A lipid-leakage model for Alzheimer's Disease

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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 (mainly albumin-bound) 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 induce oxidative stress, stimulate microglia-driven neuroinflammation, and inhibit neurogenesis. Simultaneously, the larger, more lipid-laden lipoproteins, characteristic of the external plasma but not the CNS, cause endosomal-lysosomal abnormalities, amyloidosis and the formation of tau tangles, all characteristic of AD. In most cases (certainly in late-onset, noninherited forms of the disease) amyloidosis and tau tangle formation are consequences of this external lipid invasion, and in many ways more symptomatic of the disease than 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 neurodegeneration is far more pronounced in AD than in ARBD most likely results from the greater heterogeneity of the lipid assault in AD compared with ethanol alone.

The lipid-leakage model, described here, arguably provides the first cohesive, multi-factorial explanation of AD that best accounts for all currently known major risk factors, and credibly explains all AD-associated pathologies, including those, such as endosomal-lysosomal dysfunction and excessive lipid droplet formation, that have been too readily overlooked by other accounts of this disease.

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

A lipid-leakage model for Alzheimer's Disease

1 Introduction

Alzheimer's disease is a neurodegenerative disorder first described by the German physician Lois Alzheimer in 1907 (Stelzmann, Norman Schnitzlein & Reed Murtagh, 1995). 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 (Hardy, 2006; Castellani & Perry, 2012).

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

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.

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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 (Terry et al., 1991; Bowman & Quinn, 2008; Pimplikar, 2009). 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; Castellani & Perry, 2012).

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) (Cummings et al., 1998; Takechi et al., 2010a).

This has led some researchers to propose that the Aβ deposits may originate from outside the brain (Deane et al., 2009; Takechi et al., 2010a). 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

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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) i.e. out of the brain, as well as alternative efflux mechanisms (Lam et al., 2001; Deane et al., 2009; Takechi et al., 2010a). Additionally, the brain appears to have more than adequate enzymatic mechanisms for eradicating excess Aβ arising from faulty transport (Iwata et al., 2000; Takechi et al., 2010a). 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 (Iadecola & Gorelick, 2003; Ujiie et al., 2003; Dickstein et al., 2006; Popescu et al., 2009; Kook et al., 2012). 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 (Namba, Tsuchiya & Ikeda, 1992; Takechi et al., 2009), as well as other large molecular-weight proteins such as albumin, fibrinogen and immunoglobulins (D'Andrea, 2003; Bowman & Quinn, 2008; Cortes-Canteli & Strickland, 2009; Ryu & McLarnon, 2009; Johnson et al., 2018). Also, AD brains stain for Evans Blue, which is normally substantially excluded by the BBB (Ujiie et al., 2003; Paul, Strickland & Melchor, 2007; Cortes-Canteli & Strickland, 2009).

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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., 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 (Stein, Alvarez & McKee, 2014). These include large-scale neuronal loss, severe memory deficits, extensive tau tangles and, frequently in advanced cases, diffuse amyloid plaques (Stein, Alvarez & McKee, 2014). Crucially, CTE appears to be strongly associated with BBB disruption (Chodobski, Zink & Szmydynger-Chodobska, 2011; Stein, Alvarez & McKee, 2014; Doherty et al., 2016; Johnson et al., 2018; Farrell et al., 2019). Finally, the many risk factors for LOAD include ApoE4 (Liu et al., 2013), hypertension (Kivipelto et al., 2002), diabetes (Goldbourt 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; Mazzone et al., 2010; Prasad et al., 2014; Alluri et al., 2015; Girouard, 2016).

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

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2012; Gosselet et al., 2013), increasing matrix metalloproteinase expression (Hartz et al., 2012), oxidative stress (Thomas et al., 1997), increasing apoptosis (Blanc et al., 1997; Fossati, Ghiso & Rostagno, 2012) and dysregulating calcium homoeostasis (Blanc et al., 1997; Kook et al., 2012). Finally, there is further indirect evidence that Aβ can damage the BBB, for example, in cases of cerebral amyloid angiopathy (CAA) (Carrano et al., 2011; Fossati, Ghiso & Rostagno, 2012; Hartz et al., 2012; 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

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anywhere else in the human body and includes unusually strong tight junctions between endothelial cells, as well as a lack of endothelial fenestrations and endocytotic/transcytotic activity, a surrounding belt of basal lamina and large numbers of specialist cells such as pericytes and astrocytes (the latter attaching to the brain capillaries by so-called foot processes), and the presence of numerous efflux transporters (Rubin & Staddon, 1999; Dietschy & Turley, 2004; Abbott, Rönnbäck & Hansson, 2006; Carson et al., 2006).

Because of this architecture the BBB is known to substantially exclude lipids that remain bound to, or within, their normal transport partners (Jeske & Dietschy, 1980; Dietschy & Turley, 2004; Hamilton & Brunaldi, 2007; Zhang & Liu, 2015). Evidence (outlined in 2.4-2.5) suggests that unregulated external lipid influx, resulting from BBB compromise, or otherwise, will damage the brain. In the case of FFAs this will occur in at least three ways: (1) oxidative stress, lipid peroxidation and mitochondrial damage resulting from excess FFAs accumulation within neurons; (2) neuroinflammation; (3) disruption of neurogenesis, all characteristics that have been associated with AD (Markesbery, 1997; Hensley, 2010; Moreno-Jiménez et al., 2019). 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., 2008), particularly in connection with amyloidosis and tau tangles.

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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 some of the same overall effects on the brain as exposure to one major class 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

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brain from chronic alcohol exposure are the result not only of neurodegeneration but also of reduced levels of neurogenesis (Fadda & Rossetti, 1998; Nixon, 2006; Crews, 2008; Morris et al., 2009).

Recent studies also demonstrate that the neurodegenerative effects of chronic alcohol abuse may be reversible (Pfefferbaum et al., 1997a; Crews & Nixon, 2009), 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

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

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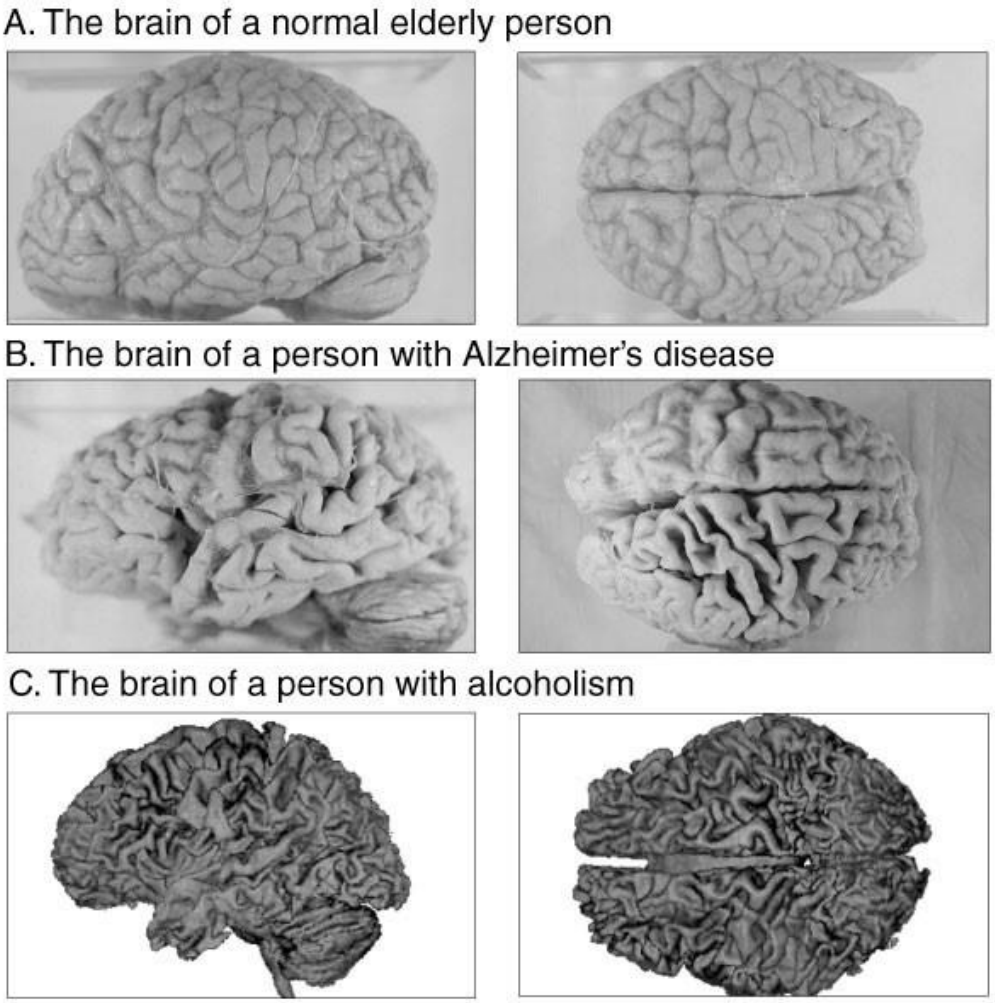
168 Figure 1), and whole brain MRI scans (Figure 2), (Sullivan, Adron Harris & Pfefferbaum; Fox et
169 al., 2001; Zahr, Kaufman & Harper, 2011; Teipel et al., 2015).
170



171

172 **Figure 1. Visual comparisons of the brains of (A) normal elderly person; (B) a person with AD and (C) a**
173 **chronic alcoholic. Source: (a & b) (Tyas, 2002); (c) (Rosenbloom, Pfefferbaum & Sullivan, 1995).**

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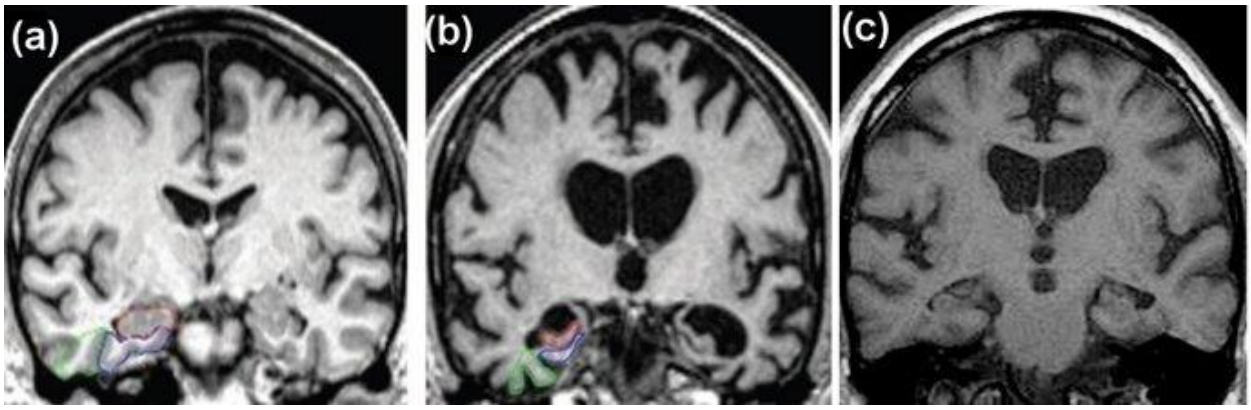
174



175 **Figure 2. Coronal plane MRI comparison between brains of (a) a normal person and (b) a typical AD case**
176 **(Duara et al., 2008) and that of (c) a patient with alcohol-related brain damage ("Alcoholic dementia, MRI**
177 **scan"). Outlined areas in (a) & (b) correspond to hippocampus (outlined in red); entorhinal cortex (blue) and**
178 **perirhinal cortex (green). Sources: (a & b) (Duara et al., 2008); (c) (Science Photo Library, 2019).**

179

180 ### 2.1.1 Brain shrinkage

181

182 Such scans typically reveal pronounced similarities between the two diseases in their pattern of
183 neurodegeneration, including evidence of brain shrinkage (Pfefferbaum et al., 1992, 1997a; Kril
184 & Halliday, 1999; Thompson et al., 2007; Hua et al., 2008; Paul et al., 2008; Spreng & Turner,
185 2013), loss of cortical folding (involving widening of sulci and thinning of gyri) (Harper & Kril,
186 1985; de la Monte SM, 1988; Pfefferbaum et al., 1997a; Hua et al., 2008), enlargement of
187 ventricles (de la Monte SM, 1988; Pfefferbaum et al., 1997a; Silbert et al., 2003; Hua et al.,
188 2008; Nestor et al., 2008; Wobrock et al., 2009), (especially the lateral ventricles), together with

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189 shrinkage of the hippocampus and entorhinal cortex (Fadda & Rossetti, 1998; White, Matthews
190 & Best, 2000; Beresford et al., 2006; Hua et al., 2008; Duara et al., 2008) and thinning of the
191 corpus callosum (Harper & Kril, 1988; Pfefferbaum et al., 1996; Estruch et al., 1997; Teipel et
192 al., 2002; Frederiksen et al., 2011; Preti et al., 2012).
193
194 On their own, such similarities could be dismissed as the effects of general brain shrinkage and
195 other generalised damage. However, the similarities appear to run much deeper than this, with
196 many of the same regions of the brain principally affected in both cases, especially early on in
197 the disease process. In particular, both AD and ARBD appear to be substantially "frontal"
198 diseases, as suggested by physiological, behavioural and sensory studies, in line with imaging
199 studies of both diseases (Pfefferbaum et al., 1997b; Kril & Halliday, 1999; Harper, 2007; Hall et
200 al., 2008; Grothe, Heinsen & Teipel, 2012; Schmitz et al., 2016).
201

202 ### 2.1.2 Basal forebrain damage in AD and ARBD

203
204 Measurements of brain volume reveal both diseases to be associated with significant shrinkage
205 in the frontal region of the brain, particularly the prefrontal cortex and basal forebrain regions
206 (Pfefferbaum et al., 1997a; Fadda & Rossetti, 1998; Moselhy, Georgiou & Kahn, 2001; Teipel et
207 al., 2005; Hall et al., 2008; Grodin et al., 2013), including the cholinergic basal forebrain

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208 projection system (Arendt et al., 1989; Muir, 1997; Fadda & Rossetti, 1998; Teipel et al., 2005;
209 Miki et al., 2014). This is backed up by studies in animal models, which suggest that chronic
210 exposure of the brain to ethanol causes a specific pattern of degeneration, including a marked
211 loss of cholinergic neurons, accompanied by a reduction in acetylcholine and choline
212 acetyltransferase activity (Arendt et al., 1989; Floyd et al., 1997; Fadda & Rossetti, 1998;
213 Mufson et al., 2003; Miki et al., 2014). Again, this is very similar to what is seen in AD (Muir,
214 1997; Baskin et al., 1999; Auld et al., 2002; Mufson et al., 2008), which is, indeed, why the
215 cholinergic hypothesis was proposed in the 1980s (Contestabile, 2011).
216
217 Related behavioural evidence pointing towards frontal damage as a factor in both diseases
218 includes personality changes (Bózzola, Gorelick & Freels, 1992; Chatterjee et al., 1992; Oscar-
219 Berman et al., 1997; Moselhy, Georgiou & Kahn, 2001; Talassi et al., 2007; Echeburúa, De
220 Medina & Aizpiri, 2007; Ball et al., 2010), disinhibition and impulsivity (Chen et al., 2007; Ball
221 et al., 2008; Crews & Boettiger, 2009; Dick et al., 2010; Bidzan, Bidzan & Pąchalska, 2012;
222 Finger et al., 2017), confabulation (Kern et al., 1992; Brun & Andersson, 2001; Tallberg &
223 Almkvist, 2001; Attali et al., 2009; Maurage et al., 2011; Rensen et al., 2015) and a noticeable
224 tendency towards perseverative behaviour. This last attribute is readily apparent in individuals
225 with AD (Bayles et al., 2004; Serna, Pigot & Rialle, 2007; Pekkala et al., 2008; Kaufman, 2015;
226 De Lucia, Grossi & Trojano, 2015), while studies in adult and adolescent rodents chronically

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exposed to ethanol (but given a nutritionally adequate diet) point towards a similar pattern of behavioural and neurological deficit (Vetreno et al.; Obernier et al., 2002; Crews & Nixon, 2009; Kroener et al., 2012; Acheson et al., 2013; Sullivan & Pfefferbaum, 2014; Badanich et al., 2016), confirming findings in humans (Giancola, Peterson & Pihl, 1993; Oscar-Berman et al., 1997; Fadda & Rossetti, 1998; Ratti et al., 2002; Dirksen et al., 2006; Oscar Berman, 2009). Possibly such behaviour involves deficits in the dopamine system (McNamara & Albert, 2004; Campos-García Rojas et al., 2015), principally centred in the frontal lobe, as well as of the cholinergic system (McNamara & Albert, 2004). But certainly it is known that various forms of motor perseveration and similar behavioural inertias are frequently associated with damage to the frontal lobes (Luria, 1965; Stuss & Benson, 1984; Ridley, 1994; Munakata, Morton & Stedron, 2003).

There is also very strong experimental evidence suggesting that, from comparatively early on, both AD and ARBD are associated with olfactory deficits (Ditraglia et al., 1991; Collins, Corso & Neafsey, 1996; Mesholam RI et al., 1998; Christen-Zaech et al., 2003; Doty, 2005; Rupp et al., 2006; Maurage et al., 2011; Velayudhan et al., 2013), although not always perceptible to demented patients (Doty, Reyes & Gregor, 1987). These are also very likely to involve damage to the basal forebrain, including the olfactory bulb (Ohm & Braak, 1987; Collins, Corso & Neafsey, 1996; Obernier et al., 2002; Christen-Zaech et al., 2003; Rupp et al., 2006) and

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246 cholinergic systems (Arendt et al., 1989; Mundiñano et al., 2013; Doty, 2013; D'Souza &
247 Vijayaraghavan, 2014), amongst others.
248
249 More generally, both forms of dementia are associated with deficits in executive functions (Rupp
250 et al., 2006; Duarte et al., 2006; Harper, 2007; Ball et al., 2008; Marshall et al., 2011; Houston et
251 al., 2014; Weiss et al., 2014), such as attentional and inhibitory control, working memory and
252 reasoning - i.e. those faculties which allow problem-solving, planning, self-control and the
253 attainment of goals. Clearly there are difficulties separating the immediate effects of drinking
254 alcohol from the long-term neurodegenerative effects of alcoholism, as well as questions as to
255 what degree executive function is under the control of the frontal region. Nevertheless, taken
256 collectively, the evidence presented here points to a strong involvement of the frontal lobe
257 degeneration in both ARBD and AD.
258

259 ### 2.1.3 Medial temporal lobe damage in AD and ARBD

260
261 As well as the basal forebrain, the medial temporal lobe is also found to be significantly
262 atrophied in both ARBD and AD (Bengochea & Gonzalo, 1990; Smith et al., 1992; Fadda &
263 Rossetti, 1998; Korf et al., 2004; Duara et al., 2008; Vetreno, Hall & Savage, 2011). This is most
264 obvious in the hippocampus but is also in immediately adjoining regions, such as the entorhinal

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cortex and perirhinal cortex (Squire, Amaral & Press, 1990; Jernigan et al., 1991; Ibáñez et al., 1995; Sullivan et al., 1995; Fadda & Rossetti, 1998; Juottonen et al., 1998; Traissard et al., 2006; Augustinack et al., 2013; Velayudhan et al., 2013; Hirni et al., 2016; Topiwala et al., 2017).

Given the well-established link between the hippocampus and memory formation (Riedel & Micheau, 2001), it is unsurprising, therefore, that AD is associated with anterograde amnesia (AA), including severe deficits in spatial memory (Sun et al., 2005; Cherrier et al., 2005; Hort et al., 2007; Vlček, 2011; Moodley et al., 2014; Zhu et al., 2017). However, such deficits in ARBD appear to be minor (Vetreno, Hall & Savage, 2011; Ridley, Draper & Withall, 2013), once one has discounted the temporary effects of acute ethanol intoxication (Boulouard et al., 2002) and (Wernicke-)Korsakoff Syndrome, resulting from vitamin B1 deficiency (Ridley, Draper & Withall, 2013). Certainly, permanent AA in alcoholics appears to be mainly associated with Korsakoff Syndrome (Parkin, 1991; Joyce, 1994; Vetreno, Hall & Savage, 2011; Fama, Pitel & Sullivan, 2012; Ridley, Draper & Withall, 2013), rather than from chronic exposure to alcohol itself. Moreover, chronic alcohol-associated AA appears to be reversible, unlike AA in Alzheimer's (Fein et al., 1990, 2006; Pfefferbaum et al., 1995, 1998; Parsons & Nixon, 1998; Ridley, Draper & Withall, 2013), and much of the damage appears to result immediately after cessation of drinking (Fadda & Rossetti, 1998; Vetreno, Hall & Savage, 2011).

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Nevertheless, there is sufficient evidence in animal models to suggest that both acute and chronic alcohol exposure may lead to pronounced deficits in spatial memory (Santín et al., 2000; Silvers et al., 2003; Pires et al., 2005; Assunção et al., 2007; Cippitelli et al., 2010; García-Moreno & Cimadevilla, 2012), evidence that appears to be mirrored in humans, as well as other primates (Bowden & McCarter, 1993; Beatty et al., 1997; Tapert et al., 2001; Weissenborn & Duka, 2003; Silvers et al., 2003; Taffe et al., 2010). Certainly, caution is required here, as other areas of the brain are known to be involved in spatial memory processing, including the prefrontal cortex (Seamans, Floresco & Phillips, 1998; Jones & Wilson, 2005). However, the association of acute and chronic alcohol exposure with various hippocampal deficits and with impaired spatial learning (Bowden & McCarter, 1993; Givens, 1995; Santín et al., 2000; Beresford et al., 2006; Wilson et al., 2017; Ji et al., 2018) strongly suggest a likely linkage mechanism between the two phenomena.

Similarly, so-called “blackout” episodes, commonly associated with drinking large amounts of alcohol over short periods of time (Goodwin, Crane & Guze, 1969; White, 2003), are clearly largely defined by and associated with AA (White, 2003; Nelson et al., 2004; Perry et al., 2006), appearing to involve both the frontal lobe and hippocampal regions (White, 2003; Oscar-Berman et al., 2004; Alderazi & Brett, 2007; Vetreno, Hall & Savage, 2011; Wetherill, Schnyer & Fromme, 2012; Hermens & Lagopoulos, 2018). In particular, chronic alcoholism appears to act

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303 synergistically with the normal ageing process to exacerbate the memory and other cognitive
304 deficits commonly resulting from the latter (Pfefferbaum et al., 1992; Kim et al., 2012; Sabia et
305 al., 2014; Guggenmos et al., 2017; Rehm et al., 2019).
306
307 Whatever the reason, the similarities between AD and ARBD listed above would seem to
308 provide the most obvious reason why heavy drinking appears to be associated with a higher risk
309 of developing Alzheimer's and other dementias (Anttila et al., 2004; Järvenpää et al., 2005; Kim
310 et al., 2012; Schwarzinger et al., 2018; Sabia et al., 2018). The fact that people with the ApoE4
311 allele appear to have a much greater risk of developing dementia as a result of drinking ethanol
312 (including even light-to-moderate drinking), compared with non-carriers of the allele (Dufouil et
313 al., 2000; Mukamal et al., 2003; Anttila et al., 2004; Kim et al., 2012; Downer, Zanjani & Fardo,
314 2014), would seem only to add further weight to this association.
315

316 ### 2.1.4 Summary of similarities between AD and ARBD

317
318 In summary AD and ARBD show a strikingly similar pattern of neurological damage,
319 particularly evident in the basal forebrain and hippocampal region of the medial temporal region,
320 accompanied by marked degeneration in the cholinergic projection system. In keeping with this
321 pattern of damage both AD and ARBD sufferers show deficits in executive function, olfaction

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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 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.

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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, 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 (Brindley, 1991; Ahmadian et al., 2007).

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 (Young, 1990; Vance & Vance, 2008). Such

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lipoprotein-mediated FA transport appears to allow only very restricted access to the postnatal brain across the BBB, given its architecture, mentioned earlier (Beffert et al., 1998; Björkhem & Meaney, 2004; Elliott, Weickert & Garner, 2010; Orth & Bellosta, 2012), with only much smaller, less lipid-rich high-density lipoproteins (HDL) appearing to cross the BBB in any quantity (Wang & Eckel, 2014).

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 (Ballmer, 2001; van der Vusse, 2009; Schiff, Maddrey & Sorrell, 2011) and cannot pass readily through the BBB (Nag, 2003; Banks, 2006, 2008), it has until recently been assumed that albumin-bound FFAs must also be largely excluded, in the same way as lipoprotein-associated FFAs. The reason for this conclusion comes not just from the structural properties of the BBB mentioned above, but also from the widespread expression within BBB endothelial cells of efflux pumps, such as P-glycoprotein, which have hydrophobic molecules amongst their principal ligands (Rubin & Staddon, 1999). This would seem to suggest that even unbound FFAs (either those unloaded from albumin or never loaded in the first place) would tend to be pumped back out of the brain in the same way that all large lipophilic molecules tend to be (Roninson, 1992).

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379 Together, such features would appear to provide an obvious reason why, almost uniquely
380 amongst organs, the brain does not rely on the external supply of FAs (certainly in albumin-
381 bound form) as a primary energy source (Schönfeld & Reiser, 2013; Jha & Morrison, 2018).
382 This is despite the fact that the brain has a high energy requirement, and other organs with high
383 energy needs, such as the heart and kidney, preferentially oxidise FAs (Johnson et al., 1990;
384 Schönfeld & Reiser, 2013). Instead, during the fasting state when glucose availability is low, the
385 liver will typically transform plasma FFAs into much smaller ketone bodies, which, having been
386 transported through the BBB, are used as an energy source by the brain (Sokoloff, 1973; Owen,
387 2005; Yang et al., 2019).
388
389 However, it has become increasingly clear in recent years that the BBB does not exclude FFAs
390 from the brain (Karmi et al., 2010; Schönfeld & Reiser, 2013; Panov et al., 2014; Murphy, 2017)
391 and the most likely reason for why the brain does not use them extensively for its energy needs is
392 that they would prove toxic to neurons (Schönfeld & Reiser, 2013; Speijer, Manjeri &
393 Szklarczyk, 2014; Ioannou et al., 2019). (Another possible reason is that the rate of ATP
394 generation from FAs is slower than from glucose and ketone bodies, meaning that FAs may not
395 be able to yield ATP fast enough for rapidly firing neurons, especially under conditions of
396 sustained activity (Schönfeld & Reiser, 2013).)
397

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Recent evidence suggests a key role for astrocytes in protecting neurons from FA-mediated lipotoxicity. It appears that they do this in at least two ways. Firstly, they internalise medium-chain-length FAs, breaking them down by β-oxidation and secreting a proportion as ketone bodies, or the much shorter chain-length FA butyrate, both of them much less toxic to neurons (Edmond et al., 1987; Ebert, Haller & Walton, 2003; Schönfeld & Reiser, 2013; Plötz et al., 2017; Sonnay et al., 2019). Secondly, they directly take up excess FFAs from hyperactive neurons, preventing oxidative stress and other forms of lipotoxic damage, as well as preventing accumulation of lipid droplets in the neuronal cytoplasm (Unger et al., 2010; Nguyen et al., 2017; Ioannou et al., 2019).

This second mechanism appears to involve neuronal exocytosis of ApoE-containing lipoprotein-like lipid particles, and subsequent endocytosis by astrocytes into lipid droplets (Ioannou et al., 2019). Furthermore, neurons that express the ApoE4 allele appear not to secrete FAs as efficiently as wild-type ApoE, resulting in the greater lipid peroxidation and other forms of lipotoxic damage mentioned above (Ioannou et al., 2019).

Collectively, then, astrocytes appear to protect neurons by importing FAs from neurons and from the immediate external interstitial fluid, and then either utilising them for generating ATP or ketone bodies/butyrate (both as a result of β-oxidation), or else storing them within lipid droplets

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(as TAGs) for future use. Except perhaps in times when other energy sources are not available, astrocytes appear to export most of the ketone bodies and butyrate for neuronal usage, relying on FFAs for much of their own energy needs.

As a consequence, neuronal energy metabolism primarily relies on lactate, glucose, ketone bodies or butyrate in preference to FAs (Schönfeld & Reiser, 2013; Jha & Morrison, 2018), thus protecting neurons from oxidative stress, mitotoxicity and lipotoxicity (Reynolds & Hastings, 1995; Schönfeld & Reiser, 2013, 2017; Ioannou et al., 2019). This may explain why neurons are reported to have relatively poor antioxidative defences, certainly compared to astrocytes (Bolaños et al., 1995; Schönfeld & Reiser, 2013), despite, at first sight, being more obviously at risk from oxidative damage as a result of their high activity levels and correspondingly much higher energy consumption (Attwell & Laughlin, 2001; Schönfeld & Reiser, 2013).

Certainly, such an explanation appears to account for why FFAs are not used for neuronal energy metabolism, despite seemingly being available in substantial quantity for this purpose, and FFAs providing about twice the energy content of glucose and similar sugars (Speijer, Manjeri & Szklarczyk, 2014).

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435 But this still leaves a number of important questions unresolved. Most importantly, what
436 happens to the FFAs, once they cross the BBB, given that albumin transport is no longer
437 available to them (Olsson et al., 1968; Roheim et al., 1979; Cipolla, 2009; Schönfeld & Reiser,
438 2013)? And how are they transported? In the absence of any obvious alternatives to albumin in
439 the CNS, some form of lipoprotein-mediated transport seems the most obvious alternative,
440 mirroring the situation in the plasma compartment outside the CNS. However, there are
441 important differences between lipoprotein transport in the CNS and lipoprotein transport in the
442 plasma compartment.
443
444 In contrast to what is seen in plasma, as described above, the principal apolipoproteins expressed
445 in the CNS (including Apo E, D and J (Danik et al., 1999; Elliott, Weickert & Garner, 2010))
446 associate into lipoprotein particles that are relatively small (typically less than 20nm) and lipid
447 poor, containing modest amounts of lipids (Roheim et al., 1979; Ladu et al., 2000; Vance &
448 Vance, 2008). Such CNS lipoprotein particles tend to resemble High-Density Lipoproteins
449 (HDL) (Roheim et al., 1979; Ladu et al., 2000; Elliott, Weickert & Garner, 2010; Rang, 2012)
450 much more than the larger ApoB-associated lipoproteins that predominate outside the CNS.
451
452 Furthermore, astrocytes are known to be a principal source of many of these CNS-originating
453 apolipoproteins, particularly Apo E and J (Ladu et al., 2000; Mahley, Weisgraber & Huang,

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2006; Elliott, Weickert & Garner, 2010), and lipoproteins have been isolated from the conditioned medium of astrocytic cultures (Danik et al., 1999). The fact that astrocytic foot processes are estimated to cover as much as 99% of the brain surface of capillaries (Johanson, 1980; Pardridge, 2005; Wilhelm et al., 2016), would seem to provide an obvious route of entry for FFAs that have managed to detach from their albumin transport partners and pass through the BBB. They can then be assembled into HDL-like lipoproteins within the astrocyte body and secreted into the interstitial fluid of the brain compartment, for onward transport and uptake by neurons and glial cells (Farmer, Kluemper & Johnson, 2019).

From the above description, it would appear that FA transport and metabolism in the CNS is very different from that seen in the rest of the body. In particular, there appears to be little, if any, non-lipoprotein FA transport in the CNS and, on average, CNS lipoproteins are much smaller than their plasma equivalents. In many respects, FA transport seems more tightly controlled in the brain compartment than outside it. Certainly, it is hard to see how such differences would be possible without a substantially intact BBB, especially given the much smaller size of the CNS compartment.

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2.2.2 Cholesterol metabolism

Numerous studies have shown that, except in very early foetal development, almost all cholesterol in the CNS is of local origin, relying on endogenous de novo biosynthesis rather than external, lipoprotein-mediated provision (Dietschy & Turley, 2004; Björkhem & Meaney, 2004; Elliott, Weickert & Garner, 2010; Orth & Bellosta, 2012). 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 (Pfrieger, 2003; Dietschy & Turley, 2004; Elliott, Weickert & Garner, 2010).

Moreover, cholesterol turnover in the mature CNS is very low, typically only around 5% of the turnover seen in the rest of the body (Dietschy & Turley, 2004; Björkhem & Meaney, 2004; Orth & Bellosta, 2012). A major reason for this is that a large proportion of such cholesterol remains locked up within the insulating myelin sheath that permanently encases the axons of many neurons, particularly within the white matter of the brain (Zhang & Liu, 2015). Much of this myelination takes place early in organismal development (Deoni et al., 2012).

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,

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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 (Young, 1990; Vance & Vance, 2008; Rang, 2012). Thus, for reasons of size (along with the other reasons explained above), much cholesterol of non-CNS origin is unable to cross the BBB (Kay et al., 2003; Björkhem & Meaney, 2004; Elliott, Weickert & Garner, 2010; Orth & Bellosta, 2012).

By contrast, within the brain and wider CNS, cholesterol is transported within the same HDL-like lipoproteins described in the previous section. As explained, such lipoproteins tend to be small, compared to many of their plasma counterparts, typically containing only modest amounts of cholesterol and other lipids (Vance & Vance, 2008).

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 (Pardridge & Mietus, 1980; Dietschy & Turley, 2004). Compared to the rest of the body the mature CNS compartment is distinguished by a much lower circulation of lipids, with apparently restricted external lipid supplementation and a set of lipoproteins that

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509 are noticeably smaller and less lipid-rich. Much of this difference can be accounted for by the
510 BBB, and by the fact that ApoB is not produced in the brain.
511
512 Given that this distinction appears to have first emerged comparatively early in vertebrate
513 evolution (Abbott, 2005; Bundgaard & Abbott, 2008), it seems plausible that serious disruption
514 to the BBB will have lipid-related consequences. This can be inferred from the fact that the
515 mature brain compartment has evolved for so long to function in an environment low in
516 circulating lipids compared with the rest of the body. And, given the relative volumes of the two
517 compartments, it seems likely the brain will be the most vulnerable to lipid incursion if they are
518 no longer separated by the BBB.
519

520 2.3 The causes of BBB disruption in the lipid-leakage model

521
522 Clearly, an explanation of how the BBB becomes disrupted in AD is central to the lipid-leakage
523 model. It is generally established that the BBB slowly degrades with age (Farrall & Wardlaw,
524 2009; Popescu et al., 2009), providing a simple reason, according to the model, why LOAD
525 incidence is also closely correlated with age. But any model with such disruption at its centre
526 needs to account for the many inherited and non-inherited risk factors that accelerate the onset of
527 AD.

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528

529 In FAD this can accounted for by Aβ, which, as explained earlier, is known to impair BBB
530 integrity (Thomas et al., 1997; Su et al., 1999; Marco & Skaper, 2006; Takechi et al., 2010a),
531 especially in association with the ApoE4 genotype (Premkumar et al., 1996; Olichney et al.,
532 1996; Alonzo et al., 1998; Fryer et al., 2003). This may be partly explained by the fact that,
533 more generally, ApoE protects the BBB, with its absence leading to progressive BBB leakage, in
534 excess of what is seen as a result of normal ageing (Mulder et al., 2001; Methia et al., 2001;
535 Hafezi-Moghadam, Thomas & Wagner, 2007). Compared to the other ApoE isoforms, however,
536 ApoE4 is associated with impaired BBB function, particularly involving tight junctions, whose
537 integrity is critical to the BBB's capacity to exclude a wide range of molecules (Salloway et al.,
538 2002; Nishitsuji et al., 2011; Bell et al., 2012).

539

540 However, recent studies have suggested that Aβ has an important function as a regulatory
541 apolipoprotein, being highly expressed in both the liver and small intestine, and associated with
542 triglyceride-rich lipoproteins of similar origin (Galloway et al., 2007; Mamo et al., 2008;
543 Takechi et al., 2010a). In absorptive enterocytes, Aβ is seen to collocate with $ApoB_{48}$, forming
544 chylomicrons, with enterocytic levels of Aβ and plasma levels of Aβ-associated chylomicrons
545 both increasing in response to a diet high in saturated fats (Galloway et al., 2007; Pallebage-
546 Gamarallage et al., 2010).

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547

548 In a standard transgenic mouse model of AD in which Aβ is overproduced, disease progression
549 and onset were seen to be strongly correlated with rates of secretion into the blood of TAG-rich,
550 Aβ-associated lipoproteins, and with their subsequent plasma levels (Takechi et al., 2010a). Such
551 overproduction, whether resulting from dietary causes or from direct Aβ over-expression, leads
552 to BBB disruption (Mamo et al., 2008; Takechi et al., 2010a; Pallebage-Gamarallage et al.,
553 2010).

554

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

561

562 This suggests that the aetiology of both familial and late-onset forms of AD could be linked
563 through excess levels of TAG-rich chylomicrons. In the former case this would primarily result
564 from over-production of Aβ, whilst in the latter case it would primarily result from dietary
565 causes. This in turn would lead, in both cases, to BBB disruption (which can be exacerbated by

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566 other factors, as explained above) and to the characteristic neurodegenerative effects outlined
567 below. However, evidence for such chylomicron excess as a general characteristic of AD is
568 limited at present and is not a requirement of the model.
569

570 2.4 AD-relevant consequences of lipid influx to the brain

571 2.4.1 Oxidative stress

572 In recent years a considerable body of evidence has accumulated that suggests that AD-affected
573 brains are subject to high levels of oxidative stress (Markesbery, 1997; Huang, Zhang & Chen,
574 2016). This evidence includes increased protein and DNA oxidation (Smith et al., 1991;
575 Mecocci, MacGarvey & Beal, 1994; Markesbery, 1997; Korolainen et al., 2002; Santos et al.,
576 2012), as well as an increase in lipid peroxidation (Subbarao, Richardson & Ang, 1990; Bradley-
577 Whitman & Lovell, 2015), together with various associated peroxidation biomarkers (Lovell et
578 al., 1997; Bradley-Whitman & Lovell, 2015). Such lipid peroxidation may account for an
579 observed decrease in the levels of polyunsaturated FAs, which appear to be more vulnerable to
580 such peroxidation (Markesbery, 1997; Conquer et al., 2000; Tsaluchidu et al., 2008; Fotuhi,
581 Mohassel & Yaffe, 2009; Dyall, 2010; Huang, Zhang & Chen, 2016). Other indications of
582 oxidative stress in AD-affected brains include raised levels of advanced glycation end-products,

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583 that is to say proteins or lipids that have become glycated (Smith et al., 1994; Markesbery, 1997;
584 Sasaki et al., 1998; Drenth et al., 2017).
585
586 Perhaps not surprisingly, there has been much focus on the role of Aβ and amyloid plaques as
587 principal drivers of this oxidative stress in AD (Markesbery, 1997; Huang, Zhang & Chen,
588 2016). Certainly, there is substantial evidence to suggest that both Aβ and its precursor APP
589 contain high affinity binding sites for metal such as copper, zinc and iron, with amyloid plaques
590 seen to be highly enriched with these metals, some of which are redox-active (Barnham et al.,
591 2003; Huang et al., 2004; Smith, Cappai & Barnham, 2007; Strozyk et al., 2009; Liu et al.,
592 2019). And subsequent findings have led many researchers to propose a positive feedback
593 mechanism whereby Aβ amyloidosis and metal-induced oxidative stress reinforce each other,
594 thus contributing strongly to AD-associated neuropathology (Huang et al., 2004; Smith, Cappai
595 & Barnham, 2007; Strozyk et al., 2009; Faller, 2009).
596
597 However, despite more than 20 years of research into this relationship, there are still many
598 questions that remain unresolved, not least concerning the respective roles of copper and zinc
599 (Cuajungco & Fagét, 2003; Atrián-Blasco, Conte-Daban & Hureau, 2017; Drew, 2017).
600 Furthermore, there is, as yet, no convincing evidence that therapeutic metal chelation has any

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601 substantial impact, if at all, in slowing down AD progression, leading some to question the
602 relevance of such metal-induced oxidative stress to AD (Drew, 2017; Liu et al., 2019).
603
604 But there are many other ways in which AD might lead to oxidative stress, without requiring the
605 involvement of metals. In particular, neuroinflammation triggered by the presence of Aβ,
606 provides a straightforward reason why oxidative stress should increase with AD progression,
607 given the well-established link between neuroinflammation and increased levels of reactive
608 oxygen and nitrogen species (Agostinho, Cunha & Oliveira, 2010; Dyall, 2010; González-Reyes
609 et al., 2017). This is addressed in more detail in the next section.
610
611 As explained later, a key prediction of the lipid-leakage model is that an increase in Aβ
612 production will occur as a direct consequence of lipid invasion from outside the brain.
613 Therefore, oxidative stress, as a consequence of Aβ-driven neuroinflammation, can be easily
614 accounted for by the model. And, as explained below, FA invasion may drive neuroinflammation
615 more directly, acting on same pathways that drive ethanol-induced neuroinflammation. Thus,
616 there are good reasons for believing that FA-driven neuroinflammation alone is sufficient to
617 account for
618

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However, the description of FA metabolism in section 2.2.1 above suggests another, even more direct, way in which the lipid-leakage model can account for oxidative stress in AD. Substantial damage to the BBB will mean that the brain is exposed to albumin-bound FFAs and, larger, more lipid-rich lipoproteins, originating from the external plasma compartment.

As a consequence, it may be that astrocytes are no longer able to protect neurons from excessive FA accumulation, leading to lipid peroxidation and other forms of oxidative stress. Certainly, there is much evidence to suggest that lipid homoeostasis becomes badly disrupted in AD (Foley, 2010; Di Paolo & Kim, 2011; Farmer, Kluemper & Johnson, 2019). Indeed, in the earliest reports of the disease, by Alois Alzheimer and colleagues, there are numerous references to various intracellular lipid inclusions and other lipid-related abnormalities within the brain of affected subjects (Stelzmann, Norman Schnitzlein & Reed Murtagh, 1995; Di Paolo & Kim, 2011).

Given that normal lipid homoeostasis appears to be critical to preventing excessive oxidative stress within the brain, as described earlier, it can easily be appreciated how breakdown of the BBB, as predicted by the lipid-leakage model, might lead to appreciable increases in such stress.

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2.4.2 Neuroinflammation

Extensive research has established that neuroinflammation is an important cause of ethanol-induced neurodegeneration (Syapin & Hickey, 2006; Blanco & Guerri, 2007; Crews, 2008; Crews & Nixon, 2009) and that microglia are central agents of such inflammation (Syapin & Hickey, 2006; Crews, 2008; Zhao et al., 2013; Walter & Crews, 2017). 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 (Gehrmann, Matsumoto & Kreutzberg, 1995; Dissing-Olesen et al., 2007; Yang et al., 2010), 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 (Crews & Vetreno, 2014). 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.

Ethanol activation of microglia (Crews & Vetreno, 2014), is accompanied by upregulation of the transcription factor NF-κB (Zou & Crews, 2010; Alfonso-Loeches et al., 2010) and other

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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 (Chait & Kim, 2010; Wang et al., 2012). And TLR4 activation in adipocytes by saturated FAs (and perhaps by some unsaturated FAs) is an essential step in lipid-induced type 2 diabetes mellitus (Shi et al., 2006; Chait & Kim, 2010), which is now thought to be substantially inflammatory in nature (Wellen & Hotamisligil, 2005; Shi et al., 2006; Donath & Shoelson, 2011). In support of this, knockdown or ablation of TLR4 has been shown to inhibit both FFA-induced and ethanol-induced inflammation (Shi et al., 2006; Chait & Kim, 2010; Alfonso-Loeches et al., 2010; Wang et al., 2012), as well as protecting against FA-induced diabetes.

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Given how responsive microglia are to pathological stimuli (Kreutzberg, 1996; Rock et al., 2004; Rangaraju et al., 2015; Lenz & Nelson, 2018), one could reasonably 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 determined, the fact that saturated fatty acyl groups are known to be crucial to TLR4 recognition of LPS (TLR4's principal pathogenic ligand) (Hwang, 2001) suggests that FFAs should have a substantially higher affinity than ethanol for TLR4. Thus the relatively low levels of FFAs seen in plasma (generally agreed to fall within an average range of 0.3-0.6 mM (Belfort et al., 2005; Huber & Kleinfeld, 2017)) should be sufficient to generate a steady level of neuroinflammation, following major BBB insult, especially if they are accompanied by pathogen-associated LPS, as seen in ethanol-induced liver injury (Nagy, 2003). Thus it may be this, rather than TLR4 stimulation by amyloid (Walter et al., 2007), that is the primary driver of microglial-based neuroinflammation in LOAD.

2.4.3 Inhibition of neurogenesis

Ethanol-induced neuroinflammation has also been linked to inhibition of neurogenesis (Nixon & Crews, 2002; Crews & Nixon, 2009), with many studies suggesting that such neurogenetic deficits are almost as important a factor as neuroinflammation in ethanol-mediated brain

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693 degeneration (Crews & Nixon, 2009). Here too, TLR4, and other ethanol-sensitive toll-like
694 receptors, are likely to have a prime inhibitory role (Barak, Feldman & Okun, 2014; Crews et al.,
695 2017), diminishing proliferation of adult neuronal progenitor cells (NPCs) and restricting
696 neuronal differentiation from NPCs. Such inhibition would obviously be most apparent in the
697 main adult neurogenic niches, i.e. the subgranular and subventricular zones, which provide new
698 neurons and glial cells to (respectively) the hippocampus and the olfactory bulb (Ming & Song,
699 2011). This could explain the deficiencies in learning and olfaction common to both AD and
700 ARBD.
701
702 Furthermore, current evidence indicates that the overall level of neurodegeneration is determined
703 almost as much by the relentlessness of the ethanol assault as by the concentrations involved
704 (Nixon & Crews, 2002; Nixon, 2006; Crews & Nixon, 2009). Thus, one can reasonably infer
705 that constant exposure of the brain to plasma levels of FFAs is likely to overwhelm the brain's
706 capacity to recover, especially in the elderly. Such a conclusion is further supported by evidence
707 that inhibition of neurogenesis, by both ethanol and FFAs, does not need to rely on the TLR4
708 receptor alone, and may, in fact, depend more on GABAergic effects, as explained in the next
709 section.
710

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2.5 GABAergic effects

Recent research has indicated a possible role for the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the development of AD (Rissman & Mobley, 2011; Wu et al., 2014; 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 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.

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729 In the 1950s onward, Samson and Dahl and other groups showed that injection of FFAs induced
730 light anaesthesia in a range of mammals (Samson Jr, Dahl & Dahl, 1956; White & Samson,
731 1956; Matsuzaki & Takagi, 1967; McCandless, 1985). Anaesthetic potency increases (up to an
732 undetermined cut-off) with FFA chain length (and thus hydrophobicity), in line with Meyer-
733 Overton (Samson Jr, Dahl & Dahl, 1956; White & Samson, 1956; Dahl, 1968; Perlman &
734 Goldstein, 1984), falling within the low millimolar range (expressed both as moles per litre and
735 moles per kilogram of body weight) and showing similar potencies to structurally comparable 1-
736 alcohols (including ethanol) (Alifimoff, Firestone & Miller, 1989), as well as to alkanes (Hau,
737 Connell & Richardson, 2002) and aldehydes (Deneer, Seinen & Hermens, 1988).
738
739 Given the general correlation between hydrophobicity and anaesthetic potency first described by
740 Meyer-Overton (Evers & Crowder, 2009), it would perhaps be surprising if fatty acids did not
741 show similar anaesthetic potencies to structurally very similar fatty alcohols (Ueda & Suzuki,
742 1998; Matsuki et al., 1999; Frangopol & Mihailescu, 2001; Evers & Crowder, 2009), nor, given
743 the established anaesthetic properties of various steroids (Kappas & Palmer, 1963; Belelli &
744 Lambert, 2005), should it be a surprise that other lipids might display similar properties.
745
746 The immediate significance of lipids' anaesthetic properties to dementia lies in the fact that, at
747 concentrations well below those needed for clinical anaesthesia, the vast majority of anaesthetic

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agents are known to cause AA (Orser, 2007; Bonin & Orser, 2008; Evers & Crowder, 2009). Such low-level anesthesia-induced AA is now known to involve extrasynaptic GABAARs (Orser, 2007; Bonin & Orser, 2008) whose subunit composition (including either α5 or δ subunits) gives them sufficient sensitivity to respond to low levels of ambient GABA (Brickley & Mody, 2012). It is the resulting low-level inhibitory currents, termed "tonic inhibition", which is associated with AA (Cheng et al., 2006; Nutt et al., 2007; Sikka, Beaman & Street, 2015). (By contrast lower-affinity synaptic GABAARs, with different subunit compositions, respond only to the higher concentrations of GABA released within their associated synapses, with the resulting phasic inhibition causing the other anaesthetic effects (Farrant & Nusser, 2005; Bonin & Orser, 2008; Evers & Crowder, 2009), including analgesia, immobility and unconsciousness.) In support of this, pharmacological and genetic knockdown of extrasynaptic α5- and δ-containing $GABA_A$Rs in mice has been shown to improve performance on learning and memory tasks (Collinson et al., 2002; Shen et al., 2010; Clarkson et al., 2010), possibly by lowering the threshold for long-term potentiation (Liu et al., 2010; Martin et al., 2010; Whissell et al., 2013).

The reason for all this is that GABAARs have associated ion channels, which become permeable to chloride (and, to a lesser extent, HCO_3) ions, in response to GABA ligation (Grover et al., 1993; Li & Xu, 2008; Sigel & Steinmann, 2012). Upon such activation, chloride ions flow through these GABAAR channels in a direction determined by their electrochemical gradient.

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767 Since mature neurons maintain an excess of chloride ions externally, the normal response to
768 GABA binding is therefore for these negative ions to flow in through the GABAAR channels,
769 increasing the negative membrane potential and thereby hyperpolarising (i.e. inhibiting) the
770 affected neuron (Kaila, 1994; Li & Xu, 2008). Tonic inhibition is just the extrasynaptic form of
771 this (Petrini et al., 2004; Jia et al., 2005). The majority of anaesthetic agents (including those that
772 are only weakly anaesthetic, such as ethanol) are known to enhance this GABA binding, acting
773 as positive allosteric modulators (Orser et al., 1998; Krasowski, 2003). Accordingly, they tend
774 to inhibit normal activity in mature neurons of the CNS (Orser et al., 1998; Krasowski &
775 Harrison, 1999; MacIver, 2014).
776
777 However, recent research has shown that the same high-affinity extrasynaptic GABAARs that
778 mediate tonic inhibition in mature neurons (Yeung et al., 2003; Brickley & Mody, 2012) also
779 play a significant role in neurogenesis and neuronal plasticity (Liu et al., 2005; Bordey, 2007).
780 In support of this, pharmacological and genetic suppression of tonic GABA inhibition, including
781 by down-regulation of extrasynaptic GABAAR activity, is associated with marked
782 improvements in functional recovery after stroke (Clarkson et al., 2010; Paik & Yang, 2014).
783 This is in agreement with findings that suggest that increased GABA tonic inhibitory currents, in
784 the days after stroke, hinder recovery (Clarkson et al., 2010; Clarkson, 2012).
785

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786 Since the extrasynaptic GABAARs containing the δ-subunit are known to be especially sensitive
787 to positive modulation by ethanol (Wei, Faria & Mody, 2004; Meera et al., 2010) this may
788 explain alcohol-mediated neurodegeneration seen in ARBD. As explained earlier, disruption of
789 neurogenesis appears to be critical to the neurodegenerative effects of ethanol upon the brain.
790 Specifically, chronic exposure of the brain to ethanol is characterised from comparatively early
791 on by erosion of the hippocampal region (Morris et al., 2009; Crews & Nixon, 2009), loss of
792 interneurons (the primary product of neurogenesis (Mandyam, 2013)), AA (White et al., 2004;
793 Sanday et al., 2013) and olfactory deficits (Ditraglia et al., 1991; Collins, Corso & Neafsey,
794 1996).
795
796 An obvious explanation for these findings is inhibition of neurogenesis in the SGZ and SVZ,
797 given that the former supplies neurons to other hippocampal regions (Eriksson et al., 1998; Ming
798 & Song, 2011), whilst the latter is known to replenish the olfactory bulb interneurons via the
799 rostral migratory stream (Ming & Song, 2011; Lim & Alvarez-Buylla, 2016). Since much
800 evidence suggests that FFAs have, on average, similar, if not higher, anaesthetic potency levels
801 to ethanol (Samson Jr, Dahl & Dahl, 1956; Walker et al., 1970; Pringle, Brown & Miller, 1981;
802 Wong et al., 1997; Ueda & Suzuki, 1998; Frangopol & Mihailescu, 2001), implying a similar
803 affinity for GABAARs, it may well be that chronic exposure of the brain to excess FFAs over

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804 many years will have similar results. This would provide an explanation of, why AD and ARBD
805 share these hallmark effects on the brain.
806
807 A complicating factor here is that, in immature neurons, the chloride gradient is reported to be in
808 the reverse direction to that of their mature counterparts (Ben-Ari & Holmes, 2005; Li & Xu,
809 2008). That is to say, chloride ions are held internally in excess of their external levels. If so,
810 GABA binding to GABAARs could reasonably be expected to activate such precursor neurons
811 and, by extension, one would expect anaesthetic agents (and other positive modulators) to
812 overactivate them. A further consideration is that such precursor cells initially exhibit few
813 synapses, with most GABAARs having a subunit composition typical of extrasynaptic
814 GABAARs in mature neurons (Henschel, Gipson & Bordey, 2008; Song et al., 2012; Pallotto &
815 Deprez, 2014), with synapses only tending to emerge later as the neuronal precursors mature and
816 become integrated (synaptically and otherwise) with the existing network (Ge et al., 2007; Ben-
817 Ari et al., 2007; Ming & Song, 2011). So GABAARs in these cells tend to have a high affinity
818 for ambient GABA, and one would expect the dominant response to GABA stimulation to be
819 tonic activation (Ming & Song, 2011; Song et al., 2012). So, if ethanol (and, as we are arguing
820 here, by extension, FFAs) abnormally enhance this effect, one should expect to see overgrowth
821 rather than erosion in adult neurogenic regions. Why is this not so?
822

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One mechanism that might explain such neurogenetic deficits in the SGZ and SVZ, is GABA-mediated feedback inhibition. Recent discoveries suggest that non-synaptic paracrine GABA signalling provides information on population size to control proliferation and migration of neural progenitor cells in the SVZ (Liu et al., 2005; Bordey, 2007; Ge et al., 2007; Pallotto & Deprez, 2014). Specifically, adult SVZ neuroblasts synthesise and release GABA, which acts on GABAARs in neural stem cells, inhibiting NSC division and thus effectively applying a brake on neurogenesis. In confirmation of this, removal of neuroblasts is seen to release this brake.

The specific details of this appear to have been provided by a study of neurogenesis in postnatal rat striatum (Nguyen et al., 2003). Here, the growth factor EGF was seen to decrease GABA production and release in PSA-NCAM+ neural precursor cells, leading to their proliferation. A number of experiments suggested that GABA was indeed acting on GABAARs in an autocrine/paracrine mechanism to prevent cell proliferation by inhibiting cell cycle progression. Application of GABAAR antagonists inhibited proliferation, whereas positive allosteric modulators decreased it. As with other immature neuronal cell lineages, GABA-mediated GABAAR activation elicited inward currents (indicating outward flows of negatively-charged chloride ions), leading to tonic inhibition of the mitogen-activated protein kinase cascade and an increase of intracellular calcium levels (Nguyen et al., 2003).

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842 This agrees with the findings of the Liu study, which showed that, at least in GFAP-expressing
843 neural progenitor cells in the SVZ, GABAAR activation limits progression through the cell cycle
844 (Liu et al., 2005). It also suggests that, at least in the SVZ, adult neurogenesis is regulated by the
845 same mechanisms that govern embryonic neurogenesis, where, for instance, GABA is seen to
846 direct neuroblast migration, stimulating random mobility by promoting elevation of cytosolic
847 Ca2+ levels (Barker et al., 1998; Ge et al., 2007), similar to what is seen in adult neurogenesis
848 (LoTurco et al., 1995). While some related studies have shown that such effects appear to
849 promote neuronal fate selection (Tozuka et al., 2005), the overall impression is that GABA
850 stimulation also seems to limit proliferation (Barker et al., 1998; Nguyen et al., 2003). However,
851 more recently, doubts have been raised about whether such tonic GABA-mediated depolarisation
852 is sufficient to open voltage-gated calcium channels enough to permit substantial increases in
853 intracellular calcium in the way proposed, requiring other explanations (Bordey, 2007).
854
855 An alternative explanation is that an epigenetic mechanism, involving histone H2AX
856 phosphorylation following sustained GABAAR activation by GABA, inhibits DNA synthesis
857 and cell cycle progression, and therefore proliferation of adult neural stem cells (Fernando et al.,
858 2011). It is not clear that this mechanism also applies to SGZ neurogenesis but, if so, it could
859 explain why GABAergic stimulation is similarly associated with quiescence of adult precursor
860 cells in this niche (Duveau et al., 2011; Song et al., 2012; Pallotto & Deprez, 2014).

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But it may be that such involved explanations are not necessary, as recent research has brought into question the prevailing orthodoxy concerning GABA activation of immature neurons (Valeeva et al., 2016; Zilberter, 2016), concluding that, overall, GABA action on the neonatal brain is inhibitory. If this proves correct, and is found to be true also for adult neurogenic regions, then ethanol-induced deficits in neurogenesis can be simply explained as a result of excess inhibition.

Either way, assuming ethanol inhibition of neurogenesis in the SVZ and SGZ is mediated by GABAARs, then FFAs are likely to have a similar effect. This is because a number of studies point towards GABAARs as the most likely target and mediator of FFA's limited anaesthetic properties, not least the well-established anaesthetic effects (alluded to earlier) of structurally similar n-alkanes, n-alcohols and n-aldehydes. Furthermore, as with FFAs, anaesthetic potency increases with chain length but only up to a certain "cut off" length (Alifimoff, Firestone & Miller, 1989; Chiou et al., 1990; Wick et al., 1998; Frangopol & Mihailescu, 2001; Hau, Connell & Richardson, 2002; Lugli, Yost & Kindler, 2009)). This, together with direct evidence that the n-alcohols act on GABAARs (Wick et al., 1998; Davies, 2003), as does the endogenous, FA, anaesthetic oleamide (Lees et al., 1998; Laws et al., 2001; Coyne et al., 2002), suggests a common binding site. More direct evidence for this comes from the observed antagonising

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effects of long-chain FFAs on GABAAR-mediated anaesthesia by volatile anaesthetics (Hanada, Tatara & Iwao, 2004; Yamakura, 2004), along with other evidence of direct interactions between FFAs and GABAARs (Koenig & Martin, 1992; Witt & Nielsen, 1994; Zhang & Xiong, 2009).

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

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899 substantially enter the brain, unlike in ARBD, where ethanol can pass through the BBB
900 relatively unhindered (Laterra et al., 1999). Consequently, in AD the brain is also exposed to
901 other molecules from which it is normally protected, including lipoproteins, which are much
902 larger and more lipid-laden than those normally found within the CNS compartment.
903
904 There is good reason to think that such lipoproteins may account for the amyloid plaques that
905 characterize AD. It has been known for some time that excess cholesterol is associated with
906 increased amyloidogenesis.
907

908 2.6.1 The role of excess cholesterol in amyloidogenesis

909
910 Cholesterol may have a role in increasing proteolytic production of amyloidogenic Aβ from
911 APP, as opposed to production of alternative non-amyloidogenic fragments (Bodovitz & Klein,
912 1996; Xiong et al., 2008; Nicholson & Ferreira, 2010). This appears to result from the influence
913 of cholesterol stimulation on an amyloidogenic pathway involving β- and γ-secretases (two
914 proteases involved in APP proteolysis) (Xiong et al., 2008), as well as on a non-amyloidogenic
915 pathway involving α-secretase (Kojro et al., 2001) (Figure 3.). Increasing the levels of
916 cholesterol stimulates the amyloidogenic pathway, at the same time inhibiting the non-
917 amyloidogenic pathway (Wolozin, 2004; Xiong et al., 2008). In contrast, cholesterol depletion,

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by various processes, inhibits the amyloidogenic pathway and enhances non-amyloidogenic processing, resulting in lower levels of Aβ (Simons et al., 1998; Kojro et al., 2001).

Amyloidogenic processing appears to be initiated within cholesterol-rich lipid rafts (Ehehalt et al., 2003; Rushworth & Hooper, 2011; Nixon, 2017; Habchi et al., 2018) (especially in early endosomes (Arriagada et al., 2007; Nixon, 2017)), whilst non-amyloidogenic processing occurs in the main phospholipid-rich region of the neuronal plasma membrane (Xiong et al., 2008; Grimm et al., 2013). This suggests that an important part of cholesterol's influence on amyloidogenic processing may be a consequence of its essential role as a major constituent of these lipid rafts, a conclusion that is well-supported in the literature (Ehehalt et al., 2003; Vetrivel & Thinakaran, 2010; Nixon, 2017).

Certainly, some studies indicate that brain cholesterol levels may be raised in AD, compared to non-demented, brains (Kivipelto et al., 2001; Xiong et al., 2008; Jin et al., 2018; Wingo et al., 2019), although not all studies concur (Ledesma & Dotti, 2005). That cholesterol may be directly associated with amyloid plaque formation is supported by brain imaging studies, which show Aβ collocated with cholesterol within amyloid deposits in brain samples from AD-affected humans and other species (Mori et al., 2001; Burns et al., 2003; Xiong et al., 2008).

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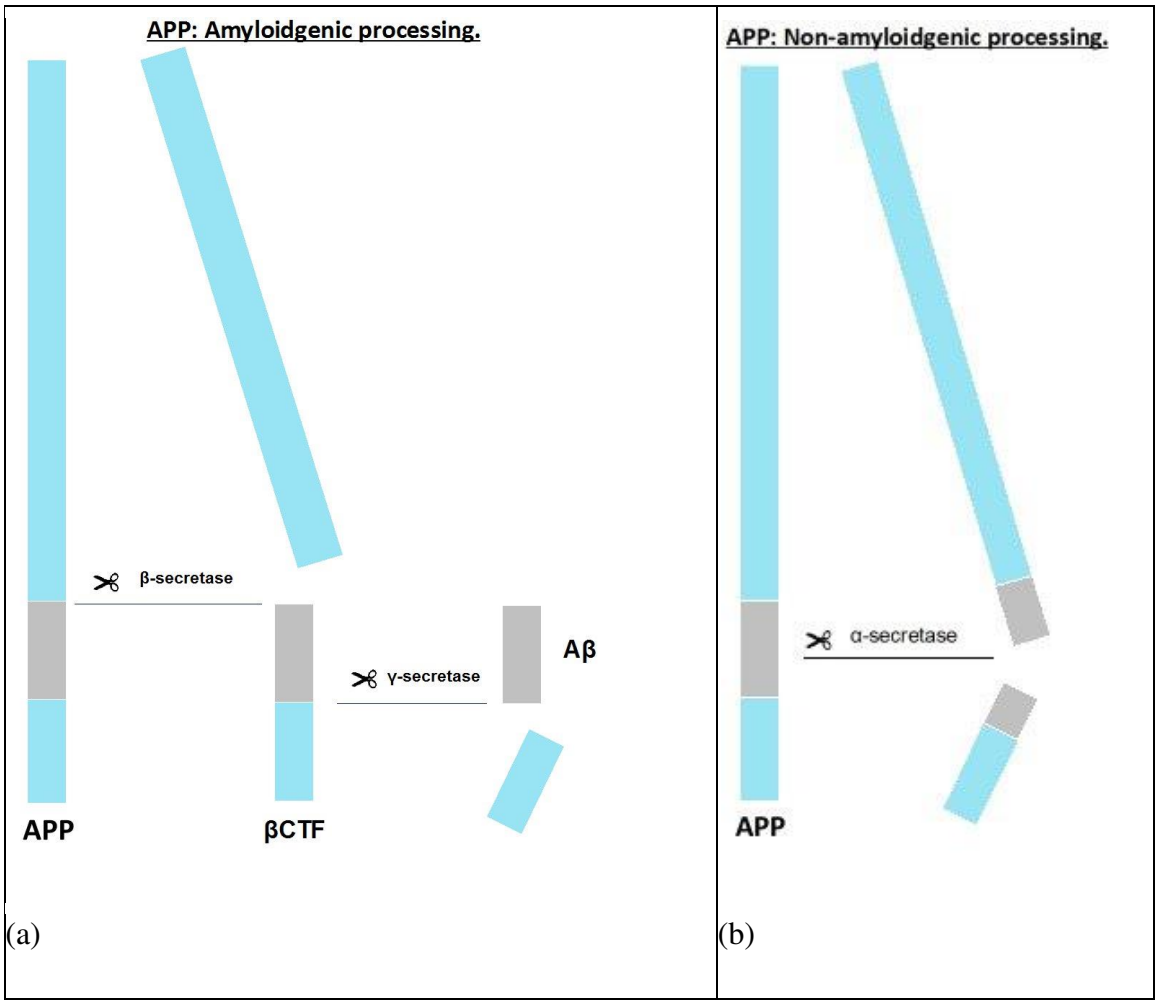
937



938

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

940

941

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

Indirect evidence of raised brain cholesterol levels as a causal factor in AD comes from studies of human AD brains. Such brains show abnormalities in the endosomal-lysosomal system compared to normal brains, together with neurofibrillary (tau) tangles (Cataldo et al., 2000; Xu et al., 2018). Such endosomal pathway overactivity and compartmental enlargement appears to be an early marker in AD, especially in pyramidal neurons, populations of which are known to be vulnerable in AD (Cataldo et al., 1996; Morrison & Hof, 2002; Nixon, 2017; Fu, Hardy & Duff, 2018).

Interestingly, a very similar pathology is also seen in mouse and other models of DS (Cataldo et al., 2000, 2008; Arriagada et al., 2007; Jiang et al., 2010). 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.,

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961 2001). Such studies, whilst often contradictory in their results, collectively point to various
962 failings in cholesterol uptake, transport and recycling, and in abnormal endosomal-lysosomal
963 pathway behaviour. Such reported failings include excessive uptake of exogenous LDL-derived
964 cholesterol (Liscum & Faust, 1987), excessive synthesis of endogenous cholesterol (Liscum &
965 Faust, 1987), enlarged early endosomes (Jin et al., 2004; Nixon, 2004), accumulation of
966 unesterified cholesterol in late endosomes and lysosomes (Nixon, 2004; Sobo et al., 2007),
967 defective post-lysosomal cholesterol transport (Roff et al., 1991) and redistribution of lysosomal
968 hydrolases to early endosomes (Jin et al., 2004).
969
970 Yet such reports commonly claim that other aspects of cholesterol internalisation (and
971 endosomal-lysosomal pathway behaviour) appear to be normal, particularly in the case of initial
972 cholesterol uptake and early endosome behaviour (Nixon, 2004). However, a very similar
973 phenotype is observed in a Chinese hamster ovary (CHO) cell mutant, which has a normal copy
974 of NPC1 (the late endosome/lysosome-residing protein most commonly associated with NPC
975 disease (Nixon, 2004)) , and of the HE/NPC2 protein (also associated with NPC, although less
976 commonly) yet still exhibits NPC-like pathology (Frolov et al., 2001). In this mutant late sterol
977 trafficking is reported to be normal despite obvious cholesterol accumulation in late endosomes/
978 lysosomes (Frolov et al., 2001). Instead, cholesterol build-up occurs as a result of much-
979 increased LDL-R binding, probably leading to cholesterol uptake being in excess of the normal

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capacity of the cell to dispose of it (Frolov et al., 2001). Evidence in support of this conclusion includes the finding that LDL starvation of this mutant resulted in the disappearance of the cholesterol-laden aberrant late endosome compartment (characteristic also of NPC) that had previously been observed, only for this compartment to reappear with the restoration of LDL feeding (Frolov et al., 2001).

More generally, another study, using a human fibroblast model, appears to provide further evidence for this conclusion. It found endosomal-lysosomal pathology in a number of inherited sphingolipid-storage disorders (Puri et al., 1999). In almost all cases such pathology showed strong similarities with that seen in NPC, with a marked reduction in the accumulation of both cholesterol and a representative sphingolipid within the Golgi complex, accompanied by their increased accumulation within many punctate cytoplasmic structures that also appeared to be associated with the NPC1 protein (Puri et al., 1999).

The authors conclude that the observed pathology most likely results from a build-up of cholesterol (which is known to associate with high affinity to sphingolipids (Brown, 1998; Lönnfors et al., 2011)) within endosomes and lysosomes, since the reported pathology was seen to disappear following cholesterol depletion, being replaced with normal endosomal-lysosomal behaviour (Puri et al., 1999). However the same pathology could also be induced in normal cells

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by application of excess external cholesterol in the form of low-density lipoprotein (LDL) (Puri et al., 1999), similar to what is described for the CHO mutant mentioned above (Frolov et al., 2001), and in line with another study linking raised levels of plasma membrane cholesterol with correspondingly enlarged early endosomes in hippocampal neurons (Cossec et al., 2010).

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

In further support of this hypothesis, inhibition of CYP46A1 (a protein indirectly responsible for cholesterol clearance from the brain through the BBB (Lütjohann et al., 1996; Lund, Guileyardo & Russell, 1999)) in mouse hippocampal neurons has been shown to lead to accumulation of neuronal cholesterol. This, in turn, is associated with a distinctive AD-like pathology, including marked changes in endosomes (increasing both in size and number), Aβ peptide production, tau phosphorylation, endoplasmic reticulum stress and apoptosis, and eventually hippocampal atrophy and cognitive impairment (Djelti et al., 2015; Ayciriex et al., 2017).

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1018 It has been argued earlier that the presence of a BBB has resulted in the brain (and the rest of the
1019 CNS) evolving to have a different lipid system to the rest of the body, one characterised by a
1020 much lower lipid turnover, and smaller, less lipid-dense lipoproteins. If so, it should therefore
1021 not be unexpected that substantial damage to the BBB, leading to long-term exposure to a
1022 systemic lipid system characterised by high lipid turnover and larger, more lipid-dense
1023 lipoproteins, will result in neurons and other brain cells becoming overloaded and displaying the
1024 kind of abnormalities described above.
1025

1026 ### 2.6.3 The role of the β-secretase-induced C-terminal fragment (βCTF)

1027

1028 Certainly, this interpretation fits in well with the evidence presented above, given that cellular
1029 LDL-cholesterol uptake is known to be dependent on the endosomal-lysosomal pathway, by way
1030 of receptors possibly bound within lipid rafts (Vance & Vance, 2008; Sun et al., 2010; Pompey
1031 et al., 2013; Nixon, 2017). Furthermore, APP seems to be central to endosomal-lysosomal
1032 pathology, as the latter can be induced by APP over-expression, or by the C-terminal fragment
1033 that remains after β–secretase cleavage of APP (Jiang et al., 2010; Nixon, 2017), but prior to γ–
1034 secretase cleavage (Fig. 3).
1035

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Such cleavage is known to take place in early endosomes (Cataldo et al., 2000; Arriagada et al., 2007) 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). Furthermore, treatments, or presenilin mutations, that increase levels of Aβ without increasing levels of βCTF do not result in endosomal-lysosomal pathology (Cataldo et al., 2000; 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 (Cataldo et al., 2003; 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 (Miaczynska et al., 2004; Zhu et al., 2007; Nixon, 2017). This stabilises the monomeric GTPase protein Rab5 in its GTP-bound, activated form, and therefore amplifies the Rab5 signalling associated with early endosomes (Gorvel et al., 1991; Grbovic et al., 2003; Mishra et al., 2010), leading in turn to the enlarged endosomes seen in both AD and DS (Kim et al., 2016; Nixon, 2017). Thus, taken collectively,

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

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., 2008), 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

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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 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.

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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 particular) to evolve in ways that make it highly vulnerable to lipid incursion from the non-CNS compartment. In particular, it is predicted that exposure to the higher cholesterol content of the more lipid-rich lipoproteins from outside the CNS will lead to cholesterol overload in neurons and other CNS-specific cell types. This in turn will result in endosomal-lysosomal pathology, tau tangles and excessive formation of Aβ, similar to what is seen in AD.

In support of this hypothesis, similar endosomal-lysosomal pathology is seen in NPC, a disease characterised by faulty cholesterol transport, resulting in the accumulation of unesterified

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cholesterol in late endosomes and the formation of tau tangles. Likewise, excess cholesterol has been shown to increase amyloidogenesis by stimulating amyloidogenic processing of APP at the expense of the non-amyloidogenic pathway, resulting in increased levels of Aβ. During this amyloidogenic processing, high levels of the intermediate βCTF fragment are produced, which have been shown to trigger endosomal-lysosomal abnormalities similar to those observed in early AD progression. (Presumably, the reason Aβ levels are much lower in NPC than in AD is because cholesterol build-up tends to affect late endosomes in the former disease, rather than early endosomes where Aβ is produced.)

But cholesterol is not the whole story here. Breakdown of the BBB also exposes the brain to higher levels of FFAs. It is argued here that such exposure will lead to neuroinflammation, as a result of these FFAs stimulating microglia by binding to TLR4 and other microglial receptors, similar to how FFAs activate macrophages outside the CNS and to how ethanol triggers microglial-mediated neuroinflammation.

This may help explain why the overall structural pattern of damage to the brain inflicted by long-term alcohol abuse so strongly resembles that seen in AD, and why there are similar behavioural deficits. In particular, frontal regions of the brain (especially the prefrontal cortex and basal forebrain) suffer significant shrinkage in both ARBD and AD, helping to explain why both

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diseases are associated with deficits both in olfaction and in executive functions requiring attentional and inhibitory control, reasoning, problem-solving, the setting of goals and of planning. Similarly, both ARBD and AD are associated with shrinkage of the medial temporal lobes, including pronounced atrophy of the hippocampus and entorhinal cortex, resulting in the anterograde amnesia so characteristic of AD, along with more specific deficits in spatial memory.

However, it is hard to explain how such similarities might occur as a result of neuroinflammation alone. Studies have shown that inhibition of neurogenesis plays almost as important a role in ARBD, which would better explain why the principal areas of brain atrophy in ARBD and AD, the frontal and medial temporal regions, also host two of the principal neurogenic niches of the brain, the subventricular and subgranular zones. These provide new cells for the prefrontal cortex and the hippocampus, respectively. It is argued here that the principal mechanism by which ethanol inhibits such neurogenesis, involving extrasynaptic GABAARs, means that such regions are also likely to be similarly affected by long-term exposure to other molecules with weakly anaesthetic properties, including FFAs. Whilst the mechanism by which such inhibition occurs appears to be complex, and may well involve other receptors and pathways, these shared properties, and the shared mechanism seen in most forms of anaesthesia (Bertaccini, Trudell & Franks, 2007), suggest that long-term neurodegeneration will result in both cases.

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Whilst this aspect of the lipid-leakage model might be considered to be its most speculative, it may help to explain why general anaesthesia is also considered a potential risk factor for AD (and dementia in general) amongst elderly patients (Bohnen et al., 1994; Eckenhoff et al., 2004; Xie & Tanzi, 2006; Vanderweyde et al., 2010; Fodale et al., 2010; Papon et al., 2011; Chen et al., 2014), as well as being associated with marked deterioration in those already affected with AD (Bone & Rosen, 2000; Xie et al., 2007; Planel et al., 2007; Papon et al., 2011). However, such an association is still a matter of dispute (Needham, Webb & Bryden, 2017), and a number of studies suggest that, where it does occur, anaesthesia-related deterioration is accompanied by increases in Aβ synthesis and oligomerisation, and by tau hyperphosphorylation (Eckenhoff et al., 2004; Xie & Tanzi, 2006; Xie et al., 2007; Planel et al., 2007; Fodale et al., 2010; Papon et al., 2011). If so, this tends to rule out any GABA-related mechanism.

But these are not the only reasons for suspecting a link with GABAARs. Ever since the first practical anaesthetic agents were discovered in the middle of 19th century (Robinson & Toledo, 2012), and later shown (independently) by Hans Horst Meyer and Charles Ernest Overton to display a remarkable correlation between potency and hydrophobicity (Sandberg & Miller, 2003; Lugli, Yost & Kindler, 2009), there has been considerable interest in their mechanism of action. Following the findings of Franks and Lieb in the 1980s this interest has focused on hydrophobic

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sites on membrane proteins (Franks & Lieb, 1990), particularly those of the Cys-loop ligand-gated ion channel superfamily, which includes inhibitory GABAARs and glycine receptors, as well as the excitatory acetylcholine and 5-HT3 serotonin receptors (Jenkins et al., 2001; Bertaccini, Trudell & Franks, 2007; Thompson, Lester & Lummis, 2010).

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, particularly, 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 (Ming & Song, 2011) 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 low anaesthetic potencies, 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

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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, Gregório & Martel, 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 such transporters, it is argued here, is 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 neuroinflammation. 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

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is generally agreed that, in vertebrates, the neurons of the suprachiasmatic nucleus (SCN) provide a central role (Stephan & Zucker, 1972; Cohen & Albers, 1991; Ehlen & Paul, 2009; Albers et al., 2017). Furthermore, within the SCN it is clear that GABAARs play a critical role, including in their extrasynaptic form (Ehlen & Paul, 2009; McElroy et al., 2009; Hu et al., 2016; Albers et al., 2017; McNeill, Walton & Albers, 2018), with some estimates suggesting that over 90% of SCN neurons express and respond to GABA (McNeill, Walton & Albers, 2018). A number of studies have shown that ethanol modulates circadian clock regulation (Prosser, Mangrum & Glass, 2008; Ruby et al., 2009; Brager et al., 2011; Prosser & Glass, 2015), including by its action at low concentrations on extrasynaptic GABAARs (McElroy et al., 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.

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, Balouch & Tabet, 2017), when amnesia and other AD-associated deficits

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are only beginning to be noticeable, it seems likely that what is being seen has a physiological as well as a purely psychological basis.

An obvious challenge with the lipid-leakage model is how it explains FAD. In the vast majority of cases (Wu et al., 2012; Lanoiselée et al., 2017) these result from mutations in Aβ-related genes, primarily in presenilin-1 (PSEN1), but also in APP and presenilin-2 (PSEN2). As shown in Figure 3, APP is the precursor protein from which Aβ is cleft, as a result of the amyloidogenic pathway, whilst PSEN1 and PSEN2 provide catalytic components of the γ-secretase (Lanoiselée et al., 2017), responsible for the final step in such Aβ formation. Similarly, as stated earlier, an additional copy of the APP gene, such as is seen in Down's Syndrome, is associated with a much-increased risk of developing early-onset AD. This would appear to strongly suggest that it is amyloidogenesis rather than lipid-leakage that causes AD. However, it should be remembered that the lipid-leakage model assigns an important role for Aβ in BBB disintegration, a role well-supported by the literature. Also, as stated earlier, experimental results have shown that Aβ has a role as a regulatory apolipoprotein, with raised levels of Aβ being associated with increased secretion of lipid-rich lipoproteins, including chylomicrons. Taken together, it can be seen how overexpression of Aβ, as seen in FAD, will result in lipid invasion the same way as it does in LOAD. Similarly, because ApoE has been shown to protect the BBB against damage, with

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ApoE4 associated with BBB impairment, it can be seen how the lipid-leakage model can perfectly adequately account for ApoE genotype as an important risk factor for AD.

Moreover, because it explains LOAD as a consequence of all forms of BBB damage, rather than just as a result of amyloidogenesis, the model arguably provides a better explanation than the amyloid hypothesis for why LOAD is so much more common than FAD. Ultimately, anything that substantially damages the BBB, including simple wear and tear, is likely to result in AD. For this reason, attempting to treat AD by inhibiting amyloidogenesis alone is unlikely to be an effective treatment. By the time AD is diagnosed, even in the case of FAD, it is likely that the BBB damage will be too advanced to benefit much from such inhibition.

Rather, the model predicts that effective treatment will need to have several goals, including protecting the BBB from further damage (and, if possible, reversing any damage that has already occurred), reducing levels of FFAs entering the brain (by other means), inhibiting neuroinflammation and preventing inhibition of neurogenesis.

Finally, it can be argued that the explanation of LOAD provided by the model is more consistent with the majority of highly prevalent pathologies in the elderly. Excluding cancer, which is really a multitude of pathologies with often very different genetic and biochemical origins, some

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form of mechanical failure would seem to be central to them all. In particular, stroke and heart disease are known to be associated with rupture of blood vessels. For this reason, the lipid-leakage model, in placing failure of the BBB at the heart of LOAD aetiology, would seem to sit more comfortably than alternative explanations with our current understanding of other common devastating diseases of the elderly.

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. Indeed, rather than attempting to treat AD by reducing the extent of amyloid plaques and tau tangles, the model clearly suggests that treatment would be greatly more efficacious if it were to focus on more "upstream" factors. This most obviously includes treatments to repair and prevent further damage to the BBB, and to reduce levels of invading FFAs and lipid-rich lipoproteins within the brain. The model also suggests that treatments to reduce FFA-mediated neuroinflammation and inhibition of neurogenesis would also be efficacious. Certainly, treatments focused on specific aspects of AD pathology have yet to show meaningful efficacy. It is argued here that this is because they have all been based on models of AD that are too

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simplistic, resulting in treatments that are too narrowly-focused and missing the most efficacious targets. By contrast, the lipid-leakage model shows AD to be a much more complex disease, explaining why it is associated with so many distinct brain pathologies. Whilst this implies that effective treatment may prove more challenging than once hoped, the better understanding of the disease provided by the model will surely greatly improve the chances of discovering such treatments.

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