opposite direction (Deane et al., 2009) ie out of the brain, as well as alternative efflux mechanisms (Takechi et al., 2010a) (Deane et al., 2009) (Lam et al., 2001). Additionally, the brain appears to have more than adequate enzymatic mechanisms for eradicating excess Aβ arising from faulty transport (Takechi et al., 2010a) (Iwata et al., 2000). Disruption of the BBB would thus seem to be a more plausible explanation for extravasation of Aβ into the brain.

In support of such an explanation, AD is associated with BBB disruption (Popescu et al., 2009) (Dickstein et al., 2006) (Kook et al., 2012) (Ujiie et al., 2003) (Iadecola & Gorelick, 2003). Evidence for this includes the fact that AD brains contain proteins that would normally be excluded by the BBB, most significantly apolipoprotein B, which is found in amyloid plaques along with Aβ (Takechi et al., 2009) (Namba, Tsuchiya & Ikeda, 1992), as well as other large

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molecular-weight proteins such as albumin, fibrinogen and immunoglobulins (Bowman & Quinn, 2008) (Ryu & McLarnon, 2009) (Cortes-Canteli & Strickland, 2009) (D'Andrea, 2003). Also, they stain for Evans Blue, which is normally substantially excluded by the BBB (Ujiie et al., 2003) (Cortes-Canteli & Strickland, 2009) (Paul, Strickland & Melchor, 2007).

Similarly, proteins such as S100B, normally only found in the CNS and considered a good marker of BBB disruption (Marchi et al., 2004), are present in systemic plasma in AD cases (Takechi et al., 2010c) (Takechi et al., 2010b). Further evidence that BBB disruption may lead to AD also comes in the form of Chronic Traumatic Encephalopathy (CTE). This is a progressive degenerative condition, commonly affecting athletes and others with a history of brain trauma, which typically shows many similarities with AD, including large-scale neuronal loss, severe memory deficits, extensive tau tangles and, frequently in advanced cases, diffuse amyloid plaques (Stein, Alvarez & McKee, 2014) and appears to be strongly associated with BBB disruption (Doherty et al., 2016) (Farrell et al., 2019)[*more references?*]. Finally, the many risk factors for LOAD include ApoE4 (Liu et al., 2013), hypertension (Kivipelto et al., 2002), diabetes (Schnaider Beeri et al., 2004), smoking (Durazzo et al., 2014) and head injury (Gottlieb, 2000), all of which are associated with vascular damage (Salloway et al., 2002) (Girouard, 2016) (Prasad et al., 2014) (Mazzone et al., 2010) (Alluri et al., 2015).

There is also substantial experimental evidence of Aβ directly compromising the BBB (Kook et al., 2012) (Gosselet et al., 2013) (Jancsó et al., 1998) (Farkas et al., 2003) (Tai et al., 2010), by altering tight junction protein distribution and expression in brain endothelial cells (Kook et al., 2012) (Gosselet et al., 2013) (Tai et al., 2010) (Hartz et al., 2012) (Ohtsuki et al., 2007),

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increased matrix metalloproteinase expression (Hartz et al., 2012), oxidative stress (Thomas et al., 1997), increased apoptosis (Fossati, Ghiso & Rostagno, 2012) (Blanc et al., 1997) and dysregulated calcium homoeostasis (Kook et al., 2012) (Blanc et al., 1997). Finally, there is indirect evidence that Aβ can damage the BBB, for example, in cases of cerebral amyloid angiopathy (CAA) (Hartz et al., 2012) (Fossati, Ghiso & Rostagno, 2012) (Carrano et al., 2011) (Magaki et al., 2018).

The simplest interpretation of these findings is that Aβ has a dual role in AD progression, first disrupting the BBB, and then causing neurodegeneration by deposition in the brain. But, whilst there is abundant evidence that Aβ is toxic to the brain (Pimplikar, 2009), so are many of the other molecules that a disrupted BBB could be expected to let through [*such as?*]. If Aβ does play a major role in disrupting the BBB then any proposed model of AD must take into account what role the intact BBB plays in the human body, particularly with regard to the brain.

Unfortunately, nearly a century after the BBB was first discovered, its full role is still a matter of conjecture. What was considered to be a primary function, ensuring “immune privilege”, is now known to be far more limited and nuanced than once thought (Carson et al., 2006) (Harris et al., 2014). Nevertheless, it would appear from its unique architecture that the BBB’s main purpose is to exclude certain cells and molecules from the brain. This architecture is found hardly anywhere else in the human body and includes tight junctions between endothelial cells, together with numerous efflux transporters (Carson et al., 2006) (Rubin & Staddon, 1999).

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One class of molecules that the BBB excludes or, certainly, substantially limits, is lipids. Evidence (outlined in 2.4-2.5) suggests that excess lipid influx, resulting from BBB compromise, or otherwise, will damage the brain in *at* least two ways: (a) neuroinflammation and (b) disruption of neurogenesis, both characteristics that have been associated with AD [*other references?*]. Other characteristics, such as endosomal-lysosomal pathway disruption, amyloidosis and tau tangle formation can also be explained by lipid influx in the form of external lipoproteins (2.6). These are rich in cholesterol, which has also been linked with AD (Simons et al., 2001) (Wolozin, 2004) (Xiong et al., 2008a), particularly in connection with amyloidosis and tau tangles.

In support of this, a recent study has reported the presence of lipids, including long-chained triglycerides, within fibrillar Aβ plaques (Kiskis et al., 2015), consistent with the evidence, previously alluded to, of the presence of apolipoprotein B within amyloid plaques.

Based on the above evidence, the lipid-leakage model argues that breakdown of the BBB, by Aβ or other means, and the subsequent influx of lipids, leads to lipid-driven neurodegeneration and dysfunction, including the long-term form known as Alzheimer's disease. According to this hypothesis, it is peripheral lipids, not Aβ, that primarily drive AD.

One reason for believing this is the similarity between the overall structural pattern of neurodegeneration seen in AD and that seen in ARBD, resulting from chronic exposure of the brain to ethanol. Ethanol passes relatively easily through the BBB and, for the reasons argued below, can be expected to have similar overall effects on the brain as exposure to one major class

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of lipids, FFAs, but without the amyloid plaques, tau tangles and endosomal-lysosomal abnormalities seen in AD. (See 2.4-2.5.)

This suggests that further study of ARBD may yield insights into the aetiology of AD. One area of potential overlap emerges from extensive evidence that the detrimental effects observed in the brain from chronic alcohol exposure are the result not only of neurodegeneration but also of reduced levels of neurogenesis (Fadda & Rossetti, 1998a) (Crews, 2008) (Morris et al., 2010) (Nixon, 2006).

Recent studies also demonstrate that the neurodegenerative effects of chronic alcohol abuse may be reversible (Pfefferbaum et al., 1997) (Crews & Nixon, 2009b), following the cessation of ethanol treatment. This could mean that if neuroinflammation and neurogenetic inhibition could be ameliorated then the neurodegenerative effects of AD may also be reversible, giving hope of finding effective treatments for the disease.

2 Evidence and explanation of the model

It follows from the above, that a full appreciation of the lipid-leakage model requires an understanding of the similarities between AD and ARBD.

2.1 Similarities between AD & ARBD

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That AD and ARBD may share common elements in their aetiology is apparent from comparisons of brains of individuals with either disease, including direct visual comparisons (see Figure 1), and whole brain MRI scans (Figure 2), (Sullivan, Adron Harris & Pfefferbaum) (Teipel et al., 2015) (Zahr, Kaufman & Harper, 2011) (Fox et al., 2001).

Figure 1. Visual comparisons of the brains of (A) normal elderly person; (B) a person with AD and (C) a chronic alcoholic. Source [*references?*].

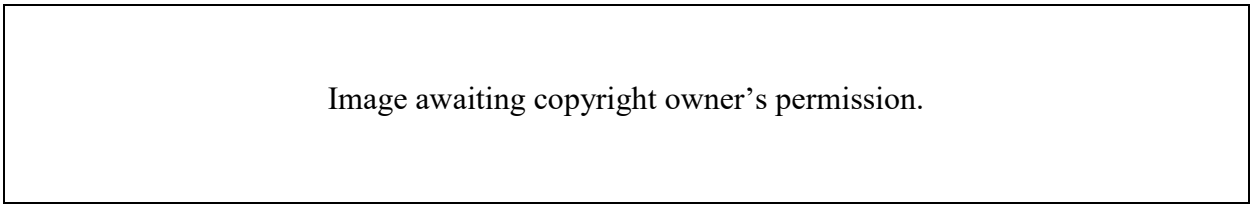

Figure 2. Coronal plane MRI comparison between brains of (a) a normal person and (b) a typical AD case **(Duara et al., 2008)** and that of (c) a patient with alcohol-related brain damage **("Alcoholic dementia, MRI scan")**. Outlined areas in (a) & (b) correspond to hippocampus (outlined in red); entorhinal cortex (blue) and perirhinal cortex (green). Source: [*references?*].

2.1.1 Brain shrinkage

Such scans typically reveal pronounced similarities between the two diseases in their pattern of neurodegeneration, including evidence of brain shrinkage (Pfefferbaum et al., 1997) (Hua et al., 2008) (Rando et al., 2011) (Thompson et al., 2007), loss of cortical folding (involving widening of sulci and thinning of gyri) (Pfefferbaum et al., 1997) (Hua et al., 2008) (Harper & Kril, 1985)

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("Brain With Alzheimer's Disease") (de la Monte SM, 1988), enlargement of ventricles (Pfefferbaum et al., 1997) (Hua et al., 2008) ("Brain With Alzheimer's Disease") (de la Monte SM, 1988) (especially the lateral ventricles), together with shrinkage of the hippocampus and entorhinal cortex (Duara et al., 2008) (Hua et al., 2008) ("Brain With Alzheimer's Disease") (White, Matthews & Best, 2000) (Beresford et al., 2006) (Fadda & Rossetti, 1998b) and thinning of the corpus callosum (Estruch et al., 1997) (Frederiksen et al., 2011).

On their own, such similarities could be dismissed as the effects of general brain shrinkage and other generalised damage. However, the similarities appear to run much deeper than this, with many of the same regions of the brain principally affected in both cases, especially early on in the disease process. In particular, both AD and ARBD appear to be "frontal" diseases, as suggested by physiological, behavioural and sensory studies ("The Neurotoxicity of Alcohol (Chapter 2, Alcohol and the Brain: Neuroscience and Neurobehaviour)") (Hall et al., 2008a) (Gallagher & Colombo, 1995) [*more references?*].

2.1.2 Basal forebrain damage in AD and ARBD

Measurements of brain volume reveal both diseases to be associated with significant shrinkage in the frontal region of the brain, particularly the prefrontal cortex and basal forebrain regions (Pfefferbaum et al., 1997) (Fadda & Rossetti, 1998b) (Hall et al., 2008b) (Teipel et al., 2005) (Grodin et al., 2013), including the cholinergic basal forebrain projection system (Fadda & Rossetti, 1998b) (Teipel et al., 2005) (Muir, 1997) (Arendt et al., 1989a) (Miki et al., 2014).

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This is backed up by studies in animal models, which suggest that chronic exposure of the brain to ethanol causes a specific pattern of degeneration, including a marked loss of cholinergic neurons, accompanied by a reduction in acetylcholine and choline acetyltransferase activity (Fadda & Rossetti, 1998b) (Arendt et al., 1989a) (Miki et al., 2014) (Floyd et al., January) (Mufson et al., 2003). Again, this is very similar to what is seen in AD (Muir, 1997) (Baskin et al., 1999) [*, which is, indeed, why the cholinergic hypothesis was proposed in the 1980s?*].

Related behavioural evidence pointing towards frontal damage as a factor in both diseases includes personality changes [*references?*], disinhibition (Ball et al., 2008a) (Crews & Boettiger, 2009), confabulation (Attali et al., 2009) (Tallberg & Almkvist, 2001) (Maurage et al., 2011) (Brun & Andersson, 2001)and a noticeable tendency towards perseverative behaviour. This last attribute is readily apparent in individuals with AD (Serna, Pigot & Rialle, 2007) (Nagahama et al., 2003), while studies in adult rats chronically exposed to ethanol (but given a nutritionally adequate diet) point towards a similar pattern of behavioural and neurological deficit (Obernier et al., 2002a) [*references?*], confirming findings in humans (Fadda & Rossetti, 1998b) (Oscar-Berman et al., 1997). Possibly such behaviour involves deficits in the dopamine system [*references?*], principally centred in the frontal lobe, as well as of the cholinergic system. But certainly it is known that various forms of motor perseveration and similar behavioural inertias can be clearly associated with damage to the frontal lobes (Luria, 1965) [*more references?*].

There is also very strong experimental evidence suggesting that, from comparatively early on, both AD and ARBD are associated with olfactory deficits (Maurage et al., 2011) (Mesholam RI et al., 1998) (Collins, Corso & Neafsey, 1996) (Doty, 2005) (Velayudhan et al., 2013a)

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(Ditraglia et al., 1991) (Christen-Zaech et al., 2003) (Rupp et al., 2006), although not always perceptible to demented patients (Doty, Reyes & Gregor, 1987). [*(This may reflect a general lack of olfactory awareness in humans and its much-diminished role compared to other mammals* (Sela & Sobel, 2010).*)*] These are also very likely to involve damage to the basal forebrain, including the olfactory bulb (Collins, Corso & Neafsey, 1996) (Christen-Zaech et al., 2003) (Rupp et al., 2006) (Ohm & Braak, 1987) (Obernier et al., 2002b) and cholinergic systems (D'Souza & Vijayaraghavan, 2014) (Arendt et al., 1989b) (Mundiñano et al., 2013) ("Smell and the Degenerating Brain | The Scientist Magazine®," 2013), amongst others.

More generally, both forms of dementia are associated with deficits in executive functions ("The Neurotoxicity of Alcohol (Chapter 2, Alcohol and the Brain: Neuroscience and Neurobehaviour)") (Rupp et al., 2006) (Ball et al., 2008b) (Weiss et al., 2014) (Marshall et al., 2011) (Houston et al., 2014) (Duarte et al., 2006), such as attentional and inhibitory control, working memory and reasoning - i.e. those faculties which allow problem-solving, planning, self-control and the attainment of goals. Clearly there are difficulties separating the immediate effects of drinking alcohol from the long-term neurodegenerative effects of alcoholism, as well as questions as to what degree executive function is under the control of the frontal region. Nevertheless, taken collectively, the evidence presented here points to a strong involvement of the frontal lobe degeneration in both ARBD and AD.

2.1.3 Medial temporal lobe damage in AD and ARBD

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As well as the basal forebrain, the medial temporal lobe is also found to be significantly atrophied in both ARBD and AD (Duara et al., 2008) ("Brain With Alzheimer's Disease") (Fadda & Rossetti, 1998b) (Jobst et al., 1992) (Bengochea & Gonzalo, 1990) (Korf et al., 2004) (Vetreno, Hall & Savage, 2011). This is most obvious in the hippocampus but is also in immediately adjoining regions, such as the entorhinal cortex and perirhinal cortex (Traissard et al., 2006) (Velayudhan et al., 2013b) (Sullivan & Pfefferbaum, 2014) (Augustinack et al., 2013) (Jaatinen & Rintala, 2008) (Hirni et al., 2016).

Given the well-established link between the hippocampus and memory formation, it is unsurprising, therefore, that AD is associated with anterograde amnesia (AA), including severe deficits in spatial memory [*references?*]. However, such deficits in ARBD are less clear-cut. Most examples of AA in alcoholics are associated with Korsakoff Syndrome [*references?*], i.e. assumed to be the result of long-term vitamin B1 deficiency rather than from chronic alcohol, even if this assumption may not always be merited, given the tendency to diagnose the Syndrome primarily by symptoms. Moreover, chronic alcohol-associated AA appears to be reversible, unlike AA in Alzheimer's. Nevertheless, there is sufficient evidence in animal models to suggest that both acute and chronic alcohol exposure lead to pronounced deficits in spatial memory (Cippitelli et al., 2010) (García-Moreno & Cimadevilla, 2012) (Santín et al., 2000) (Assunção et al., 2007), evidence that appears to be mirrored in humans (Bowden & McCarter, 1993) [*more references?*].

Overall, anterograde amnesia (AA) predominates in both forms of dementia, with retrograde amnesia tending to emerge later in disease progression (Weintraub, Wicklund & Salmon, 2012)

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[*more references?*]. This would seem to reinforce the overall pattern of degeneration, in which AD and ARBD are both principally characterised by atrophy of the frontal and medial temporal regions, with generalised neocortical involvement emerging only later [*references?*]. One explanation for this is that both the frontal and medial temporal regions have a higher proportion of pyramidal cells, larger neurons that are thought to be more vulnerable to various stresses (Morrison & Hof, 2002) (Hof, Morrison & Cox, 1990) [*more references?*]. Whatever the reason, the similarities between AD and ARBD listed above would seem to provide the most obvious reason binge drinking is associated with a higher risk of developing Alzheimer's and related dementias ("Binge Drinking in Midlife and Dementia Risk") [*more references?*].

2.1.4 Summary of similarities between AD and ARBD

In summary AD and ARBD show a strikingly similar pattern of neurological damage, particularly evident in the basal forebrain and hippocampal region of the medial temporal region, accompanied by marked degeneration in the cholinergic projection system. In keeping with this pattern of damage both AD and ARBD sufferers show deficits in executive function, olfaction and anterograde memory (especially spatial memory) formation and a tendency towards perseverative behaviour.

Taken together, these similarities would seem more than sufficient to warrant further investigation. Yet it is hard to explain the mechanism by which long-term exposure of the brain to two such different molecules, ethanol and Aβ, vastly different in size and sharing no obvious

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chemical or physical properties in common, should lead to such a similarly distinctive pattern of damage. Rather, it suggests that AD could be caused by molecules whose effects are likely to be more similar to those of ethanol. One such candidate is FFAs which, for reasons discussed later, share some crucial properties of ethanol and other aliphatic 1-alcohols (including fatty alcohols). However, in order to appreciate how FFAs can become a major driver of AD, one must first understand the differences between lipid metabolism either side of the BBB.

2.2 Differences between lipid metabolism on either side of the BBB

Whatever the exact biological role of the BBB may be, it is clear that many aspects of lipid metabolism and transport greatly differ either side of it. This is most apparent in the case of fatty acids (FAs) and cholesterol.

2.2.1 Fatty acid metabolism

For efficient transport within plasma, the vast majority of FAs, being highly hydrophobic, must travel within lipoproteins or must be bound to the protein serum albumin to improve solubility (Vance & Vance, 2008) (van der Vusse, 2009) .

Immediately after eating, dietary FAs, bound to glycerol as triacylglycerol esters (TAGs) and transported within the class of lipoproteins known as chylomicrons, constitute a major proportion of the plasma transport pool (Vance & Vance, 2008) (Rang, 2012). At the same time,

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high blood glucose levels associated with satiety lead to hepatic neogenesis of FAs and glycerol, with the resulting TAGs being transported in the blood within Very Low Density Lipoproteins (VLDLs) (Vance & Vance, 2008) (Rang, 2012). During subsequent plasma transport most of the TAGs within chylomicrons and VLDLs are taken up by tissues, principally adipocytes and muscle cells [*references?*].

The chylomicrons and VLDLs are relatively large (typically within a range of 30-80nm and 100-1000nm, respectively (Vance & Vance, 2008) (Rang, 2012)) and lipid-rich by virtue of their association with ApoB isoforms. ApoB is synthesised only in the liver and in enterocytes and thus is normally unavailable to the CNS (Vance & Vance, 2008) (Young, 1990). Such lipoprotein-mediated FA transport appears to allow only very restricted access to the postnatal brain across the BBB, largely composed, as it is, of endothelial cells, held together by tight junctions and lacking in fenestrations and transcytotic vesicles (Carson et al., 2006) (Rubin & Staddon, 1999) (Orth & Bellosta, 2012) (Elliott, Weickert & Garner, 2010) (Björkhem & Meaney, 2004) (Nag, 2003).

During the fasting state, adipocytes release stored FFAs directly back into the bloodstream, with the majority being subsequently bound to serum albumin (Vance & Vance, 2008) (van der Vusse, 2009). Because serum albumin is created almost exclusively in the liver (van der Vusse, 2009) (Ballmer, 2001) (Schiff, Maddrey & Sorrell, 2011) and cannot pass readily through the BBB (Nag, 2003) (Banks, 2008) (Banks, 2006), it has until recently been assumed that albumin-bound FFAs must also be largely excluded. Support for this hypothesis comes from the widespread expression within BBB endothelial cells of efflux pumps, such as P-glycoprotein,

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334 which have hydrophobic molecules amongst their principal ligands (Rubin & Staddon, 1999).
335 Together, such features would appear to provide an obvious reason why, almost uniquely
336 amongst organs, the CNS does not rely on the external supply of FAs (especially in albumin-
337 bound form) for its energy and other needs. Instead, it appears to rely almost totally on ketone
338 bodies (breakdown products of FAs, almost solely produced in the liver [*references?*]), both
339 during maturation of neurons and glial cells in young age, and when glucose levels alone are
340 insufficient, such as during fasting (Laffel & Lori Laffel, 1999) (Schönfeld & Reiser, 2013).
341
342 Not all experimental evidence supports this hypothesis (Mitchell & Hatch, 2011). For instance,
343 palmitic acid and arachidonic acid have been observed to pass into brain microvessels from
344 plasma in rats (Williams et al., 1997), as have octanoic and myristic acids (Spector, 1988). This
345 has led some observers to question the extent of fatty acid exclusion from the brain by the BBB.
346 However, such transport proteins as have been identified appear to be limited to specific areas of
347 the brain and development stages, most obviously in the case of fatty acid transport proteins
348 (Mitchell & Hatch, 2011) [*more references?*]. Meanwhile, diffusion, while potentially providing
349 a generalised means of transport, is likely to be too slow to allow substantial FA provision to the
350 brain, given the large size of FA molecules (Dalvi et al., 2014) [*more references?*].
351

352 ### 2.2.2 Cholesterol metabolism

353
354 Numerous studies have shown that, except in very early foetal development, almost all
355 cholesterol in the CNS is of local origin, relying on endogenous de novo biosynthesis rather than

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external, lipoprotein-mediated provision (Orth & Bellosta, 2012) (Elliott, Weickert & Garner, 2010) (Björkhem & Meaney, 2004) (Dietschy & Turley, 2004). This appears to be true for a wide range of animals, including birds and mammals, with much of cholesterol production for neuronal consumption being delegated to local astrocytes (Elliott, Weickert & Garner, 2010) (Dietschy & Turley, 2004) (Pfrieger, 2003).

Moreover, cholesterol turnover in the mature CNS is very low, typically only around 5% of the turnover seen in the rest of the body (Orth & Bellosta, 2012) (Björkhem & Meaney, 2004) (Dietschy & Turley, 2004). In keeping with this, the principal apolipoproteins expressed in the CNS (including Apo E, D & J (Elliott, Weickert & Garner, 2010) (Danik et al., 1999)) associate into lipoprotein particles that are relatively small (typically less than 20nm) and lipid poor, containing modest amounts of cholesterol and other lipids (Vance & Vance, 2008) [*more references?*]. Such CNS lipoprotein particles tend to resemble High-Density Lipoproteins (HDL) (Rang, 2012) much more than the larger ApoB-associated lipoproteins that predominate outside the CNS (Elliott, Weickert & Garner, 2010) [*more references?*].

In the rest of the body (and thus on the other side of the BBB) a large proportion of cholesterol is either of dietary origin or else the result of neogenesis in the liver (Vance & Vance, 2008) (Rang, 2012). From there much of it is transported in the same large, lipid-rich, ApoB-containing lipoproteins (i.e. chylomicrons and VLDLs) that also transport dietary and liver-derived FAs (Vance & Vance, 2008) (Rang, 2012) (Young, 1990). Thus, for reasons of size (along with the other reasons explained above), much cholesterol of non-CNS origin is unable to cross the BBB

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(Orth & Bellosta, 2012) (Elliott, Weickert & Garner, 2010) (Björkhem & Meaney, 2004) (Kay et al., 2003).

2.2.3 Overall differences in lipid transport either side of the BBB

Certainly, from birth onwards (Saunders et al., 1999), the BBB separates two compartments with very different lipid systems (Dietschy & Turley, 2004) (Pardridge & Mietus, 1980). Compared to the rest of the body the mature CNS compartment is distinguished by a much lower circulation of lipids, with minimal external lipid supplementation and a set of lipoproteins that are noticeably smaller and less lipid-rich [*references?*]. Much of this difference can be accounted for by the BBB, and by the fact that ApoB is not produced in the brain.

Given that this distinction appears to have first emerged comparatively early in vertebrate evolution (Bundgaard & Abbott, 2008) [*more references?*], it seems plausible that serious disruption to the BBB will have lipid-related consequences. This can be inferred from the fact that the mature brain compartment has evolved for so long to function in an environment low in circulating lipids compared with the rest of the body. And, given the relative volumes of the two compartments, it seems likely the brain will be the most vulnerable to lipid incursion if they are no longer separated by the BBB.

2.3 The causes of BBB disruption in the lipid-leakage model

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Clearly, an explanation of how the BBB becomes disrupted in AD is central to the lipid-leakage model. It is generally established that the BBB slowly degrades with age (Popescu et al., 2009) (Farrall & Wardlaw, 2009), providing a simple reason, according to the model, why LOAD incidence is also closely correlated with age. But any model with such disruption at its centre needs to account for the many inherited and non-inherited risk factors that accelerate the onset of AD.

In FAD this can accounted for by Aβ, which, as explained earlier, is known to impair BBB integrity (Takechi et al., 2010a) (Thomas et al., 1997) (Su et al., 1999) (Marco & Skaper, 2006), especially in association with the ApoE4 genotype (Alonzo et al., 1998) [*more references?*]. Numerous studies show that ApoE protects the BBB, with its absence leading to progressive BBB leakage, in excess of what is seen as a result of normal ageing (Hafezi-Moghadam, Thomas & Wagner, 2007) (Methia et al., 2001) (Mulder et al., 2001). Compared to the other ApoE isoforms, however, ApoE4 is associated with impaired BBB function, particularly involving tight junctions, whose integrity is critical to the BBB's capacity to exclude a wide range of molecules (Salloway et al., 2002) (Nishitsuji et al., 2011) (Bell et al., 2012).

However, recent studies have revealed that Aβ has an important function as a regulatory apolipoprotein, being highly expressed in both the liver and small intestine, and associated with triglyceride-rich lipoproteins of similar origin (Takechi et al., 2010a) (Mamo et al., 2008) (Galloway et al., 2007). In absorptive enterocytes, Aβ is seen to collocate with $ApoB_{48}$, forming chylomicrons, with enterocytic levels of Aβ and plasma levels of Aβ-associated chylomicrons

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both increasing in response to a diet high in saturated fats (Galloway et al., 2007) (Pallebage-Gamarallage et al., 2010).

In a standard transgenic mouse model of AD in which Aβ is overproduced, disease progression and onset were seen to be strongly correlated with rates of secretion into the blood of TAG-rich, Aβ-associated lipoproteins, and with their subsequent plasma levels (Takechi et al., 2010a). Such overproduction, whether resulting from dietary causes or from direct Aβ over-expression, leads to BBB disruption (Takechi et al., 2010a) (Mamo et al., 2008) (Pallebage-Gamarallage et al., 2010).

This explains, amongst other things, why amyloid plaques in human brains show immunoreactivity for ApoB, similar to that seen in the brains of AD mouse models (Takechi et al., 2010a) (Namba, Tsuchiya & Ikeda, 1992). For the reasons stated earlier, such ApoB deposition is only possible if the BBB has been disrupted in some way, as well as being consistent with the premise that invading, lipid-rich, lipoproteins are primary actors in endosomal pathology (as described in 2.6.2) and amyloid plaque formation.

This suggests that the aetiology of both familial and late-onset forms of AD could be linked through excess levels of TAG-rich chylomicrons. In the former case this would primarily result from over-production of Aβ, whilst in the latter case it would primarily result from dietary causes. This in turn would lead, in both cases, to BBB disruption (which can be exacerbated by other factors, as explained above) and to the characteristic neurodegenerative effects outlined

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below. However, evidence for such chylomicron excess as a general characteristic of AD is limited at present and is not a requirement of the model.

2.4 Likely neuroinflammatory consequences of lipid influx to the brain

2.4.1 Neuroinflammation

Extensive research has established that neuroinflammation is an important cause of ethanol-induced neurodegeneration (Crews, 2008) (Crews) [*more references?*] and that microglia are central agents of such inflammation (Crews, 2008) [*more references?*]. This central role is perhaps unsurprising, given that the "immune-privileged" status conferred on the brain by the BBB leaves microglia as the primary immune cell (Kaur et al., 2010) (Yang et al., 2010), a role not seen as a rule in macrophages in the rest of the body. Their ability to perform this role seems to depend in large part on being abnormally sensitive to a wide range of ligands (Yang et al., 2010) (Dissing-Olesen et al., 2007) (Gehrmann, Matsumoto & Kreutzberg, 1995), and this, in turn, helps to explain why chronic ethanol, largely unobstructed by the BBB, causes such extensive inflammatory damage to the brain over time (Fadda & Rossetti, 1998b) [*more references?*]. Additionally, the mechanism through which this occurs suggests that FAs, provided they could pass through the BBB in quantity, would have similar inflammatory effects, since both are known to powerfully activate the same critical receptor.

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Ethanol activation of microglia (Crews, 2008), is accompanied by upregulation of the transcription factor NF-κB (Zou & Crews, 2010) (Alfonso-Loeches et al., 2010), and other macromolecules known to be involved in inflammation and in the immune response. The evidence suggests that toll-like receptors, particularly TLR4, a receptor that binds bacterial lipopolysaccharide (LPS), appear to be central to such activation and the subsequent neuroinflammation (Alfonso-Loeches et al., 2010) (Fernandez-Lizarbe, Montesinos & Guerri, 2013).

If TLR4 is central to ethanol-induced neuroinflammation then there seems every reason to think that FFAs entering the brain would have similar neuroinflammatory effects. Saturated (but not, apparently, unsaturated) FAs are known to activate TLR4 in macrophages, leading in turn to activation of NF-κB and the other pro-inflammatory molecules referred to earlier (Wang et al., 2012) (Chait & Kim, 2010). And TLR4 activation in adipocytes by saturated FAs (and perhaps by some unsaturated FAs) is an essential step in lipid-induced diabetes mellitus (Chait & Kim, 2010) (Shi et al., 2006), which is now thought to be substantially inflammatory in nature [*references?*]. In support of this, knockdown or ablation of TLR4 has been shown to inhibit both FFA-induced and ethanol-induced inflammation (Alfonso-Loeches et al., 2010) (Wang et al., 2012) (Shi et al., 2006) [*more references?*] .

Given the much greater overall sensitivity of microglia to pathological stimuli (compared to other macrophages) (Rock et al., 2004) [*more references?*], one would expect activation by both ethanol and FFAs to result in far more vigorous inflammatory activity than seen in other parts of the body. And, whilst the relative affinities of ethanol and FFAs for TLR4 have yet to be

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488 determined, the fact that saturated fatty acyl groups are known to be crucial to TLR4 recognition
489 of LPS (TLR4's principal pathogenic ligand) (Hwang, 2001) suggests that FFAs should have a
490 substantially higher affinity than ethanol for TLR4. Thus the relatively low levels of FFAs seen
491 in plasma (generally agreed to fall within an average range of 0.3-0.6 mM [*references?*]) should
492 be sufficient to generate a steady level of neuroinflammation, following major BBB insult,
493 especially if they are accompanied by pathogen-associated LPS, as seen in ethanol-induced liver
494 injury (Nagy, 2003). Thus it may be this, rather than TLR4 stimulation by amyloid (Walter et al.,
495 2007), that is the primary driver of microglial-based neuroinflammation in LOAD.
496

497 2.4.2 Inhibition of neurogenesis

498

499 Ethanol-induced neuroinflammation has also been linked to inhibition of neurogenesis (Crews &
500 Nixon, 2009a) [*more references?*], with many studies suggesting that such neurogenetic deficits
501 are almost as important a factor as neuroinflammation in ethanol-mediated brain degeneration
502 (Crews, 2008) [*more references?*] . Here too, TLR4 is likely to have a prime inhibitory role
503 (Barak, Feldman & Okun, 2014) [*more references?*], diminishing proliferation of adult neuronal
504 progenitor cells (NPCs) and restricting neuronal differentiation from NPCs. Such inhibition
505 would obviously be most apparent in the main neurogenic niches, i.e. the subgranular and
506 subventricular zones, which provide new interneurons to (respectively) the hippocampus and the
507 olfactory bulb [*references?*]. This could explain the deficiencies in learning and olfaction
508 common to both AD and ARBD.
509

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Furthermore, current evidence indicates that the overall level of neurodegeneration is determined almost as much by the relentlessness of the ethanol assault as by the concentrations involved (Crews, 2008) (Crews & Nixon, 2009a) (Nixon & Crews, 2002). Thus, one can reasonably infer that constant exposure of the brain to plasma levels of FFAs is likely to overwhelm the brain's capacity to recover, especially in the elderly. Such a conclusion is further supported by evidence that inhibition of neurogenesis, by both ethanol and FFAs, does not need to rely on the TLR4 receptor alone, and may, in fact, depend more on GABAergic effects, as explained in the next section.

2.5 GABAergic effects

Recent research has indicated a possible role for the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the development of AD (Wu et al., 2014) (Rissman & Mobley, 2011) (Jo et al., 2014), with a number of possible mechanisms being suggested. One such mechanism, GABA-induced tonic inhibition within the hippocampus, provides an obvious explanation of why AD is characteristically associated with AA. However, the proposed source of this excess GABA within hippocampal-resident reactive astrocytes, does not have much support in the literature, either for AD or ARBD.

The lipid-leakage model provides an alternative mechanism, extending beyond tonic inhibition, and accounting for the coexistence of AA in AD and ARBD, as well as other similarities, including similar patterns of neurodegeneration within two major neurogenic niches, the SGZ

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and SVZ. Underlying this common mechanism is the proven affinity of ethanol, and likely affinity of FFAs, for GABAA receptors (GABAARs), as well as the recently-discovered role of high-affinity extrasynaptic GABAARs in both tonic inhibition and anaesthesia-associated amnesia.

In the 1950s onward, Samson and Dahl and other groups showed that injection of FFAs induced light anaesthesia in a range of mammals (Samson Jr, Dahl & Dahl, 1956) (White & Samson, 1956) (Matsuzaki & Takagi, 1967) (McCandless, 1985). Anaesthetic potency increases (up to an undetermined cut-off) with FFA chain length (and thus hydrophobicity), in line with Meyer-Overton (Samson Jr, Dahl & Dahl, 1956) (White & Samson, 1956) (Dahl, 1968) (Perlman & Goldstein, 1984), falling within the low millimolar range (expressed both as moles per litre and moles per kilogram of body weight) and showing similar potencies to structurally comparable 1-alcohols (including ethanol) (Alifimoff, Firestone & Miller, 1989) , as well as to alkanes (Hau, Connell & Richardson, 2002) and aldehydes (Deneer, Seinen & Hermens, 1988).

Given the general correlation between hydrophobicity and anaesthetic potency first described by Meyer-Overton (Evers & Crowder, 2009), it would perhaps be surprising if fatty acids did not show similar anaesthetic potencies to structurally very similar fatty alcohols (Evers & Crowder, 2009) (Ueda & Suzuki, 1998) (Matsuki et al., 1999) (Frangopol, 2001), nor, given the established anaesthetic properties of various steroids (Kappas & Palmer, 1963) (Belelli & Lambert, 2005), should it be a surprise that other lipids might display similar properties.

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554 The immediate significance of lipids' anaesthetic properties to dementia lies in the fact that, at
555 concentrations well below those needed for clinical anaesthesia, the vast majority of anaesthetic
556 agents are known to cause AA (Evers & Crowder, 2009) (Orser, 2007) (Bonin & Orser, 2008a).
557 Such low-level anesthesia-induced AA is now known to involve extrasynaptic GABAARs
558 (Orser, 2007) (Bonin & Orser, 2008b) whose subunit composition (including either α5 or δ
559 subunits) gives them sufficient sensitivity to respond to low levels of ambient GABA (Brickley
560 & Mody, 2012). It is the resulting low-level inhibitory currents, termed "tonic inhibition", which
561 is associated with AA (Nutt et al., 2007) (Cheng et al., 2006) (Sikka, Beaman & Street, 2015).
562 (By contrast lower-affinity synaptic GABAARs, with different subunit compositions, respond
563 only to the higher concentrations of GABA released within their associated synapses, with the
564 resulting phasic inhibition causing the other anaesthetic effects (Evers & Crowder, 2009) [*more*
565 *references?*], including analgesia, immobility and unconsciousness.) In support of this,
566 pharmacological and genetic knockdown of extrasynaptic α5- and δ-containing $GABA_A$Rs in
567 mice has been shown to improve performance on learning and memory tasks (Collinson et al.,
568 2002) (Clarkson et al., 2010) (Shen et al., 2010), possibly by lowering the threshold for long-
569 term potentiation (Martin et al., 2010) (Whissell et al., 2013) (Liu et al., 2010).
570
571 The reason for all this is that GABAARs have associated ion channels, which become permeable
572 to chloride (and, to a lesser extent, HCO_3) ions, in response to GABA ligation (Li & Xu, 2008)
573 [*more references?*]. Upon such activation, chloride ions flow through these GABAAR channels
574 in a direction determined by their electrochemical gradient. Since mature neurons maintain an
575 excess of chloride ions externally, the normal response to GABA binding is therefore for these
576 negative ions to flow in through the GABAAR channels, increasing the negative membrane

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potential and thereby hyperpolarising (i.e. inhibiting) the affected neuron (Li & Xu, 2008) (Kaila, 1994). Tonic inhibition is just the extrasynaptic form of this (Petrini et al., 2004) (Jia et al., 2005). The majority of anaesthetic agents (including those that are only weakly anaesthetic, such as ethanol) are known to enhance this GABA binding, acting as positive allosteric modulators (Krasowski, 2003) (Orser et al., 1998). Accordingly, they tend to inhibit normal activity in mature neurons of the CNS (Orser et al., 1998) (Krasowski & Harrison, 1999) (MacIver, 2014).

However, recent research has shown that the same high-affinity extrasynaptic GABAARs that mediate tonic inhibition in mature neurons (Brickley & Mody, 2012) (Yeung et al., 2003) also play a significant role in neurogenesis and neuronal plasticity (Bordey, 2007a) (Liu et al., 2005). In support of this, pharmacological and genetic suppression of tonic GABA inhibition, including by down-regulation of extrasynaptic GABAAR activity, is associated with marked improvements in functional recovery after stroke (Clarkson et al., 2010) (Paik & Yang, 2014). This is in agreement with findings that suggest that increased GABA tonic inhibitory currents, in the days after stroke, hinder recovery (Clarkson et al., 2010) (Clarkson, 2012).

Since the extrasynaptic GABAARs containing the δ-subunit are known to be especially sensitive to positive modulation by ethanol (Meera et al., 2010) (Wei, Faria & Mody, 2004) this may explain alcohol-mediated neurodegeneration seen in ARBD. As explained earlier, disruption of neurogenesis appears to be critical to the neurodegenerative effects of ethanol upon the brain. Specifically, chronic exposure of the brain to ethanol is characterised from comparatively early on by erosion of the hippocampal region (Crews, 2008) (Nixon & Crews, 2002), loss of

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600 interneurons (the primary product of neurogenesis (Mandyam, 2013)), AA (White et al., 2004)
601 (Sanday et al., 2013) and olfactory deficits (Collins, Corso & Neafsey, 1996) (Ditraglia et al.,
602 1991).
603
604 An obvious explanation for these findings is inhibition of neurogenesis in the SGZ and SVZ,
605 given that the former supplies interneurons to other hippocampal regions (Eriksson et al., 1998)
606 [*more references?*], whilst the latter is known to replenish the olfactory bulb interneurons via the
607 rostral migratory stream (Lim & Alvarez-Buylla, 2016) [*more references?*]. Since much
608 evidence suggests that FFAs have similar, if not higher, anaesthetic potency levels to ethanol
609 (Ueda & Suzuki, 1998) (Frangopol & Mihailescu, 2001) (Samson, Dahl & Dahl, 1956) (Pringle,
610 Brown & Miller, 1981) (Walker et al., 1970) (Wong et al., 1997) implying a similar affinity for
611 GABAARs, it may well be that chronic exposure of the brain to excess FFAs over many years
612 will have similar results, explaining why AD and ARBD share these hallmark effects on the
613 brain.
614
615 A complicating factor here is that, in immature neurons, the chloride gradient is reported to be in
616 the reverse direction to that of their mature counterparts (Li & Xu, 2008) (Ben-Ari & Holmes,
617 2005). That is to say, chloride ions are held internally in excess of their external levels. If so,
618 GABA binding to GABAARs could reasonably be expected to activate such precursor neurons
619 and, by extension, one would expect anaesthetic agents (and other positive modulators) to
620 overactivate them. A further consideration is that such precursor cells initially exhibit few
621 synapses, with most GABAARs having a subunit composition typical of extrasynaptic
622 GABAARs in mature neurons (Henschel, Gipson & Bordey, 2008) (Pallotto & Deprez, 2014)

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623 (Song et al., 2012), with synapses only tending to emerge later as the neuronal precursors mature
624 and become integrated (synaptically and otherwise) with the existing network (Ming & Song,
625 2011) (Ge et al., 2007) (Ben-Ari et al., 2007). So GABAARs in these cells tend to have a high
626 affinity for ambient GABA, and one would expect the dominant response to GABA stimulation
627 to be tonic activation (Song et al., 2012) (Ming & Song, 2011). So, if ethanol (and, as we are
628 arguing here, by extension, FFAs) abnormally enhance this effect, one should expect to see
629 overgrowth rather than erosion in adult neurogenic regions. Why is this not so?
630
631 One mechanism that might explain such neurogenetic deficits in the SGZ and SVZ, is GABA-
632 mediated feedback inhibition. Recent discoveries suggest that non-synaptic paracrine GABA
633 signalling provides information on population size to control proliferation and migration of
634 neural progenitor cells in the SVZ (Liu et al., 2005) (Pallotto & Deprez, 2014) (Ge et al., 2007)
635 (Bordey, 2007b). Specifically, adult SVZ neuroblasts synthesise and release GABA, which acts
636 on GABAARs in neural stem cells, inhibiting NSC division and thus effectively applying a
637 brake on neurogenesis. In confirmation of this, removal of neuroblasts is seen to release this
638 brake.
639
640 The specific details of this appear to have been provided by a study of neurogenesis in postnatal
641 rat striatum (Nguyen et al., 2003). Here, the growth factor EGF was seen to decrease GABA
642 production and release in PSA-NCAM+ neural precursor cells, leading to their proliferation. A
643 number of experiments suggested that GABA was indeed acting on GABAARs in an
644 autocrine/paracrine mechanism to prevent cell proliferation by inhibiting cell cycle progression.
645 Application of GABAAR antagonists inhibited proliferation, whereas positive allosteric

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646 modulators decreased it. As with other immature neuronal cell lineages, GABA-mediated
647 GABAAR activation elicited inward currents (indicating outward flows of negatively-charged
648 chloride ions), leading to tonic inhibition of the mitogen-activated protein kinase cascade and an
649 increase of intracellular calcium levels (Nguyen et al., 2003).
650
651 This agrees with the findings of the Liu study, which showed that, at least in GFAP-expressing
652 neural progenitor cells in the SVZ, GABAAR activation limits progression through the cell cycle
653 (Liu et al., 2005). It also suggests that, at least in the SVZ, adult neurogenesis is regulated by the
654 same mechanisms that govern embryonic neurogenesis, where, for instance, GABA is seen to
655 direct neuroblast migration, stimulating random mobility by promoting elevation of cytosolic
656 Ca2+ levels (Ge et al., 2007) (Barker et al., 1998), similar to what is seen in adult neurogenesis
657 (LoTurco et al., 1995). While some related studies have shown that such effects appear to
658 promote neuronal fate selection (Tozuka et al., 2005), the overall impression is that GABA
659 stimulation also seems to limit proliferation (Nguyen et al., 2003) (Barker et al., 1998).
660 However, more recently, doubts have been raised about whether such tonic GABA-mediated
661 depolarisation is sufficient to open voltage-gated calcium channels enough to permit substantial
662 increases in intracellular calcium in the way proposed, requiring other explanations (Bordey,
663 2007b).
664
665 An alternative explanation is that an epigenetic mechanism, involving histone H2AX
666 phosphorylation following sustained GABAAR activation by GABA, inhibits DNA synthesis
667 and cell cycle progression, and therefore proliferation of adult neural stem cells (Fernando et al.,
668 2011). It is not clear that this mechanism also applies to SGZ neurogenesis but, if so, it could

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669 explain why GABAergic stimulation is similarly associated with quiescence of adult precursor
670 cells in this niche (Pallotto & Deprez, 2014) (Song et al., 2012) (Duveau et al., 2011).
671
672 But it may be that such involved explanations are not necessary, as recent research has brought
673 into question the prevailing orthodoxy concerning GABA activation of immature neurons
674 (Valeeva et al., 2016) (Zilberter, 2016), concluding that, overall, GABA action on the neonatal
675 brain is inhibitory. If this proves correct, and is found to be true also for adult neurogenic
676 regions, then ethanol-induced deficits in neurogenesis can be simply explained as a result of
677 excess inhibition.
678
679 Either way, assuming ethanol inhibition of neurogenesis in the SVZ and SGZ is mediated by
680 GABAARs, then FFAs are likely to have a similar effect. This is because a number of studies
681 point towards GABAARs as the most likely target and mediator of FFA's limited anaesthetic
682 properties, not least the well-established anaesthetic effects (alluded to earlier) of structurally
683 similar n-alkanes, n-alcohols and n-aldehydes. Furthermore, as with FFAs, anaesthetic potency
684 increases with chain length but only up to a certain "cut off" length (Alifimoff, Firestone &
685 Miller, 1989) (Hau, Connell & Richardson, 2002) (Frangopol & Mihailescu, 2001) (Chiou et al.,
686 1990) (Wick et al., 1998) (Lugli, Yost & Kindler, 2009)). This, together with direct evidence
687 that the n-alcohols act on GABAARs (Wick et al., 1998) (Davies, 2003), as does the
688 endogenous, FA, anaesthetic oleamide (Lees et al., 1998) (Coyne et al., 2002) (Laws et al.,
689 2001), suggests a common binding site. More direct evidence for this comes from the observed
690 antagonising effects of long-chain FFAs on GABAAR-mediated anaesthesia by volatile
691 anaesthetics (Yamakura, 2004) (Hanada, Tatara & Iwao, 2004), along with other evidence of

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direct interactions between FFAs and GABAARs (Zhang & Xiong, 2009) (Koenig & Martin, 1992) (Witt & Nielsen, 1994).

Taken together, a strong body of evidence points to the likelihood that FFAs, entering the brain through a damaged BBB (and therefore much in excess of their normal levels), will, if maintained over the long-term, tend to seriously disrupt neurogenesis by acting on GABAARs. Given the presence of major sites of neurogenesis in the SGZ and SGZ, this will principally manifest itself in anterograde amnesia and olfactory deficits. The first of these is of course the primary behavioural abnormality seen in AD, whilst the second has been argued to be another common (if less obvious) outcome. But, as described above, these are also seen in ARBD, driven by excess exposure to ethanol, which is known to act on GABAARs, accounting for the similarities between AD and ARBD detailed above.

2.6 AD-specific consequences of brain exposure to external lipids

If the above account explains many of the similarities seen between AD and ARBD, it does not explain why, unlike ARBD, AD is characterised by profuse plaques and tangles. The lipid-leakage model of AD explains this by the fact that the BBB has to be disrupted for fatty acids to substantially enter the brain, unlike in ARBD, where ethanol can pass through the BBB relatively unhindered [*references?*]. Consequently, in AD the brain is also exposed to other molecules from which it is normally protected, including lipoproteins, which are much larger and more lipid-laden than those normally found within the CNS compartment.

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There is good reason to think that such lipoproteins may account for the amyloid plaques that characterize AD. It has been known for some time that excess cholesterol is associated with increased amyloidogenesis.

2.6.1 The role of excess cholesterol in amyloidogenesis

Cholesterol may have a role in increasing proteolytic production of amyloidogenic Aβ from APP, as opposed to production of alternative non-amyloidogenic fragments (Xiong et al., 2008b) (Nicholson & Ferreira, 2010) (Bodovitz & Klein, 1996). This appears to result from the influence of cholesterol stimulation on an amyloidogenic pathway involving β- and γ-secretases (two proteases involved in APP proteolysis) (Xiong et al., 2008b), as well as on a non-amyloidogenic pathway involving α-secretase (Kojro et al., 2001) (Figure 3.). Increasing the levels of cholesterol stimulates the amyloidogenic pathway, at the same time inhibiting the non-amyloidogenic pathway (Wolozin, 2004) (Xiong et al., 2008b). In contrast, cholesterol depletion, by various processes, inhibits the amyloidogenic pathway and enhances non-amyloidogenic processing, resulting in lower levels of Aβ (Kojro et al., 2001) (Simons et al., 1998) [*more references?*].

Amyloidogenic processing appears to be initiated within cholesterol-rich lipid rafts (Ehehalt et al., 2003) (Rushworth & Hooper, 2011) (Nixon, 2017) (especially in early endosomes (Nixon, 2017) (Arriagada et al., 2007)), whilst non-amyloidogenic processing occurs in the main

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736 phospholipid-rich region of the neuronal plasma membrane (Xiong et al., 2008b) (Grimm et al.,
737 2013). This suggests that an important part of cholesterol's influence on amyloidogenic
738 processing may be a consequence of its essential role as a major constituent of these lipid rafts, a
739 conclusion that is well-supported in the literature (Ehehalt et al., 2003) (Nixon, 2017) (Vetrivel
740 et al., 2004) [*more references?*].
741
742 Certainly, some studies indicate that brain cholesterol levels may be raised in AD, compared to
743 non-demented, brains (Xiong et al., 2008b) [*more references?*], although not all studies concur
744 [*references?*]. That cholesterol may be directly associated with amyloid plaque formation is
745 supported by brain imaging studies, which show Aβ collocated with cholesterol within amyloid
746 deposits in AD human brain samples (Xiong et al., 2008b) [*more references?*].
747
748

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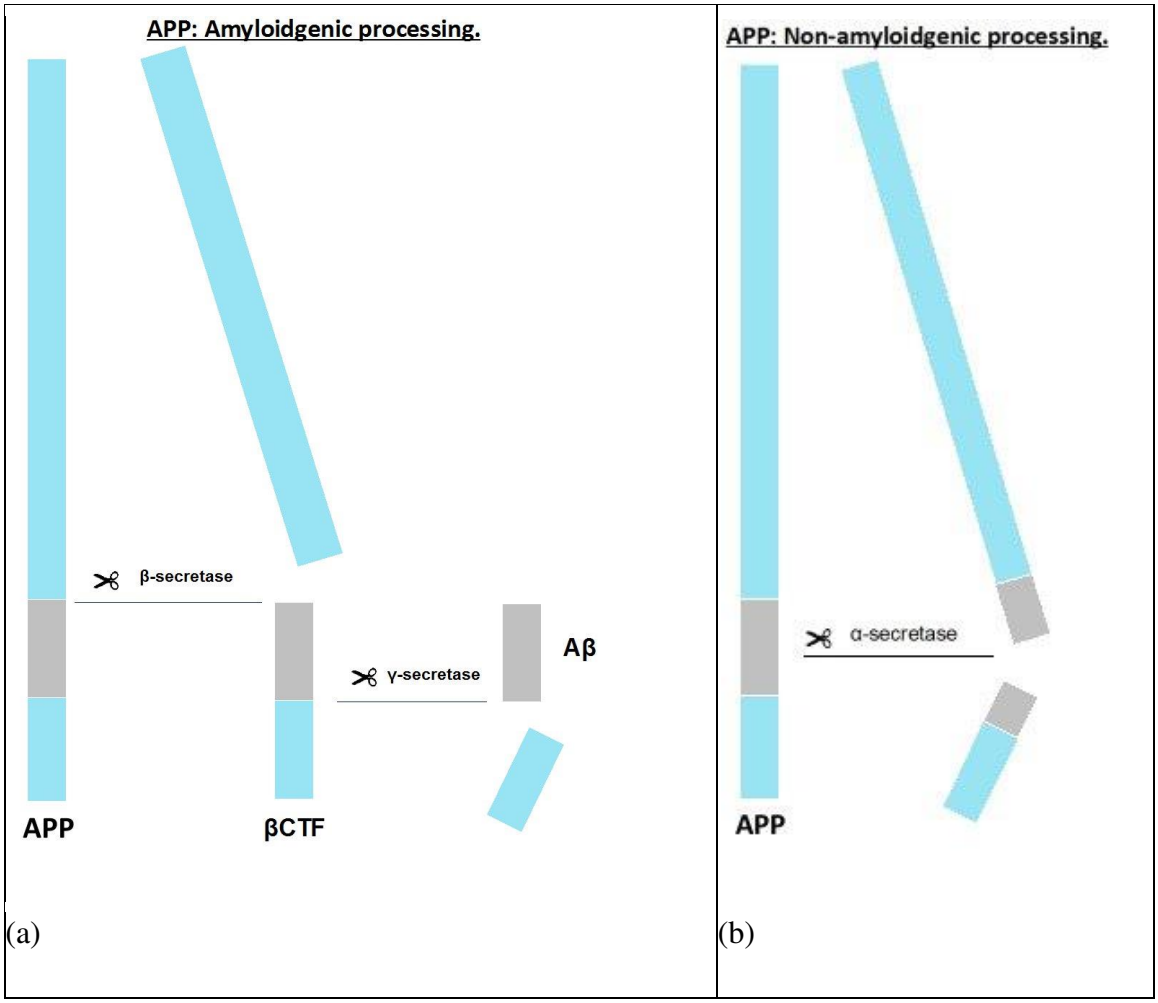

749

750 **Figure 3. (a) Amyloidogenic and (b) non-amyloidogenic processing of APP.**

751

752

753 ### 2.6.2 The role of excess cholesterol in endosomal-lysosomal pathway abnormality

754

755 Indirect evidence of raised brain cholesterol levels as a causal factor in AD comes from studies
756 of human AD brains (Cataldo et al., 2000) [*more references?*]. Such brains show abnormalities
757 in the endosomal-lysosomal system compared to normal brains, together with neurofibrillary

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(tau) tangles [*references?*]. Such endosomal pathway overactivity and compartmental enlargement appears to be an early marker in AD, especially in pyramidal neurons (which are known to be vulnerable in AD [*references?*]), and in endothelial cells [*references?*].

Interestingly, a very similar pathology is also seen in mouse and other models of DS (Arriagada et al., 2007) (Cataldo et al., 2000) (Cataldo et al., 2008) [*more references?*]. However, at least in the case of one mouse model, such pathology was seen to emerge only following lipoprotein-mediated cholesterol treatment (Arriagada et al., 2007), suggesting that cholesterol is a crucial causal factor.

Further support for this comes from a number of studies in in Niemann-Pick disease type C (NPC), a neurological disorder characterised by faulty cholesterol transport and by tau tangles (Saito et al., 2002), and in which endosomal-lysosomal pathology is also observed (Frolov et al., 2001). Such studies, whilst often contradictory in their results, collectively point to various failings in cholesterol uptake, transport and recycling, and in abnormal endosomal-lysosomal pathway behaviour. Such reported failings include excessive uptake of exogenous LDL-derived cholesterol (Liscum & Faust, 1987), excessive synthesis of endogenous cholesterol (Liscum & Faust, 1987), enlarged early endosomes (Nixon, 2004) (Jin et al., 2004), accumulation of unesterified cholesterol in late endosomes and lysosomes (Nixon, 2004) (Sobo et al., 2007), defective post-lysosomal cholesterol transport (Roff et al., 1991) and redistribution of lysosomal hydrolases to early endosomes (Jin et al., 2004).

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780 Yet such reports commonly claim that other aspects of cholesterol internalisation (and
781 endosomal-lysosomal pathway behaviour) appear to be normal, particularly in the case of initial
782 cholesterol uptake and early endosome behaviour (Nixon, 2004). However, a very similar
783 phenotype is observed in a Chinese hamster ovary (CHO) cell mutant, which has a normal copy
784 of NPC1 (the late endosome/lysosome-residing protein most commonly associated with NPC
785 disease (Nixon, 2004)) , and of the HE/NPC2 protein (also associated with NPC, although less
786 commonly) yet still exhibits NPC-like pathology (Frolov et al., 2001). In this mutant late sterol
787 trafficking is reported to be normal despite obvious cholesterol accumulation in late endosomes/
788 lysosomes (Frolov et al., 2001). Instead, cholesterol build-up occurs as a result of much-
789 increased LDL-R binding, probably leading to cholesterol uptake being in excess of the normal
790 capacity of the cell to dispose of it (Frolov et al., 2001). Evidence in support of this conclusion
791 includes the finding that LDL starvation of this mutant resulted in the disappearance of the
792 cholesterol-laden aberrant late endosome compartment (characteristic also of NPC) that had
793 previously been observed, only for this compartment to reappear with the restoration of LDL
794 feeding (Frolov et al., 2001).
795
796 More generally, another study, using a human fibroblast model, appears to provide further
797 evidence for this conclusion. It found endosomal-lysosomal pathology in a number of inherited
798 sphingolipid-storage disorders (Puri et al., 1999). In almost all cases such pathology showed
799 strong similarities with that seen in NPC, with a marked reduction in the accumulation of both
800 cholesterol and a representative sphingolipid within the Golgi complex, accompanied by their
801 increased accumulation within many punctate cytoplasmic structures that also appeared to be
802 associated with the NPC1 protein (Puri et al., 1999).

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803

804 The authors conclude that the observed pathology most likely results from a build-up of
805 cholesterol (which is known to associate with high affinity to sphingolipids (Brown, 1998)
806 (Lönnfors et al., 2011)) within endosomes and lysosomes, since the reported pathology was seen
807 to disappear following cholesterol depletion, being replaced with normal endosomal-lysosomal
808 behaviour (Puri et al., 1999). However the same pathology could also be induced in normal cells
809 by application of excess external cholesterol in the form of low-density lipoprotein (LDL) (Puri
810 et al., 1999), similar to what is described for the CHO mutant mentioned above (Frolov et al.,
811 2001), and in line with another study linking raised levels of plasma membrane cholesterol with
812 correspondingly enlarged early endosomes in hippocampal neurons (Cossec et al., 2010).

813

814 As stated earlier, LDL is not normally seen in the brain (since it requires apolipoprotein B) and
815 tends to be both larger in size and more cholesterol-rich than the HDL-like lipoproteins typically
816 seen there (Vance & Vance, 2008) (Danik et al., 1999). This suggests that externally-sourced
817 cholesterol, supplied in excess of normal brain levels, may be a causal factor of AD-related
818 endosomal abnormalities and of amyloidosis, at least in the late-onset form.

819

820 In further support of this hypothesis, inhibition of CYP46A1 (a protein indirectly responsible for
821 cholesterol clearance from the brain through the BBB (Lund, Guileyardo & Russell, 1999)
822 (Lütjohann et al., 1996)) in mouse hippocampal neurons has been shown to lead to accumulation
823 of neuronal cholesterol. This, in turn, is associated with a distinctive AD-like pathology,
824 including marked changes in endosomes (increasing both in size and number), Aβ peptide

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825 production, tau phosphorylation, endoplasmic reticulum stress and apoptosis, and eventually
826 hippocampal atrophy and cognitive impairment (Djelti et al., 2015) (Ayciriex et al., 2017).
827
828 It has been argued earlier that the presence of a BBB has resulted in the brain (and the rest of the
829 CNS) evolving to have a different lipid system to the rest of the body, one characterised by a
830 much lower lipid turnover, and smaller, less lipid-dense lipoproteins. If so, it should therefore
831 not be unexpected that substantial damage to the BBB, leading to long-term exposure to a
832 systemic lipid system characterised by high lipid turnover and larger, more lipid-dense
833 lipoproteins, will result in neurons and other brain cells becoming overloaded and displaying the
834 kind of abnormalities described above.
835

836 ### 2.6.3 The role of the β-secretase-induced C-terminal fragment (βCTF)

837
838 Certainly, this interpretation fits in well with the evidence presented above, given that cellular
839 LDL-cholesterol uptake is known to be dependent on the endosomal-lysosomal pathway, by way
840 of receptors possibly bound within lipid rafts (Vance & Vance, 2008) (Nixon, 2017) (Pompey et
841 al., 2013) (Sun et al., 2010). Furthermore, APP seems to be central to endosomal-lysosomal
842 pathology, as the latter can be induced by APP over-expression, or by the C-terminal fragment
843 that remains after β–secretase cleavage of APP (Nixon, 2017) (Jiang et al., 2010) [*more*
844 *references?*], but prior to γ–secretase cleavage (Fig. 3).
845

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Such cleavage is known to take place in early endosomes (Arriagada et al., 2007) (Cataldo et al., 2000) and appears crucial to pathology, since inhibition of β–secretase (or the substitution of APP by constructs lacking β–secretase cleavage sites) restores normal endosomal-lysosomal behaviour (Jiang et al., 2010) [*more references?*]. Furthermore, treatments that increase levels of Aβ without increasing levels of βCTF do not result in endosomal-lysosomal pathology (Jiang et al., 2010), in line with other evidence that the endosomal abnormalities seen in a mouse model of DS do not appear to be associated with abnormally high levels of Aβ (Salehi et al., 2006) (Choi et al., 2009). Meanwhile, inhibition of γ-secretase, which increases levels of βCTF at the expense of Aβ, induces endosome-lysosomal pathology in previously normal fibroblasts (Jiang et al., 2010).

The underlying reason for this appears to be that βCTF recruits the adaptor protein APPL1 (adaptor protein containing pleckstrin homology domain, phosphotyrosine binding domain, and leucine zipper motif) to Rab5 complexes on endosomes (Nixon, 2017) (Miaczynska et al., 2004) (Zhu et al., 2007). This stabilises the monomeric GTPase protein Rab5 in its GTP-bound, activated form, and therefore amplifies the Rab5 signalling associated with early endosomes (Grbovic et al., 2003) (Gorvel et al., 1991) (Mishra et al., 2010), leading in turn to the enlarged endosomes seen in both AD and DS (Nixon, 2017) (Kim et al., 2016).

(More on cholesterol? ApoE4?)

Thus, taken collectively, the evidence appears to explain the endosomal-lysosomal pathology seen in DS dementia, and in many forms of AD, by two related mechanisms.

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In the case of DS dementia, and early-onset forms of AD resulting from APP mutations, the pathology is likely to be the product of βCTF over-expression. In the case of LOAD, over-supply of cholesterol, originating from outside the brain, results in preferential up-regulation of β-secretase (Xiong et al., 2008b), leading to the same result. Amyloidosis inevitably follows in both cases, no doubt enhanced by the substantial presence of Aβ in enterocytic- and hepatic-derived lipoproteins (see 2.3). Tau tangles presumably result from amyloidosis or from a failure of cholesterol transport, by a similar mechanism to that seen in NPC.

3 Discussion

In the preceding text, evidence has been presented to support a lipid-leakage model of AD progression. This states that, in the majority of cases, if not all, AD is primarily driven by the influx of lipids of systemic non-CNS origin, following the breakdown of the BBB. From a general perspective, this emphasis on a mechanical, rather than a purely biochemical failure, would seem to provide a much better explanation of why AD is as prevalent as it is, in contrast to current models. In particular, such mechanical failure also provides a more straightforward explanation of why ageing is the primary risk factor for AD.

However, as has been shown above, many specific aspects of AD can also be said to support such a model. These include indirect evidence of BBB damage from the presence, in AD cases, of non-CNS proteins inside the brain, and of CNS proteins outside it. In particular, evidence of the presence of the systemic apolipoprotein ApoB, together with long-chain triglycerides, within

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Aβ plaques strongly suggests that, in AD, the BBB is failing to separate the highly distinctive lipid systems of the CNS and systemic non-CNS compartments in the normal way. Moreover, included amongst the non-CNS proteins mentioned earlier, are plasma proteins such as albumin, fibrinogen and immunoglobulins that are, like Apoβ100, exclusively synthesised in the liver (or, like, Apoβ48, in other non-CNS organs). Again, like Apoβ, they are of high molecular weight, meaning that they cannot readily pass through the BBB in normal circumstances.

Further support for the lipid-leakage model arises from the likelihood that the BBB will be compromised by many of the risk factors associated with AD. As well as ageing, these include brain trauma, diabetes, ApoE4 and Aβ. Similarly, CTE, a condition showing many similarities to AD, has been associated with clear evidence of BBB disruption. Finally, there is clear evidence that Aβ directly disrupts the BBB, something most obviously apparent in the case of CAA.

Why should lipid influx from outside the CNS matter so much? As explained in some detail above, there are major differences in the two lipid systems either side of the BBB. In particular, and most relevantly to AD, lipoproteins on the non-CNS side are larger and more lipid-rich than on the CNS side, thanks in large part to the presence of ApoB. Similarly, unlike on the CNS side, there is extensive transport of FFAs. Reasons for this include the absence of large FA-storing adipocytes and of albumin synthesis in the CNS, as well as the presence of the BBB itself.

But why should these differences matter? It is argued here that, whatever the original physiological function of the BBB might have been, it has allowed the CNS (and the brain in

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913 particular) to evolve in ways that make it highly vulnerable to lipid incursion from the non-CNS
914 compartment. In particular, it is predicted that exposure to the higher cholesterol content of the
915 more lipid-rich lipoproteins from outside the CNS will lead to cholesterol overload in neurons
916 and other CNS-specific cell types. This in turn will result in endosomal-lysosomal pathology,
917 tau tangles and excessive formation of Aβ, similar to what is seen in AD.
918
919 In support of this hypothesis, similar endosomal-lysosomal pathology is seen in NPC, a disease
920 characterised by faulty cholesterol transport, resulting in the accumulation of unesterified
921 cholesterol in late endosomes and the formation of tau tangles. Likewise, excess cholesterol has
922 been shown to increase amyloidogenesis by stimulating amyloidogenic processing of APP at the
923 expense of the non-amyloidogenic pathway, resulting in increased levels of Aβ. During this
924 amyloidogenic processing, high levels of the intermediate βCTF fragment are produced, which
925 have been shown to trigger endosomal-lysosomal abnormalities similar to those observed in
926 early AD progression. (Presumably, the reason Aβ levels are much lower in NPC than in AD is
927 because cholesterol buildup tends to affect late endosomes in the former disease, rather than
928 early endosomes where Aβ is produced.)
929
930 But cholesterol is not the whole story here. Breakdown of the BBB also exposes the brain to
931 higher levels of FFAs. It is argued here that such exposure will lead to neuroinflammation, as a
932 result of these FFAs stimulating microglia by binding to TLR4 and other microglial receptors,
933 similar to how FFAs activate macrophages outside the CNS and to how ethanol triggers
934 microglial-mediated neuroinflammation.
935

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936 This may help explain why the overall structural pattern of damage to the brain inflicted by long-
937 term alcohol abuse so strongly resembles that seen in AD, and why there are similar behavioural
938 deficits. In particular, frontal regions of the brain (especially the prefrontal cortex and basal
939 forebrain) suffer significant shrinkage in both ARBD and AD, helping to explain why both
940 diseases are associated with deficits both in olfaction and in executive functions requiring
941 attentional and inhibitory control, reasoning, problem-solving, the setting of goals and of
942 planning. Similarly both ARBD and AD are associated with shrinkage of the medial temporal
943 lobes, including pronounced atrophy of the hippocampus and entorhinal cortex, resulting in the
944 anterograde amnesia so characteristic of AD, along with more specific deficits in spatial
945 memory.
946
947 However, it is hard to explain how such similarities might occur as a result of neuroinflammation
948 alone. Studies have shown that inhibition of neurogenesis plays almost as important a role in
949 ARBD, which would better explain why the principal areas of brain atrophy in ARBD and AD,
950 the frontal and medial temporal regions, also host two of the principal neurogenic niches of the
951 brain, the subventricular and subgranular zones. These provide new cells for the prefrontal
952 cortex and the hippocampus, respectively. It is argued here that the principal mechanism by
953 which ethanol inhibits such neurogenesis, involving extrasynaptic GABAARs, means that such
954 regions are also likely to be similarly affected by long-term exposure to other molecules with
955 weakly anaesthetic properties, including FFAs. Whilst the mechanism by which such inhibition
956 occurs appears to be complex, and may well involve other receptors and pathways, these shared
957 properties, and the shared mechanism seen in most forms of anaesthesia [references?], suggest
958 that long-term neurodegeneration will result in both cases.

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959

960 Whilst this aspect of the lipid-leakage model might be considered to be its most speculative, it
961 may help to explain why general anaesthesia is also considered a potential risk factor for AD
962 (and dementia in general) amongst elderly patients [Bohnen 1994; Chen 2014; Vanderweyde
963 2010; Xie 2006; Fodale 2010; Papon 2011; Eckenhoff 2004], as well as being associated with
964 marked deterioration in those already affected with AD [Bone 2001; Planel 2007; Xie 2007;
965 Papon 2011]. However, such an association is still a matter of dispute [Needham 2017], and a
966 number of studies suggest that, where it does occur, anaesthesia-related deterioration is
967 accompanied by increases in Aβ synthesis and oligomerisation, and by tau hyperphosphorylation
968 [Papon 2011; Eckenhoff 2004; Xie 2006 & 2007; Fodale 2010; Planel 2007]. If so, this tends to
969 rule out any GABA-related mechanism.

970

971 But these are not the only reasons for suspecting a link with GABAARs. Ever since the first
972 practical anaesthetic agents were discovered in the middle of 19th century [reference?], and later
973 shown (independently) by Hans Horst Meyer and Charles Ernest Overton to display a
974 remarkable correlation between potency and hydrophobicity [reference?], there has been
975 considerable interest in their mechanism of action. Following the findings of Franks and Lieb in
976 the 1980s this interest has focused on hydrophobic sites on membrane proteins, particularly those
977 of the Cys-loop ligand-gated ion channel superfamily, which includes inhibitory GABAARs and
978 glycine receptors, as well as the excitatory acetylcholine and 5-HT3 serotonin receptors
979 [references?].

980

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In terms of the obvious therapeutic endpoints of anaesthesia, including coma and analgesia, the findings of such research are not likely to have any relevance either to AD or ARBD. But the role of extrasynaptic GABAARs in anaesthesia-mediated anterograde amnesia clearly does, given the importance of such amnesia in ARBD and, especially, in AD. This is especially the case now that research has shown that the same high-affinity extrasynaptic GABAARs that have been shown to play a critical role in such amnesia, also play a critical role in neurogenesis. Given that the hippocampal region is a principal region of such neurogenesis [references?], and is also known to be central to the formation of new memories (as well as being heavily degraded in both ARBD and AD), it is readily apparent how chronic exposure to ethanol, with its weakly anaesthetic properties, is able to cause progressive deterioration of this region.

But this same mechanism also appears to explain why FFAs, with similar anaesthetic potencies, Discussion are largely excluded from the brain by the BBB. This despite FFAs being highly energy-rich molecules and despite the brain being one of the most highly energy-consuming organs of the body. However one explains the requirement for the BBB to in some way protect the brain from damage from external sources, it is not clear that FFAs could not be transported across it in the way many other macromolecules, including ketone bodies, are. They could thus provide the brain with a much-needed additional energy source. Indeed, the transporter ABCB1 (also known as P-glycoprotein 1 or multidrug resistance protein 1) is already known to transport lipids, including FFAs, across the BBB in the reverse direction [Gonçalves 2011;], and its decreased expression has been associated with increased AD risk [van Assema & van Berckel 2016]. Therefore there seems little reason why the BBB could not have evolved a similar transporter in the reverse direction. That the BBB has not evolved to do so, it is argued here, is

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because FFAs, at levels commonly seen in the rest of the body, would be inimical to the normal working of the brain. As would be the case if more cholesterol-rich lipoproteins could gain access to the brain, for the reasons discussed above.

It is been shown how breakdown of the BBB, by allowing such lipid invasion, is predicted to result in the anterograde amnesia, amyloid plaques and tau tangles, so characteristic of AD, as well as endosomal-lysosomal pathology and neural inflammation. However, in pointing to GABAARs as major agents of AD progression, the lipid-leakage model may also help to explain the severe disruptions of the normal "body clock" commonly seen in patients with AD. Although the neurological mechanism behind this biological clock is yet to be fully elucidated, it is generally agreed that, in vertebrates, the neurons of the suprachiasmatic nucleus (SCN) provide a central role [Ehlen, 2009; other references?]. Furthermore, within the SCN it is clear that GABAARs play a critical role, including in their extrasynaptic form [McNeill 2018; Ehlen 2009; McElroy 2009; Hu 2016; other references?], with some estimates suggesting that over 90% of SCN neurons express and respond to GABA [McNeill 2018]. A number of studies have shown that ethanol modulates circadian clock regulation [Ruby 2009; Prosser 2008 & 2015; Brager 2011], including by its action at low concentrations on extrasynaptic GABAARs [McElroy 2009]. Given that the lipid-leakage model already proposes that FFAs inhibit neurogenesis by acting at low concentrations on extrasynaptic GABAARs to disrupt their normal behaviour, there is therefore a good reason to believe that FFAs might also be disrupting normal circadian rhythms by a very similar mechanism.

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Of course, given that disruption of the body clock in AD is primarily inferred from behavioural abnormalities, particularly in regard to sleep patterns, it may be that what is being observed is merely a secondary consequence of amnesia and the general loss of self-control associated with AD. However, given that such sleep disturbances seem to be apparent very early in AD progression [Macedo, 2017], when amnesia and other AD-associated deficits are only beginning to be noticeable, it seems likely that what is being seen has a physiological as well as a purely psychological basis.

4 Conclusion

This all points to a much more complex explanation of AD progression, in which Aβ and tau tangles are only two of the more visible factors, in many ways as much symptomatic as causative.…

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