Supplementary Material

A New Hypothesis for Alzheimer's Disease: The Lipid Invasion Model

SUPPLEMENTARY EXPLANATIONS

Problems with the amyloid cascade hypothesis

Amyloid-β (Aβ) is certainly a primary cause of neurodegeneration in Alzheimer's disease (AD) in many cases. However, there are at least four aspects of AD which are not well-explained by the amyloid cascade hypothesis.

Plaques

Several studies have shown a poor correlation between amyloid plaque distribution and disease progression [1–4]. Some AD patients show no evidence of high plaque levels [5], while other individuals with unusually high Aβ and amyloid plaque loads may be substantially cognitively unimpaired [4,6].

In addition, regional distribution of amyloid plaques does not correlate well with the clinical symptoms of memory loss, which characterize the disease. Given the role of the medial temporal lobe (MTL, especially the hippocampus) in memory formation, one would expect memory decline to be associated with large-scale amyloid plaque formation in this region. Instead, positron emission tomography (PET) imaging studies show that amyloid deposition tends to start in the frontal and posterior cingulate cortices, with obvious memory decline often preceding high MTL amyloid plaque burden by one or more decades [4,7]. By contrast, a number of PET and other non-imaging studies in humans with AD have shown that regional neurofibrillary tangle (NFT) distribution correlates much better with clinical symptoms, with NFTs appearing in the MTL in the early, symptomatic, stages of AD long before the appearance of amyloid plaques [4,8].

Most importantly, perhaps, more than twenty years since the hypothesis was first raised, no treatments aimed at preventing or eliminating amyloid plaques have so far been devised that show significant or lasting benefits in preventing or halting the progression of AD [3,4,9–11].

Aβ production

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, since individuals with non-inherited, late-onset forms of AD (LOAD) do not always display elevated production of Aβ [20,21] within the brain, even when plaques are present in quantity.

As mentioned in the main document (see section “The amyloid cascade hypothesis"), this has led some researchers to propose that excessive Aβ levels, plaques, and other Aβ aggregates may be the result of abnormally low removal of Aβ from parenchyma/cerebrospinal fluid (CSF), rather than Aβ overproduction. However, despite the strong evidence in support of this, and of excess receptor for advanced glycation end product (RAGE)-mediated Aβ influx, many other researchers remain unconvinced [12], arguing that, as well as all the different efflux receptors available to transport Aβ across the blood-brain barrier (BBB) and out of the brain (implying substantial redundancy), there would seem to be more than adequate alternative mechanisms for eradicating excess cerebral Aβ via choroid plexus efflux and parenchymal enzymatic degradation [12–15]. For instance, it is estimated that CSF is replenished some three times daily via the choroid plexus, with the epithelial cells of the plexus expressing an array of enzymes, which should, in theory, be able to hydrolyse potentially toxic proteins such as Aβ [13,14].

Collectively, such findings have led some to conclude that the origins of AD-associated cerebral Aβ deposits may lie outside of the brain, without relying on physiologically normal BBB-resident influx transport mechanisms, such as provided by RAGE or similar proteins [12]. But, if so, it is far from clear what form this might take.

AD and aging

The third challenge for the amyloid hypothesis is that AD is extremely rare in the young, and even in the middle-aged, and yet becomes widespread in the very elderly. It is not clear why amyloid-β protein precursor (AβPP) processing should display such vulnerability to the late aging process when no other comparable protein pathway appears to show such vulnerability.

If one looks at other common conditions that affect the elderly, including coronary heart disease, stroke, arthritis, and various forms of vision loss, these all, for the most part, rely on a largely structural/mechanical explanation, involving excessive pressure or general wear and tear, or both.

The amyloid hypothesis lacks such a mechanism that convincingly explains why it becomes so prevalent in old age, yet is confined only to the brain, and associated with such specific features, including plaques, NFTs, and memory loss.

AD risk factors

The fourth challenge for the amyloid hypothesis is that it does not plausibly account for other known risk factors for AD, such as hypertension [16], diabetes [17], lowered sex hormone levels [18,19], obesity [20], smoking [21], stress [22], sleep deprivation [23], and head injury [24]. There seems no obvious reason why all of these should increase levels of Aβ or amyloid plaques, or cause the various other brain pathologies associated with AD.

Evidence of BBB disruption in AD

Substantial evidence exists to demonstrate that AD is associated with BBB disruption [25–30]. This includes postmortem, biofluid, and imaging studies [31].

Many postmortem studies of human AD brains have shown evidence of infiltration of plasma-associated cells and proteins that should not be there. Among the former are extravasated red blood cells [32] and cyclo-oxygenase-2-positive macrophages, including within amyloid plaques and Aβ-containing blood vessels, as well as at the sites of impaired brain endothelial tight junctions [33]. As well as ApoB and albumin, mentioned in the main document (in the section “Evidence of a role for lipids in AD"), extravasated plasma-associated proteins found within such postmortem brains include prothrombin [34], fibrinogen [35–37], and immunoglobulin G [35,37].

In addition, postmortem human AD brains have been found to show signs of microvasculature basement membrane thinning [38], and of a deficiency in pericytes and other brain vasculature mural cells [37], among other evidence of neurovascular dysfunction [39].

Similarly, a number of studies in live human subjects have shown the presence of plasma proteins such as albumin, fibrinogen, and plasminogen, as well as the soluble form of the BBB pericyte-associated receptor protein PDGFRβ, in the CSF of those diagnosed with AD, even in the earliest cases where cognitive impairment is slight [40–50]. In many of these studies, CSF levels of these biomarkers for BBB disruption appear to correlate well with the degree of disease progression.

Likewise, a large number of imaging studies in live human subjects have shown evidence of BBB damage at every stage of AD progression [31,51], including mild cognitive impairment (MCI), a condition characterized by minor problems with cognition, typically including memory, which often develops into dementia. For instance, numerous magnetic resonance imaging (MRI) studies have shown evidence of cerebral microbleeds in the brains of individuals with MCI and AD [42,51–60], as well as of superficial siderosis [61]. Other imaging-based evidence for BBB damage comes from dynamic contrast-enhanced MRI studies showing increased leakage of a gadolinium-based contrast agent in human subjects with MCI or various degrees of AD [62–64], and an arterial spin labelling MRI study showing reduced cerebral blood flow in those diagnosed with early AD [62].

The BBB: a barrier between two different lipid systems

The architecture of the BBB is found hardly anywhere else in the human body and includes unusually strong tight junctional complexes and adherens junctions between the endothelial cells (ECs) that line thin blood capillaries [31]. There is also a paucity of endothelial fenestrations and a general lack of pinocytotic/transcytotic activity, resulting in only a very limited flow of solutes across the endothelium. Further obstacles to this flow of solutes and other molecules include a surrounding belt made up of basal lamina and a large numbers of specialist cells, particularly pericytes and astrocytes, which help regulate capillary blood flow and stabilize the BBB [65,66]. As well as providing structural support by ensheathing brain capillary endothelium, and using their contractile properties to alter capillary diameter and hence blood flow, pericytes also help regulate BBB integrity and permeability, including influencing levels of tight junction proteins, secreting basement membrane proteins, and stabilizing endothelial cell maturation, via paracrine signaling [66,67].

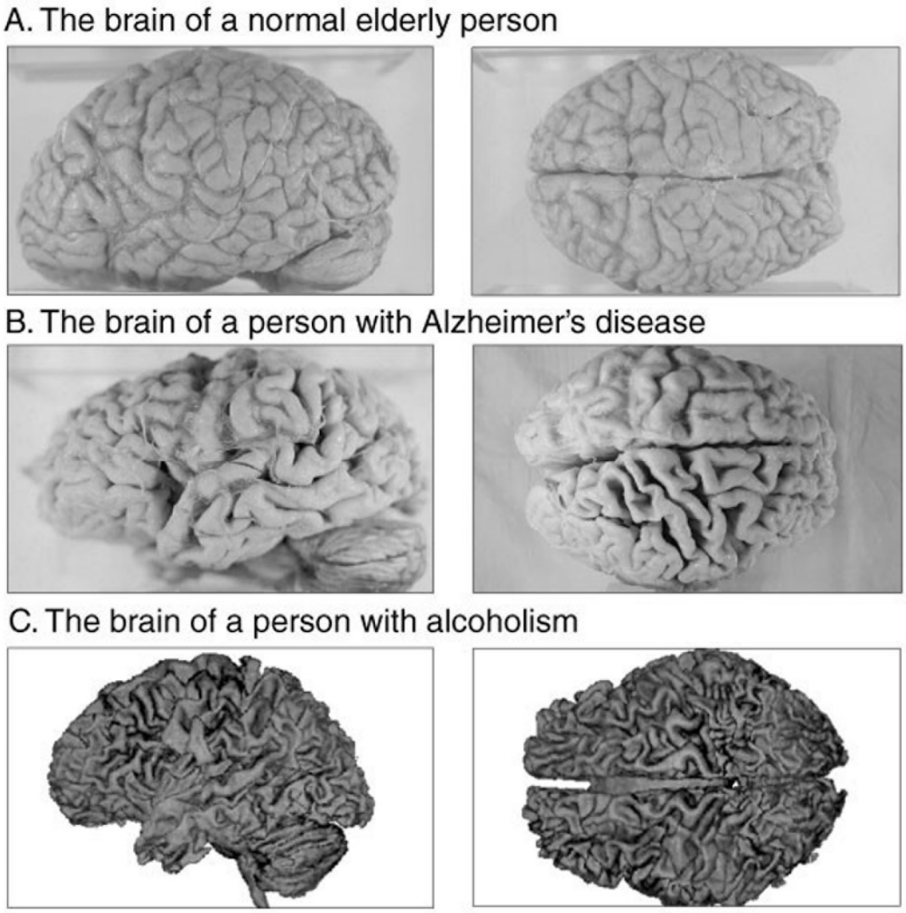
Like pericytes, astrocytes are essential for brain vasculogenesis and BBB maintenance, and for the preservation of tight junction integrity, communicating with the vascular surface by attachments called foot processes or endfeet, and regulating molecular transport across the BBB in both directions [68]. Together, these pericytes, astrocytes, endothelial cells, and the basal lamina cooperate, both structurally and functionally, to form the neurovascular unit with adjacent neurons, tightly linking localized cerebral blood flow with neuronal needs [69].

Finally, unlike capillaries found in most other organs, brain capillaries are characterized by the presence of numerous efflux transporters, principally of the ATP-binding cassette (ABC) transporter family, including P-glycoprotein 1/Multidrug resistance protein 1 (PGP/MDR1/ABCB1), Multidrug resistance-associated protein 1 (MRP1/ABCC1), and Breast Cancer Resistance Protein (BCRP/ABCG2), that eject and prevent the entry of a wide range of molecules, including many lipophilic and amphiphilic ones [30,66,70–76].

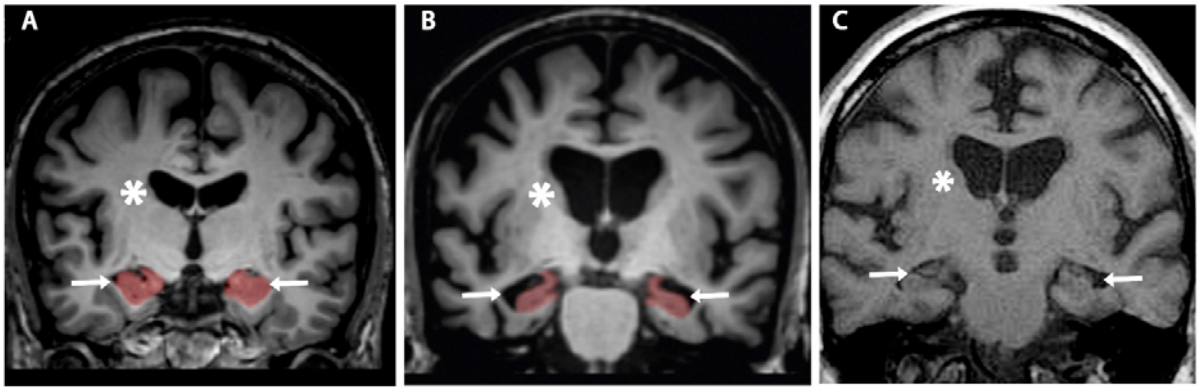
Similarities between AD and alcohol-related brain damage (ARBD)

In order to better understand the lipid invasion model of AD, it is helpful to appreciate the areas of the brain and associated behaviors that are affected by the disease, and how these are both also affected by alcoholism-associated ARBD. In particular, AD and ARBD show a strikingly similar pattern of neurological damage in terms of the specific brain regions affected. In keeping with this pattern of damage, both AD and ARBD sufferers also exhibit similar changes in cognition and behavior, although varying in degree. According to the model, many of these similarities result from shared mechanisms of ethanol and free fatty acids (FFAs) acting on particular receptors within the brain compartment. Appreciating such similarities will help in understanding the effects of external plasma FFA ingress in AD, as predicted by the lipid invasion model.

That AD and ARBD may share common elements in their etiology is apparent from comparisons of brains of individuals with either disease, including direct visual comparisons (see Supplementary Figure 1) and whole brain MRI scans (Supplementary Figure 2) [77–80].



Supplementary Figure 1. Visual comparisons of the brains of (A) normal elderly person; (B) a person with AD and (C) a chronic alcoholic.



Supplementary Figure 2. Coronal plane MRI comparison between brains of (a) a normal person and (b) a typical AD case, and that of (c) a patient with alcohol-related brain damage. White asterisks indicate lateral ventricles, white arrows point to hippocampal regions. Panels A and B are adapted from Teipel S, Drzezga A, Grothe MJ, Barthel H, Chételat G, Schuff N, Skudlarski P, Cavedo E, Frisoni GB, Hoffmann W, Thyrian JR, Fox C, Minoshima S, Sabri O, Fellgiebel A (2015) Multimodal imaging in Alzheimer's disease: validity and usefulness for early detection. *The Lancet Neurology* 14, 1037–1053, with permission from Elsevier. Panel C is reprinted with permission from Du Cane Medical Imaging Ltd/Science Photo Library (2019) Alcoholic dementia, MRI scan (http://www.sciencephoto.com/media/11152/enlarge).

Brain shrinkage

Such comparisons in humans typically reveal pronounced similarities between the two diseases in their pattern of neurodegeneration, including evidence of brain shrinkage [81–87], loss of cortical folding (involving widening of sulci and thinning of gyri) [81,84,88,89], enlargement of ventricles [81,84,88,90–92], (especially the lateral ventricles), together with shrinkage of the hippocampus and entorhinal cortex [81,93–96], and thinning of the corpus callosum [97–102].

On their own, such similarities could be dismissed as the effects of general brain shrinkage and other generalized damage. However, the similarities appear to run much deeper than this, with many of the same regions of the brain principally affected in both cases, especially early on in the disease process. In particular, both AD and ARBD appear to be substantially "frontal" diseases, as evidenced by physiological, behavioral, and sensory studies, as well as imaging studies of both diseases [82,84,103–106].

Basal forebrain damage in AD and ARBD

Measurements of brain volume in humans reveal both diseases to be associated with significant shrinkage in the frontal region of the brain, particularly the prefrontal cortex and basal forebrain regions [84,93,105,107–109], including the cholinergic basal forebrain projection system [93,109–112]. This is backed up by studies in animal models, which suggest that chronic exposure of the brain to ethanol causes a specific pattern of degeneration, including a marked loss of cholinergic neurons, accompanied by a reduction in acetylcholine and choline acetyltransferase activity [93,110,112–114]. Again, this loss of cholinergic neurons is very similar to the loss seen in AD in humans [111,115–117], which is, indeed, why the cholinergic hypothesis was proposed in the 1980s [118].

Related behavioral evidence pointing towards frontal damage as a factor in both diseases includes personality changes [108,119–124], disinhibition and impulsivity [125–130], confabulation [131–136], and a noticeable tendency towards perseverative behavior. This last attribute is readily apparent in individuals with AD [137–141]. Additionally, studies in adult and adolescent rodents chronically exposed to ethanol (but given a nutritionally adequate diet) point towards a similar pattern of behavioral and neurological deficit [142–148], confirming findings in humans [93,121,149–152]. Such behavior may involve deficits in the dopamine system

[153,154], principally centered in the frontal lobe, as well as of the cholinergic system [153]. But, certainly, it is known, from evidence in humans and higher animals, that various forms of motor perseveration and similar behavioral inertias are frequently associated with damage to the frontal lobes [155–158].

There is also strong evidence (mostly clinical) suggesting that, from comparatively early on, both AD and ARBD are associated with olfactory deficits [135,159–165], although not always perceptible to patients themselves [166]. These are also very likely to involve damage to the basal forebrain, including the olfactory bulb [146,160,162,164,167] and cholinergic systems [110,168–170].

More generally, in humans, both forms of dementia are associated with deficits in executive functions [104,126,164,171–174], such as attentional and inhibitory control, working memory and reasoning, i.e., those faculties which allow problem-solving, planning, self-control and the attainment of goals. Clearly there are difficulties separating the immediate effects of drinking alcohol from the long-term neurodegenerative effects of alcoholism, as well as questions as to what degree executive function is under the control of the frontal region. Nevertheless, taken collectively, the evidence presented here points to a strong involvement of frontal lobe degeneration in both ARBD and AD.

Medial temporal lobe damage in AD and ARBD

As well as the above-mentioned areas of the frontal lobe, the MTL is also found to be significantly atrophied in both ARBD and AD [93,96,175–178]. This atrophy is most obvious in the hippocampus but it is also found in immediately adjoining regions, such as the entorhinal cortex and perirhinal cortex as shown by postmortem, clinical, and preclinical studies in humans [93,165,179–186].

Given the well-established link between the hippocampus and memory formation [187], it is unsurprising, therefore, that AD is associated with anterograde amnesia (AA), including severe deficits in spatial memory, as shown in human patients and animal models of AD [188–192]. However, such deficits in ARBD appear to be minor in comparison [178,193], once one has discounted the temporary effects of acute ethanol intoxication [194] and Wernicke-Korsakoff Syndrome (the latter resulting from vitamin B1 deficiency) [193]. Certainly, permanent AA in alcoholics appears to be mainly associated with Korsakoff Syndrome [178,193,195–197], rather

than from chronic exposure to alcohol itself. Moreover, chronic alcohol-associated AA in humans seems to be reversible, unlike AA in AD [193,198–202]. And much of the amnesia and its associated damage appears to result immediately after refraining from drinking, as opposed to persisting with it [93,178].

At first sight, this appears to rule out MTL links between the two diseases, at least in terms of behavior. 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 [203–208], evidence that appears to be mirrored in humans, as well as other primates [204,209–213]. While other areas of the brain are also involved in spatial memory processing, including the prefrontal cortex (at least in rats) [214,215], the association of acute and chronic alcohol exposure with various hippocampal deficits and with impaired spatial learning [95,203,209,216–218] (as seen in both human and animal studies) would seem to suggest a possible linkage mechanism between the two phenomena.

Similarly, so-called “blackout” episodes, commonly associated with drinking large amounts of alcohol over short periods of time [219,220], are obviously defined by and associated with AA [220–222]. These apparently involve both the frontal lobe and hippocampal regions [178,220,223–226]. In particular, chronic alcoholism appears to act synergistically with the normal aging process in humans to exacerbate the memory and other cognitive deficits commonly resulting from aging [85,227–230].

Whatever the reason, the similarities between AD and ARBD just described would seem to provide a clear reason why heavy drinking appears to be associated with a higher risk of developing AD and other dementias [227,231–234]. The fact that people with the *APOE4* allele appear to have a much greater risk of developing dementia as a result of drinking ethanol (including even light-to-moderate drinking), compared with non-carriers of the allele [227,231,235–237], would seem to add further weight to this association.

Astrocytes, FFAs, and the brain

As stated in the main document (section "Fatty acid metabolism"), plasma-resident FFAs are largely excluded from the brain compartment by the BBB. But what happens to FFAs that make it across the BBB? The fact that astrocytic foot processes are estimated to cover as much as 99% of the outside, basolateral/abluminal (i.e. brain-facing) surface of capillary walls [238–240],

strongly suggests they will take up the vast majority of FFAs that have managed to detach from their albumin transport partners and pass through the BBB. And several other pieces of evidence suggest that astrocytes must be central to the subsequent fate of such FFAs.

Recent evidence [241] suggests a key role for astrocytes in protecting neurons from FA-mediated oxidative stress and other forms of lipotoxicity. It appears that they do this in at least two ways. Firstly, they internalize medium-chain-length FFAs, breaking them down by β-oxidation and secreting a proportion as ketone bodies, or the much shorter chain-length FFA butyrate, both of them much less toxic to neurons [241–245]. Secondly, they directly take up FFAs (many of them oxidized) from hyperactive neurons, preventing oxidative stress and other forms of lipotoxic damage, as well as preventing accumulation of lipid droplets within the neuronal cytoplasm [246–248]. These FFAs are then sequestrated within astrocytic lipid droplets and detoxified [246].

This second mechanism appears to involve neuronal exocytosis of ApoE-containing lipoprotein-like lipid particles, and subsequent endocytosis by astrocytes into lipid droplets, where oxidised FFAs are detoxified [246]. Furthermore, neurons in transgenic mice that express the *APOE4* allele appear not to secrete FAs as efficiently as neurons in mice expressing the other *APOE* isoforms, resulting in the greater lipid peroxidation and other forms of lipotoxic damage mentioned above [246].

Collectively, then, astrocytes appear to protect neurons by importing FAs from them and from the immediate external interstitial fluid. These are then utilized by the astrocytes, either for generating ATP or ketone bodies/butyrate (both following β-oxidation), or for storage within lipid droplets (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 [241,249], thus protecting neurons from oxidative stress, mitotoxicity, and lipotoxicity [241,246,250,251]. This may explain why neurons are reported to have relatively poor antioxidative defenses, certainly compared to astrocytes [241,252], 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 [241,253].

So, in answer to the question at the beginning of this section, some, if not all, of the extravasated FFAs appear to be used for cerebral energy purposes, but only after conversion to smaller, safer forms, requiring less oxygen for ATP generation. Most of the other FFAs will be esterified (mainly as TAGs or phospholipids), and then transported onwards within lipoproteins for use by other neighbouring cells. Certainly, given that albumin transport is no longer available to these extravasated FFAs, and given the absence of any obvious alternatives to albumin in the CNS [241,254–256], some form of lipoprotein-mediated transport seems the most obvious alternative.

The causes of BBB disruption in the lipid invasion model

All the major identified risk factors for AD have been shown to disrupt the BBB. However, there are some differences in the mechanism of disruption in each case. One thing common to almost all such factors is that they have been reported, in human, animal, and *in vitro* models, to impair the strength of junctions between BBB endothelial cells, primarily by lowering expression levels of tight junction (TJ) proteins, but also by other means. In particular, BBB expression levels of TJ proteins, including occludin, ZO-1, JAM-A, and various claudins (especially claudin-5) are reported to be substantially reduced in all cases, being associated with Aβ [257–259], aging [28], *APOE4* [260,261], diabetes/obesity [262,263], hypertension [264], smoking [265,266], sleep deprivation [267,268], head injury [269], stress/depression [270,271], and lowered sex hormones [272]. In addition, some of these risk factors have also been reported to be associated with other defects in TJ and adherens junction formation and functioning [28,263,267,273–276], as well as with downregulation of BBB junction-associated cytoskeletal proteins such as vimentin and tubulin [263].

Many of the changes in TJ protein expression may be driven by inflammation and oxidative stress. For instance, vascular endothelial cell exposure to tobacco smoke, which contains high levels of reactive oxygen species (ROS), has been shown to result in a strong pro-inflammatory response [277], characterized by increased levels of inflammatory cytokines, such as IL-6, TNF-α, and IL-1β. Likewise, expression of the last two cytokines is seen to be elevated in a number of brain areas, including the hippocampus, and basal forebrain, following sleep loss [278]. It is known that, in the presence of the last two cytokines at higher than physiological levels, TJ expression is altered detrimentally, leading to an increase in BBB permeability. In the case of

TNF-α, TJs between contiguous endothelial cells are redistributed [279], and in the case of IL-1β, TJ expression levels are reduced. This last is possibly the result of IL-1β-induced suppression of astrocytic production of sonic hedgehog (SHH), a protein that upregulates TJ protein expression via a canonical SHH pathway [280].

Increased BBB permeability may also increase brain exposure to external immune cells and to yet more pro-inflammatory factors [263]. This can lead to a vicious circle, promoting further BBB disruption, similar to what has been reported for diabetes and obesity [263,275]. This vicious circle is also likely to be seen in head injury, chronic sleep deprivation and stress/depression, given that these risk factors are also associated with elevated levels of the same pro-inflammatory cytokines [267,269,270]. Finally, preclinical studies indicate that one of the main ways that estrogen protects against BBB disruption is by reducing production of brain-associated ROS that would otherwise lead to decreased TJ protein expression [272]. Altogether, this suggests that chronic inflammation acting on parts of the BBB will likely result in the latter being chronically permeabilized. Normally, such levels of BBB permeabilization would be seen only rarely and only for short periods, for instance, to allow temporary access to the brain for immune cells.

Another way in which AD-associated risk factors may reduce TJ strength is by reducing numbers of pericytes, or by downregulating their activity. These important BBB component cells have been shown (at least in mice and *in vitro*) to promote junctional strength between ECs [261,281]. Pericytes seem to achieve this TJ strength promotion partly through upregulating endothelial TJ expression, starting with pericyte expression of TGF-β1, which induces phosphorylation of Smad2 and Smad3 in ECs [281]. But, in addition, TJ strengthening appears to also require pericyte suppression of a TJ degradation pathway. This pathway involves the pro-inflammatory cytokine cyclophilin A (CypA), acting via NF-κB on matrix metallopeptidase 9 (MMP-9), which cleaves TJs amongst other substrates [260,261,282].

Interestingly, in this context, pericytes in transgenic mice expressing human *APOE4* (or not expressing any *APOE* isoforms whatsoever) fail to suppress the CypA–NF-κB–MMP-9 pathway just mentioned, such suppression requiring *APOE3* or *APOE2* [260], acting on LRP1 lipoprotein receptors in pericytes. So, it would appear that, as well as by inhibiting TJ expression (as mentioned earlier), *APOE4* may cause BBB disruption by permitting degradation of existing TJs.

Further evidence of an essential role for pericytes in BBB preservation is provided by a study by Montagne and colleagues, which suggests that age-related BBB disruption in the hippocampal region of the brain is associated with substantial loss of pericytes [42]. This loss of pericytes is seen to be worse in individuals with MCI, compared to those without cognitive impairment. In addition, compared to mice with human *APOE3*, those with human *APOE4* show delayed repopulation of pericytes following brain injury, leading to slower BBB repair [261].

The above results would seem to tie in with studies in diabetic mice and *in vitro*, which show that hyperglycemia causes pericyte loss [283,284], and with other studies showing pericyte loss resulting from Aβ [65] or hypertension [285]. Finally, there is strong evidence that pericyte loss or dysfunction may contribute to BBB permeability associated with sleep loss [286]. Thus, pericytes would seem to provide an obvious answer to why a number of seemingly unrelated AD-associated risk factors (aging, Aβ, *APOE4*, brain injury, hypertension, diabetes, and sleep deprivation) are all associated with BBB disruption.

But astrocyte signaling and other astrocytic functions are also important to BBB impermeability [275,287], and it seems likely that some of the above-mentioned risk factors may disrupt the BBB by disrupting normal astrocyte functioning. For instance, it has been reported that, in a rat model of ischemia, diabetic hypoglycemia increases astrocyte cell death and damages the astrocytic end-foot lining around cerebral capillary walls [275], hence hindering rebuilding of the BBB following stroke.

Also, as mentioned earlier in this section, suppression of astrocytic production of SHH by IL-1β may explain how this cytokine lowers TJ expression by ECs. However, it has been shown that IL-1β stimulation of astrocytes also induces local neoangiogenesis, by upregulating HIF-1α, which is the regulatory subunit of the transcription factor HIF-1 [288]. The activated HIF-1 then acts on hypoxic response elements in the promoters of several genes, of which the most important in this context is VEGF-A. Astrocyte-secreted VEGF-A then stimulates EC proliferation and neoangiogenesis. Inevitably, these newly-formed brain capillaries will initially be much more leaky than the established, BBB-associated capillaries, until the complex structural arrangement of ECs, astrocytes, pericytes and basement membrane (BM) of mature BBB is fully established, as well as the required pattern of signaling (especially by pericytes and astrocytes) [287].

Relevantly, in the case of a number of the above-mentioned risk factors, neoangiogenesis is reported to be one of the mechanisms involved in BBB disruption. For instance, it has been reported that Aβ promotes neoangiogenesis and hypervascularity in a Tg2576 AD mouse model (in which Aβ is overexpressed), accompanied by TJ redistribution and BBB leakiness [273]. This is in agreement with findings of increased microvascular density both in human AD brains and in aged human brains without apparent AD-type pathology [289]. Similarly, nicotine has been shown to promote angiogenesis and increased capillary density in *in vitro* models using endothelial cells from human umbilical vein and primary human coronary artery [265]. Again, diabetes is associated with vigorous but dysfunctional angiogenesis and neovascularization [275] and the promotion of EC fenestrations [276]. What role, if any, astrocytes play in the above examples of neoangiogenesis is unclear.

However, it is clear that BBB permeability can be induced by other mechanisms, and it seems likely that some risk factors exploit these also. For instance, it may be that EC dysfunction extends beyond TJ expression. As an example, although hypertension-associated BBB disruption may be largely a product of mechanical stresses, it has been shown in mice that angiotensin II (which raises blood pressure by a number of mechanisms [290]) acting on the angiotensin II type 1 receptor, elicits increases in both paracellular and transcellular BBB permeability [291]. Although the mechanism in both cases is unclear, increased transcellular permeability almost certainly requires changes within ECs. Similarly, obesity, in both diabetics and non-diabetics alike, is associated with other forms of endothelial dysfunction, including reductions in nitric oxide release and endothelium-dependent vasodilation [292].

MMPs (specifically, MMP-9) have been mentioned in connection with TJ degradation, but they are normally associated with degradation of extracellular matrix, including BMs [293]. Amongst other functions, BMs are essential contributors to the integrity of the BBB and similar barriers [287,294]. So, it is interesting that increased MMP expression and activation appears to be critical to barrier leakiness resulting from exposure to Aβ [258,295] and tobacco smoke [266], or resulting from sleep deprivation [267]. Increased MMP-9 expression has also been observed in a mouse hypertensive model, together with decreased expression of collagen-IV, the main collagen component of the BM [264].

However, in apparent contradiction to this finding, prolonged diabetes is commonly associated with BBB BM thickening [296], which would appear to be the result of increased

collagen-IV expression, [275]. There are also a number of reports of similar thickening in human and other models of AD and CAA [297]. So, the picture is complex. The likely explanation for this apparent contradiction is that, paradoxically, BM thickening increases BBB permeability because associated alterations in the physical dimensions of meshwork, and in the electrical charge surrounding gaps between ECs, permit transport of large molecules across the BBB that would normally be excluded [296]. This includes albumin, whose presence in urine is considered an important indicator of diabetic nephropathy and, more generally, of wider microvascular disease.

It seems, then, that the BM thickness must fit within a defined thickness range for BBB impermeability. This strongly suggests that a number of BM-related factors must collectively fall within physiological limits. Most obviously this includes expression levels of component proteins (including collagen-IV, laminin, and other glycoproteins) and BM-degrading enzymes (especially MMPs such as MMP-9) [287].

In summary, while all known AD-associated risk factors are also known to disrupt the BBB, it seems likely that the mechanisms underlying this disruption are unlikely to be identical in all cases. For this reason, attempting to reduce, or even reverse, such disruption as a treatment for AD is likely to be challenging. Reliable methods for identifying the dominant underlying mechanism of disruption would greatly help in this regard. Overall, the balance of evidence suggests that focusing treatment on preserving TJs and pericyte numbers seems most likely to yield the best results, both in preserving BBB integrity and in preventing AD progression.

Curtin explanation of BBB disruption in AD

As mentioned in the main document, and proposed by the Curtin University group, it is now clear from studies in animals and humans, that Aβ has an important function as a regulatory apolipoprotein, being highly expressed in both the liver and small intestine, and associated with triglyceride-rich lipoproteins of similar origin [12,298,299]. In absorptive enterocytes, Aβ is seen to collocate with $ApoB_{48}$, forming chylomicrons, with enterocytic levels of Aβ, and plasma levels of Aβ-associated chylomicrons both increasing in response to a diet high in saturated fats [298,300].

In a standard transgenic mouse model of AD in which Aβ is overproduced, disease progression and onset were seen to be strongly correlated with rates of secretion into the blood

of TAG-rich, Aβ-associated lipoproteins and with their subsequent plasma levels [12]. Such overproduction leads to BBB disruption, irrespective of whether it results from dietary causes or from direct Aβ overexpression, [12,299,300].

This helps explain, among other things, why amyloid plaques in human brains show immunoreactivity for ApoB, similar to that seen in the brains of AD mouse models [12,301]. For the reasons stated in the main document (sections "Evidence of a role for lipids in AD" and "Fatty acid metabolism"), such ApoB deposition is generally believed to be only possible if the BBB has been disrupted in some way, as well as being consistent with the premise that invading lipoproteins, over-rich in lipids (especially cholesterol) as compared with CNS lipoproteins, are primary actors in endosomal pathology and amyloid plaque formation (as described in the main document, section "AD-specific consequences of brain exposure to external cholesterol").

This suggests a way in which the origins of both familial and late-onset forms of AD could be linked through excess plasma levels of Aβ-laden, TAG-rich chylomicrons. In the case of familial AD (FAD), overproduction of Aβ would lead to excess chylomicron formation. In the case of LOAD, excess chylomicron levels would result from high levels of saturated fat in the diet. In both cases these excess plasma chylomicron levels will lead to BBB disruption, and (according to the lipid invasion model) to the characteristic lipid-driven neurodegenerative effects outlined in the main document.

FFA-mediated changes to brain bioenergetics and oxidative stress

The bioenergetic shift observed in AD, away from glucose/lactate-dominated energy metabolism and towards ketone metabolism, is explained by the lipid invasion model by the fact that external FFA invasion will increase local FFA availability in brain interstitial fluids well above normal levels. In the presence of excess FA, *in vitro* studies have shown that astrocytes (like hepatocytes) prefer these to glucose as a primary metabolic fuel (possibly as a protective response), subsequently β-oxidizing them to meet their own energy needs, or producing ketone bodies from them [242,302–304]. Astrocytes may take up some of these invading FFAs directly, or they may be taken up indirectly from neurons, where some may have been rendered toxic through oxidative stress [246,305].

As astrocytes only account for a relatively small proportion of brain energy requirements (typically 5-15% [253]), it seems likely that they will convert the majority of excess FFAs they

take up into ketone bodies, rather than acetyl-CoA. (This will primarily be for neuronal use, rather than for meeting their own energy needs.) However, some FAs will likely remain stored within lipid droplets [246], which may account for some of the excessive lipid aggregates seen in AD, as described by Alois Alzheimer and contemporaries, and mentioned in the main document (section "The lipid factor identified by Alois Alzheimer") [306,307].

Since it is reasonably well-established that ketone body metabolism can inhibit glycolysis [308–312], it can be expected that, overall, greater ketone body availability will tend to push local brain energetics away from glucose/lactate-dominated energy metabolism towards ketone metabolism. This will tend to decrease relative levels of glycolysis and increase relative levels of oxidative phosphorylation. Among other things, this would explain the decreases in the expression of glycolytic enzymes, and in the activity of the pyruvate dehydrogenase complex seen in AD [313]. In this way, the lipid invasion model can explain the greatly reduced cerebral glucose utilization (~45%) seen in early LOAD. This reduction is considerably less than the observed reduction in cerebral oxygen usage (less than 20%), which might largely be explained by reduced cerebral blood flow [314].

Although faulty mitochondrial bioenergetics do not drive the above-mentioned ketogenic shift in the model, they are still predicted to take place. Since neurons appear to have a minimal ability for β-oxidation [241,315,316], and a very restricted ability to sequester excess lipids in lipid droplets [246], mitochondria within them are at particular risk of exposure to internalised FFAs in intact form, leading to mitochondrial pathology [241]. Among other things, such direct mitochondrial FFA exposure leads to increased proton conductance, and therefore reduced membrane potential at the inner mitochondrial membrane [317]. This in turn leads to a collapse of the electrochemical proton gradient, uncoupling of oxidative phosphorylation, and reduction in the rate of ATP production and in the calcium ion retention capacity of mitochondria [241,318].

Also, binding of FFAs to electron transport chain (ETC) complexes interferes with electron transport, generating increased superoxide production by the ETC [318,319]. Superoxide generates ROS (hydrogen peroxide, the hydroxyl radical, and peroxynitrite), and, given that neurons have poor anti-oxidative defenses [241], these in turn seem certain to cause severe lipid peroxidation, lipotoxicity, and oxidative stress. They will also lead to opening of the permeability transition pore [317], resulting in release of Ca2+ ions and pro-apoptotic factors,

such as cytochrome c, AIF, and Smac-Diablo [241,320–322]. As well as glucose hypometabolism, these above phenomena are all commonly associated with AD [314,323–326].

Extrasynaptic GABAARs and neurogenesis

In the section "Extrasynaptic GABAARs and neurogenesis" of the main text, it was argued that FFAs, like ethanol, act on GABAARs in immature neurons to inhibit neurogenesis in the SGZ and SVZ, two neurogenetic niches in the brain, involved in memory formation and olfaction, respectively. In this Supplementary section, the possible underlying mechanisms are described.

A complicating factor here is that, in immature neurons, the chloride gradient is reported to be in the reverse direction to that of their mature counterparts [327,328]. That is to say, chloride ions are held internally in excess of their external levels. If so, GABA binding to GABAARs could reasonably be expected to activate such precursor neurons and, by extension, one would expect anesthetic agents (and other positive allosteric modulators) to overactivate them. A further consideration is that such precursor cells initially exhibit few synapses, with most GABAARs having a subunit composition typical of extrasynaptic GABAARs in mature neurons [329–331]. Synapses only tend to emerge later as the neuronal precursors mature and become integrated (synaptically and otherwise) with the existing network [332–334]. So GABAARs in these cells tend to have a high affinity for ambient GABA, and one would expect the dominant response to GABA stimulation to be tonic activation [330,334].

Against this, recent research (using a novel optogenetic approach in a mouse knock-in line) has brought into question the current orthodoxy concerning GABA activation of immature neurons [335,336], concluding that, overall, GABA action on the neonatal brain is inhibitory. If confirmed, and also found to be true for adult neurogenic regions, then ethanol-induced deficits in neurogenesis can be simply explained as a result of excess inhibition.

However, another mechanism (consistent with a reversed chloride gradient in immature neurons) may explain ethanol-induced neurogenetic deficits in the SGZ and SVZ - GABA-mediated feedback inhibition. It has become clear (principally from studies in rodents) that non-synaptic paracrine GABA signaling provides information on population size to control proliferation and migration of neural progenitor cells in the SVZ [331,332,337,338]. Specifically, adult SVZ neuroblasts synthesize 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 [339]. 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 increased proliferation, whereas positive allosteric modulators decreased it.

That accords with the findings of a previously-mentioned study in brain slices of transgenic mice, by Liu and colleagues. This study showed that, at least in GFAP-expressing neural progenitor cells in the SVZ, GABAAR activation limits progression through the cell cycle [337]. It also suggests that, at least in the rodent SVZ, adult neurogenesis is regulated by the same mechanisms that govern embryonic neurogenesis, where, for instance, GABA is seen to direct neuroblast migration. GABA does this by stimulating random mobility, through promoting elevation of cytosolic Ca2+ levels [332,340] in a way similar to that seen in adult neurogenesis [341]. While some related studies in transgenic mice have shown that such effects appear to promote neuronal fate selection [342], the overall impression is that GABA stimulation also seems to limit proliferation [339,340]. However, doubts have subsequently arisen as to whether such tonic GABA-mediated depolarization is sufficient to open voltage-gated calcium channels enough to permit substantial increases in intracellular calcium in the way proposed. So, other explanations are required [338].

An alternative explanation (again from transgenic mice) is that an epigenetic mechanism, involving histone H2AX phosphorylation following sustained GABAAR activation by GABA, inhibits DNA synthesis and cell cycle progression, and therefore proliferation of adult neural stem cells [343]. It is not clear that this mechanism also applies to SGZ neurogenesis but, if so, it could explain why GABAergic stimulation is similarly associated with quiescence of adult precursor cells in this niche [330,331,344], at least in rodents.

Generally, whatever the underlying mechanism, the evidence suggests that GABA stimulation inhibits neurogenesis. Any positive allosteric modifiers of GABAARs will increase this inhibition.

The role of the β-secretase-induced C-terminal fragment (βCTF) in AD-associated endosomal-lysosomal pathology

β-secretase-induced cleavage of AβPP, resulting in the C-terminal fragment βCTF, is known to take place in early endosomes (Figs. 1, 2c, 2d) [345,346]. It appears to be crucial to AD-associated endosomal-lysosomal pathology, since inhibition of β–secretase (or the substitution of AβPP by constructs lacking β–secretase cleavage sites) restores normal endosomal-lysosomal behavior in AβPP-overexpressing human fibroblasts [347]. Furthermore, treatments, or presenilin mutations, that increase levels of Aβ without increasing levels of βCTF do not result in endosomal-lysosomal pathology [345,347]. This is in line with other evidence that the endosomal abnormalities seen in a mouse model of Down syndrome do not appear to be associated with abnormally high levels of Aβ [348–350]. Meanwhile, inhibition of γ-secretase, which leads to increased levels of βCTF at the expense of Aβ, induces endosome-lysosomal pathology in previously normal human fibroblasts [347].

In vitro studies, using human and other cell lines, indicate that the underlying reason for this observed pathology may 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 (Fig. 2i) [351–353]. This stabilizes the monomeric GTPase protein Rab5 in its GTP-bound, activated form, and therefore amplifies the Rab5 signaling associated with early endosomes [354–356], leading in turn to the enlarged endosomes seen in both AD and DS [353,357].

The role of Aβ in the lipid invasion model

The lipid invasion model gives Aβ a much more ambiguous role than it does in the amyloid cascade hypothesis. In the latter, excess Aβ is central to disease progression, being both necessary and sufficient for it. In the lipid invasion model excess Aβ is only necessary and sufficient for disease progression in the case of FAD, whereas in the case of LOAD Aβ is sufficient but not necessary. Excess Aβ is only one of a number of AD risk factors that can disrupt the BBB. Many other factors, such as hypertension and brain trauma, can also damage the BBB, all leading to lipid invasion and subsequent disease progression. Also, unlike in FAD, excess Aβ levels in LOAD result purely from exposure of neurons (and other brain cells) to

excess cholesterol within invading LDL and other large ApoB-associated lipoproteins, not from genetic abnormalities affecting AβPP processing, or other reasons.

This implies that Aβ in LOAD has a more downstream role in disease progression, more driven than driving. This suggests that, despite apparent close similarities, FAD and LOAD are in many ways very different diseases that need different treatments.

The role of APOE4 in the lipid invasion model

As well as accounting for Aβ, any model of AD must explain the importance of *APOE4* as a risk factor, being one of the strongest such factors for LOAD [358]. This is explained by *APOE4* having many roles in the lipid invasion model. Most obviously, the BBB is exposed to higher levels of Aβ in *APOE4* carriers because *APOE4* is associated with slower efflux of Aβ, together with impaired degradation, increased deposition and aggregation of this molecule. As a result, the BBB in *APOE4* carriers is more prone to Aβ-mediated damage. This explains why *APOE4* is also an important risk factor for cerebral amyloid angiopathy (CAA) [359], and tends to be associated with more severe forms of CAA, both with and without AD [360–362], and with a higher risk of cerebral microbleeds [363].

However, as explained above, *APOE4* appears to damage the BBB in other ways, being associated with impaired expression and function of TJ proteins between BBB endothelial cells. Also, pericytes in *APOE4* carriers fail to suppress an inflammatory pathway (involving NF-κB and MMP-9) that degrades TJs and basement membrane within the BBB, both critical to its structural integrity. Similarly, repopulation of BBB pericytes, following loss as a result of brain injury or aging, has been shown to be substantially delayed in those with *APOE4*, leading to slower BBB repair.

So, *APOE4* can be associated with increased BBB disruption, which means that it will typically result in higher levels of invading external lipoproteins and FFAs into the brain, according to the model. Furthermore, *APOE4* will very likely exacerbate the effects of such lipid invasion. As explained in the main document (section "Lipids as drivers of all AD pathologies"), *APOE4* is associated with lipid accumulation in glial cells, including astrocytes, and this is likely to extend to neurons. This is because, as mentioned earlier, astrocytes take up FFAs (including toxic peroxidated forms) from neurons. This involves neuronal secretion of these FFAs within ApoE-containing lipoprotein-like particles [246]. However, it has been shown that

transgenic mice expressing the *APOE4* allele appear to secrete such FAs less efficiently than those expressing other *APOE* alleles [246]. As well as leading to lipid accumulation, this means that they are likely to be at greater risk from lipid peroxidation and other forms of lipotoxic damage, on being exposed to external FFAs. Such lipid accumulation and anomalies in brain cells, are of course, hallmarks of AD that were reported by Alois Alzheimer's in his first descriptions of the disease.

Extensive research has revealed that *APOE4* exacerbates many other AD-associated pathologies, including tau hyperphosphorylation, mitochondrial dysfunction, and microglia-mediated neuroinflammation [364]. Many of these *APOE4*-mediated effects are also likely to exacerbate the effects of external lipid invasion, and thus to be directly relevant to the model.

How the model may explain apparent gender differences in AD risk

Many studies show that women appear to be at greater risk of developing AD, even after allowing for their greater longevity [18,365], although some studies contradict this [366]. If the former findings are correct, then the lipid invasion model can explain this in terms of greater vulnerability of the BBB in aging women following the menopause.

Studies in animals and *in vitro* models provide plentiful evidence that estrogen, progesterone, and testosterone help protect the BBB [272,367,368], and can attenuate damage to it [369–372]. However, following menopause, women suffer a very sharp decline in serum levels of female sex hormones going into old age, as compared to the more gradual and limited decline in testosterone seen in males over the same age range. As a result, the BBB in females may lose the protective effects of sex hormones at a greater rate than in males.

How the model explains the exponential increase in age-specific AD incidence

One important test for any model of AD is how well it explains the exponential increase in AD incidence with age. Typically, epidemiological studies find that AD incidence rates double approximately every 5 to 6 years, certainly from the age of 65 onwards [373]. In fact, there is nothing unique about AD in this respect. Most common aging-associated diseases show an exponential increase in incidence and prevalence with age, over a large proportion, if not all, of the later age range [374]. Taken together, they help to explain why human mortality also increases at an exponential rate with age, along with other animal species, a phenomenon known

as Gompertz Law [375]. Included among such diseases are stroke [376] and other cardiovascular events [377–379], most of which are considered risk factors for AD [380–383], as well as being associated with BBB damage [384,385].

So, the lipid invasion model can explain the exponential age-specific increase in AD incidence in terms of a corresponding increase in the age-specific risk of BBB damage and subsequent lipid invasion. However, no cardiovascular events show as fast a rate of increase in age-specific incidence as AD. For instance, stroke rates only double every 10 years after age 55 [376]. It may be that the aggregate damage inflicted on the BBB by the various factors listed earlier, such as *APOE4*, hypertension, diabetes, and smoking, is not merely additive in nature but in some ways synergistic. But there is currently no evidence in support of such synergism.

Nevertheless, in general terms, it is noticeable that the incidence rate for AD after the age of 60 broadly mirrors the demographic mortality rate [375]. This may be in part because the human brain is undergoing one or more aging-associated processes common to other bodily organs and tissues. If so, a prime candidate would be mitochondrial dysfunction, given that mitochondrial energy metabolism is critical to all parts of the body, not least the brain. Such dysfunction is characterized by the buildup of mtDNA mutations, a decline in respiratory chain efficiency and increased oxidative stress, amongst other phenomena [386,387].

In fact, a number of models of AD progression allocate a central role for such mitochondrial dysfunction [313,388,389]. Commonly, these explain AD's exponential age-specific increase in terms of some form of "mitochondrial death spiral", in which dysfunctional mitochondria cause other healthy mitochondria to become dysfunctional themselves, by oxidative stress, depriving them of nutrients [388], or by some other mechanism.

However, if we assume that LOAD is occurring within a brain that is, along with other organs in the body, subject to some underlying aging processes exhibiting exponential age-specific rates of incidence, it does not seem to require LOAD-associated processes to show similar rates of incidence. But certainly, more research is needed on this aspect of the model.

How the model explains the inverse correlation between AD and cancer

Another important test for any model of AD is how well it explains the inverse comorbidity seen between AD and cancer. That is to say, patients with AD show a reduced risk of cancer, with cancer survivors having a lower risk of developing AD [390]. In fact, this comorbidity

appears to be far less straightforward than just presented, in that it would seem to extend to a range of other CNS disorders, including Huntington's disease, multiple sclerosis, Parkinson's disease, and schizophrenia [391–393], while the reduced cancer risk in AD patients seems to be most pronounced in a narrow range of cancers. This includes smoking-related cancers [394,395] and non-melanoma skin cancer.

Such a complex relationship is extremely challenging to explain within a single model of AD. Among the more credible explanations is the Inverse Warburg hypothesis, which views AD as a product of age-related mitochondrial dysfunction, tending to push energy production away from glycolysis towards oxidative phosphorylation, whereas cancer tends to push it in the opposite direction [388]. However, this does not satisfactorily explain why certain cancers, as explained above, seem to be particularly disadvantaged by this bioenergetic shift, or why this inverse comorbidity also extends to other CNS disorders.

Currently the best current explanation for this complex phenomenon would seem to be that certain genes and biological pathways that increase the risk of getting AD (or the other mentioned CNS disorders) have the opposite effect on certain cancers [392,394]. Most obviously, carrying *APOE4* has been shown to substantially reduce the risk of getting prostate cancer [396], as compared to carrying *APOE3*, and to enhance the response to immunotherapy, and increase survival, in melanoma [397]. Similarly, AD is characterized by increased apoptosis and inhibition of cell proliferation, whereas cancer is characterized by the opposite properties. Clearly, this puzzling phenomenon requires deeper investigation. *APOE4* aside, the lipid invasion model cannot currently be said to provide a particularly convincing explanation for inverse comorbidity. This is an aspect of the model that needs further investigation.

Further possible implications of the model with respect to GABAARs

One specific proposal of the lipid invasion model, that invading FFAs act on extrasynaptic GABAARs to cause AA (as well as hippocampal and olfactory bulb shrinkage), might be considered the most speculative. Certainly, the exact role of the GABAAR α5 subunit in learning is complicated, and appears to be different in young and aged animals [398–400], in terms of its specific role in the formation of new memories, and in cognition. Nor is the role of hippocampal neurogenesis in the formation of new memories at all well-understood [401,402].

Clearly a lot more work needs to be done to establish whether FFAs have any such anesthetic role in AD.

But if they do, it may help to explain why general anesthesia is considered a potential risk factor for AD (and dementia in general) among elderly patients [403–409], and can cause a marked deterioration in those already affected with AD [408,410–412].

If FFAs do have an anesthetic role in AD, it 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 clarified, it is generally agreed that, in vertebrates, the neurons of the suprachiasmatic nucleus (SCN) provide a central role [413–416]. Furthermore, within this nucleus it is clear that GABAARs play a critical role, including in their extrasynaptic form [415–419], with some estimates suggesting that over 90% of SCN neurons express and respond to GABA [419].

A number of (*in vitro* and *in vivo* animal) studies have shown that ethanol modulates circadian clock regulation [420–423], including by its action at low concentrations on extrasynaptic GABAARs within the SCN [417]. So, by acting on such extrasynaptic GABAARs to disrupt their normal behavior, FFAs might also be disturbing normal circadian rhythms. This would occur by similar mechanisms to that by which FFAs are proposed, in the lipid invasion model, to cause tonic inhibition and disrupt neurogenesis in the SGZ and SVZ.

Of course, this disruption of the body clock in AD is primarily inferred from behavioral abnormalities, particularly in regard to sleep patterns. Therefore, 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, such sleep disturbances seem to be apparent very early in AD progression [23], when amnesia and other AD-associated deficits are only beginning to be noticeable. So, it seems reasonable to conclude that what is being seen has a physiological as well as a purely psychological basis, and it would be interesting to investigate this further.

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