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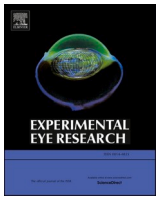

Review

Increased molar ratio of free fatty acids to albumin in blood as cause and early biomarker for the development of cataracts and Alzheimer's disease

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ABSTRACT

Cataracts and Alzheimer's disease (AD) are closely linked and are associated with aging and with systemic diseases that increase the molar ratio of free fatty acids to albumin (mFAR) in the blood. From the results of our earlier studies on the development of senile cataracts and from results recently published in the literature on the pathogenesis of Alzheimer's disease, we suggest that there is a common lipotoxic cascade for both diseases, explaining the strong connection between aging, an elevated mFAR in the blood, cataract formation, and AD.

Long-chain free fatty acids (FFA) are transported in the blood as FFA/albumin complexes. In young people, vascular albumin barriers in the eyes and brain, very similar in their structure and effect, reduce the FFA/albumin complex concentration from around 650 μmol/l in the blood to 1–3 μmol/l in the aqueous humour of the eyes as well as in the cerebrospinal fluid of the brain. At such low concentrations the fatty acid uptake of the target cells – lens epithelial and brain cells – rises with increasing FFA/albumin complex concentrations, especially when the fatty acid load of albumin molecules is mFAR>1. At higher albumin concentrations, for instance in blood plasma or the interstitial tissue spaces, the fatty acid uptake of the target cells becomes increasingly independent of the FFA/albumin complex concentration and is mainly a function of the mFAR (Richieri et al., 1993).

In the blood plasma of young people, the mFAR is normally below 1.0. In people over 40 years old, aging increases the mFAR by decreasing the plasma concentration of albumin and enhancing the plasma concentrations of FFA. The increase in the mFAR in association with C6-unsaturated FFA are risk factors for the vascular albumin barriers (Hennig et al., 1984). Damage to the vascular albumin barrier in the eyes and brain increases the concentration of FFA/albumin complex in the aqueous humour as well as in the cerebrospinal fluid, leading to mitochondrial dysfunction and the death of lens epithelial and brain cells, the development of cataracts, and AD. An age-dependent increase in the concentration of FFA/albumin complex has been found in the aqueous humour of 177 cataract patients, correlating with the mitochondria-mediated apoptotic death of lens epithelial cells, lens opacification and cataracts (Iwig et al., 2004). Mitochondrial dysfunction is also an early crucial event in Alzheimer's pathology, closely connected with the generation of amyloid beta peptides (Leuner et al., 2012). Very recently, amyloid beta production has also been confirmed in the lenses of Alzheimer's patients, causing cataracts (Moncaster et al., 2022). In view of this, we propose that there is a common lipotoxic cascade for senile cataract formation and senile AD, initiated by aging and/or systemic diseases, leading to an mFAR>1 in the blood.

1. Introduction

The aging eye lens has been characterised "as an aging paradigm par excellence" (Quinlan and Giblin, 2022). There is a close connection between senile lens cataracts and the sporadic late-onset AD. Older people with newly diagnosed cataracts have a 1.43-fold greater risk of developing AD (Lai et al., 2014). Goldstein et al. (2003) were among the first to demonstrate cytosolic amyloid-β depositions in the lenses of patients with AD. Recently, Moncaster et al. (2022) confirmed that in patients with AD the Aβ-amyloidopathy occurs in the brain as well as in lenses, causing supranuclear cataracts. Cross-sequence interactions between Aβ-peptides and peptides from α-crystallin may enhance protein aggregation processes in the aging lenses of patients with AD (Schimansky and Yadav, 2021). Cataracts emerge decades before the clinical symptoms of AD. Therefore, techniques have been developed for the

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Abbreviations

Aβ	amyloid beta
AD	Alzheimer's disease
APP	amyloid precursor protein
BSA	bovine serum albumin
FFA	free fatty acids
FFA_{H2O}	free fatty acids in the aqueous phase
GM-CSF	granulocyte macrophage colony-stimulator factor
HBS	HEPES buffered solution
HSA	human serum albumin
ICAM-1	intracellular adhesion molecule
MEM	minimal essential medium
mFAR	molar free fatty acids to albumin ratio
SEM	scanning electron microscopy
TEM	transmission electron microscopy
TNF-α	tumour necrosis factor alpha
VCAM-1	vascular cell adhesion molecule

early detection of Alzheimer's biomarkers in lenses. Advantages and limitations of the methods have been thoroughly reviewed by Fereshetian et al. (2021).

Various systemic factors such as aging, low plasma albumin, high plasma concentrations of free fatty acids (FFA), preeclampsia, cigarette smoking, obesity, diabetes mellitus, and others are risk factors for both senile cataracts and senile AD. A common feature of all these risk factors is that they raise the molar ratio of free fatty acids to albumin (mFAR) in the blood. In earlier papers (Glaesser et al., 1996; Trimborn et al., 2000; Iwig et al., 2004) we found that an mFAR>1 strongly raises the cellular uptake of free fatty acids, causing mitochondrial dysfunction and the apoptotic death of lens cells. Leuner et al. (2012) have proposed that mitochondrial dysfunction, which is known to increase with age, may be the trigger for Aβ-production and sporadic AD. Nevertheless, the real trigger for sporadic AD remains elusive (Swerdlow, 2018; Wang et al., 2020).

Here, we review results from the literature revealing how the age-dependent chronic increase of mFAR>1 in the blood causes an increase in the cellular uptake of FFA, mitochondrial dysfunction, albumin barrier impairment of vascular cells in the eyes and brain, cataract formation, and late-onset AD.

2. The increased cellular uptake of unsaturated free fatty acids activates the mitochondria-mediated apoptotic pathway in lens epithelial cells

2.1. Apoptotic death of lens epithelial cells

In both bovine (Glaesser et al., 1996) and human (Iwig et al., 2004) lens epithelial cells the apoptotic programme is initiated specifically by the increased uptake of unsaturated, cis-configured, free fatty acids (Fig. 1). Apoptotic cell death has been described as a cellular suicide programme, characterised by bleb formation, cell shrinkage, nuclear condensation, and mitochondrial dysfunction, whereas the plasma membrane integrity is maintained (Thompson, 1995). Bleb formation and cell shrinkage are early signs of lens cell apoptosis (Fig. 2). Studies with ^{14}C-linoleic acid reveal strong correlations between an increased cellular uptake of the unsaturated free fatty acid and bleb formation, cell shrinkage, and cell nucleus condensation. Furthermore, at high uptake rates, ^{14}C-linoleic acid molecules accumulate at definite sites, colocalised with emerging blebs (Trimborn et al., 2000). Blebs are formed when more unsaturated free fatty acids are imported than are utilised. Bleb formation and cell shrinkage are fully reversible. However, with the continuous availability of free fatty acids cells keep accumulating fatty acid molecules up to the stage of lipotoxic suicide (Fig. 2c).

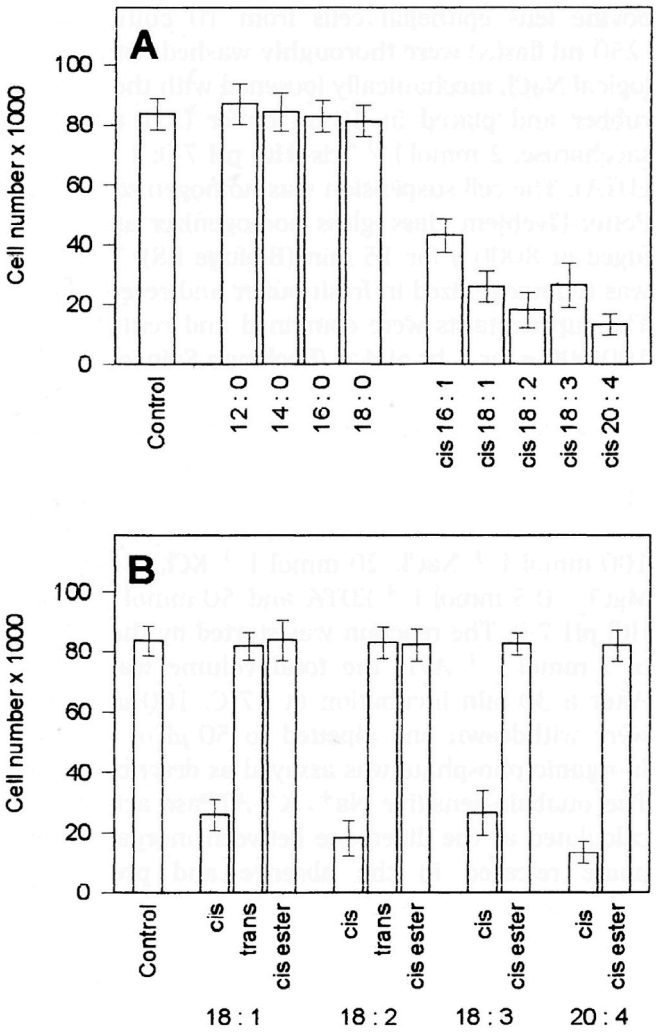

Fig. 1. Cytotoxic effects of unsaturated free fatty acids to subcultured bovine lens epithelial cells, evaluated with the cell detachment test. A) Physiologically occurring fatty acids. B) cis-, trans-, and esterified unsaturated fatty acids. 100 000 subcultured bovine lens epithelial cells were seeded per Petri-dish and precultured for 24 h in MEM plus 10% foetal calf serum. After extensive washing with HBS further culturing was done with HBS plus 10 μmol/l effector for 5 h. Thereafter, the attached vital cells were counted (ordinate) (Nguyen et al., 2000).

2.2. Mitochondrial dysfunction

The first effect after adding linoleic acid to cultured lens epithelial cells is an increase in the intracellular concentration of free calcium ions. As a slight calcium increase also occurs in a calcium-free medium, it is assumed that mitochondria and the endoplasmic reticulum, as intracellular calcium stores, are affected first, whereas the integrity of the plasma membrane appears to be maintained (Fig. 3). This, in turn, may cause a calcium-induced calcium influx (Mene et al., 1996), accompanied by cell shrinkage and cell nucleus condensation (Glanz et al., 1997). The specification of the free fatty acid cytotoxicity to lens epithelial cells, ascertained by the cell detachment test (Fig. 1), has been confirmed using the neutral red cytotoxicity assay (Iwig et al., 2004). The latter has been widely used as a rapid and very sensitive indicator of impaired mitochondrial ATP-production (Allison and Young, 1969; Skehan, 1995). On the other hand, linoleic acid does not interfere with the plasma membrane bound Na^+ K^+-ATPase or the ecto-ATPase

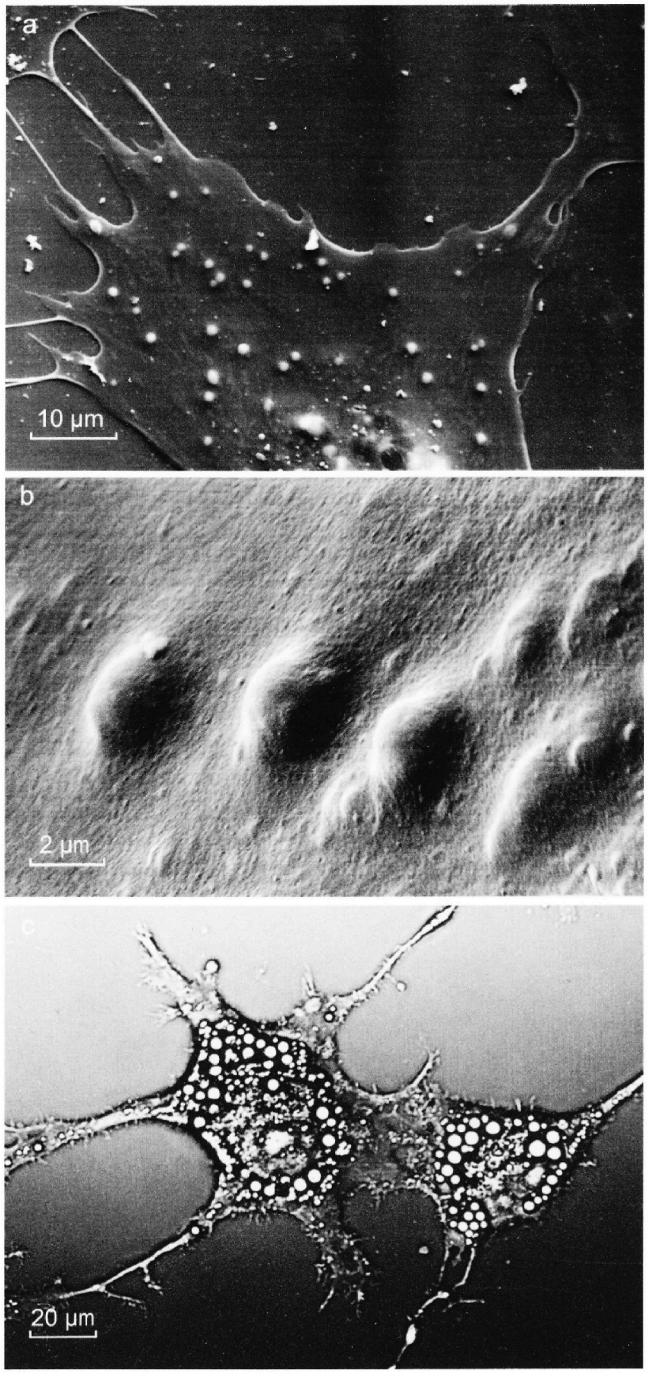

Fig. 2. Linoleic acid induced bleb formation and lipotoxic suicide of cultured lens epithelial cells. a) Bovine lens cells 1 h in HBS with 5 µmol/l linoleic acid; SEM 1150 x; b) Like a) with 10 µmol/l linoleic acid, SEM 5150 x (Glaesser et al., 1996). c) Human lens cells 8 h in MEM with 20 µmol/l linoleic acid and 1 µmol/l human serum albumin; dying cells containing bright spots, looking like lipid filled vesicles. SEM 900 x (Iwig et al., 2004).

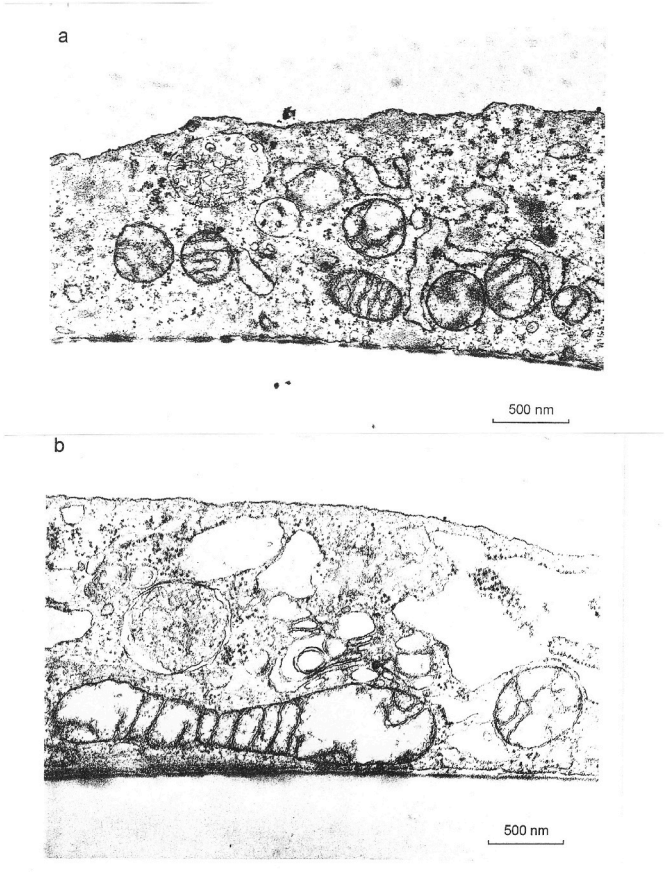

Fig. 3. Linoleic acid caused damage of mitochondria. Subcultured epithelial cells of bovine lenses, cultured on agarose coated with collagen; TEM 35600 x. a) Control, 24 h in MEM plus 2% foetal calf serum. b) 24 h in MEM plus 2% foetal calf serum, plus 30 µmol/l linoleic acid (mFAR approximately 2.5).

activities of the lens epithelial cells (Nguyen et al., 2000).

3. Crucial significance of the molar ratio of free fatty acids to albumin (mFAR) for the cellular uptake and cytotoxicity of long-chain free fatty acids (FFA)

3.1. FFA, albumin molecules and FFA/albumin complexes

In human blood, a fraction of unesterified, so-called free fatty acids circulate in a concentration normally below 600 µmol/l. In healthy, non-obese adults, the concentration of circulating FFA may vary between 160 and 520 µmol/l, with highest values occurring in the fasting period between midnight and early in the morning (Reaven et al., 1988). In blood, long-chain FFA are only free in the sense that they are not esterified, but most of them are non-covalently adhered by ionic and hydrophobic forces to albumin molecules, which serve as water-soluble carriers for the relatively water-insoluble long-chain FFA.

Human serum albumin (HSA) and bovine serum albumin (BSA) molecules are quite similar in terms of their amino acid sequences and ligand binding. Calculations from the amino acid composition of HSA with 585 amino acids and BSA with 583 amino acids reveal masses of 66438 Da and 66411 Da respectively. With respect to some covalently bound glycosyl residues, a figure of 66500 Da seems to be a reasonable recommendation for both albumins (Peters, 1996) to calculate the mFAR. Albumin molecules have multiple fatty acid binding sites with a range of affinities. In their equilibrium studies, Richieri et al. (1993) identified six definite binding sites with HSA to form FFA/albumin complexes. However, up to twelve fatty acid molecules bound per one

HSA molecule have also been reported (Ashbrook et al., 1975).

3.2. The molar ratio of free fatty acids to albumin (mFAR)

The mFAR gives the number of free fatty acid molecules, non-covalently adhered to one molecule of albumin. The average albumin concentration in the blood of healthy human adults is 42.0 ± 3.5 g/l (632 ± 53 μmol/l), ranging from 35 to 50 g/l (526–752 μmol/l) (Peters, 1996). The concentration of long-chain FFA may vary between around 100 and 600 μmol/l. Thus, the mFAR in the blood of a healthy human adult is normally below 1.0. For instance, Pickart (1983) found a ratio of 0.775 ± 0.061 in a group of 26 healthy males, aged 20–29 years.

3.3. The physiologically active free fatty acid fraction (FFA_{H2O})

When long-chain FFA are added to albumin in water solution, most of the fatty acid molecules are bound to albumin to form FFA/albumin complexes. However, according to their aqueous solubility, a small fraction of less than 0.1% of the fatty acids remains unbound or dissociates from albumin and exists in monomeric form in the aqueous phase. Although a direct interaction of the FFA/albumin complexes with the cell membranes of the target cells has been implicated in the cellular fatty acid uptake (Trigatti and Gerber, 1995), it is generally assumed that the major part of the cellular fatty acid uptake is realised via the small FFA_{H2O}-fraction. This conclusion coincides with numerous in vitro studies showing that increasing FFA_{H2O}-levels affect a large variety of physiologic cellular functions (Richieri et al., 1993).

3.4. Albumin concentration, mFAR, FFA_{H2O} and cellular uptake of FFA (Fig. 4)

Richieri et al. (1993) measured the concentration of the FFA_{H2O}-fraction (ordinate in Fig. 4a: FFA ≅ FFA_{H2O}) as a function of the albumin concentration for a fixed mFAR of 2.6; 3.5; 4.8; 5.5. At albumin concentrations near zero, up to around 2–3 μmol/l, as they occur in the aqueous humour and in the cerebrospinal fluid of young people, the FFA_{H2O}-concentration increases with both increasing concentrations of the FFA/albumin complexes (abscissa in Fig. 4a) and increasing mFAR, the fatty acid load of the complexes. However, at higher albumin concentrations, for instance in blood plasma or in interstitial tissue spaces, the FFA_{H2O}-concentration becomes increasingly independent of the FFA/albumin complex concentration and is mainly a function of the mFAR (Fig. 4a).

Fig. 4b reveals that at very low albumin concentrations increasing concentrations of the FFA/albumin complexes cause an increase in the linoleic acid uptake of human lens epithelial cells, even at a fixed mFAR = 1.

Fig. 4c demonstrates the crucial significance of an increasing mFAR for cellular fatty acid uptake. The uptake of linoleic acid increases almost linearly with mFAR values between 0.1 and 1, but exponentially with mFAR>1. This is again concurrent with the results from Richieri et al. (1993), showing that the FFA_{H2O}-concentration increases linearly at low mFAR values, but exponentially at higher mFAR. Both results also correlate with our findings that bleb formation, one of the first signs of linoleic acid cytotoxicity, only occurs when lens epithelial cells are cultured with mFAR>1 (Glaesser et al., 1996; Trimborn et al., 2000). Our data correspond with data from a model system where free fatty acid molecules move spontaneously from FFA/albumin complexes in an aqueous medium to the lipid bilayer of cell membranes (Zakim, 2000). Experimental data show that at very low FFA/albumin complex concentrations the fatty acid concentration in the lipid bilayer increases with both increasing concentrations of the FFA/albumin complexes and increasing fatty acid loads of the complexes (Noy et al., 1986; Zakim, 2000).

4. The age-dependent rise in albumin in the eyes and brain correlates with mitochondrial dysfunction, cataracts, and Alzheimer's disease

4.1. The lens

The vertebrate lens is an avascular transparent tissue, enveloped in a basement membrane, the lens capsule. The lens epithelium is located beneath the anterior capsule as a single layer of epithelial cells (Fig. 5). Near the equator, epithelial cells start to differentiate and elongate into fibre cells, which are generated throughout life and laid down layer by layer. During differentiation, fibre cells lose most of their organelles including cell nuclei and mitochondria (Bloemendal, 1981). Therefore, the single layer of epithelial cells is responsible for maintaining the homeostasis and transparency of the entire lens.

4.2. The blood-aqueous barrier

The lens is bathed in vivo in the aqueous humour. The aqueous humour is principally the product of the blood-aqueous barrier, which is located in the capillaries of the ciliary body and iris around the lens equator. The chief barriers to albumin reside in the non-pigmented epithelial cells of the ciliary body and the non-fenestrated capillary endothelium of the iris (Cole, 1984). With respect to albumin, the barriers in the eyes of young people and cattle function quite similarly. In both species, intact barriers reduce the albumin level from 600 to 700 μmol/l in blood plasma to 1–2 μmol/l in the aqueous humour. In 64% of cattle the albumin concentrations in the aqueous humour differed significantly, even between both eyes of one and the same animal (John and Glaesser, 2000). Clearly, maintaining very low albumin levels in the aqueous humour is an extremely effective and highly sensitive function of the blood-aqueous barrier of each eye. The barriers operate like membranes with a pore radius of around 104 Å (Dernouchamps and Heremans, 1975). In solution, albumin molecules are cigar-shaped. After the adhesion of long-chain FFA, the FFA/albumin molecules become rounder. The calculated axes change from 143 Å × 34 Å to 128 Å × 41 Å (reviewed in Peters, 1996). It can thus be assumed that the FFA/albumin complexes pass the barrier even more easily than albumin molecules without a fatty acid load, resulting in a higher mFAR in the aqueous humour than in blood plasma. So far, no reliable values have been obtained for the mFAR in human aqueous humour. However, in each of 10 cattle, 2 young bulls and 8 female calves, the mFAR in the aqueous humour was higher than in the blood serum. The average values in the 10 animals were 0.248 ± 0.224 in serum and 0.987 ± 0.371 in aqueous humour (John and Glaesser, 2000).

4.3. Albumin rise in aqueous humour, mitochondrial dysfunction, and lens opacification

An age-related significant rise in albumin was detected in the aqueous humour of 177 cataract patients, showing average values of below 2 μmol/l between the ages of 10 and 40 years, and up to 4 μmol/l between the ages of 80 and 90 years (Fig. 6). 25% of patients had more than 4 μmol/l, and 10% more than 6 μmol/l albumin in their aqueous humour, with some values rising to around 9 μmol/l. The increase in albumin corresponds very well to the age-dependent increase in lens opacification (Fig. 6).

The increase in albumin, ascertained via albumin antibodies, represents an age-dependent increase in the FFA/albumin complex concentration in the aqueous humour. The neutral red assay as an indicator of the mitochondrial activity was applied to investigate in vitro the influence of increasing FFA/albumin complex concentrations on the mitochondrial activity of human lens epithelial cells, using a physiological mixture of FFA. At 1 μmol/l albumin, as found in the aqueous humour of young people, 20% and 50% of the cellular neutral red uptake were inhibited with an mFAR of 7.22:1 and 24.3:1, respectively. However, at

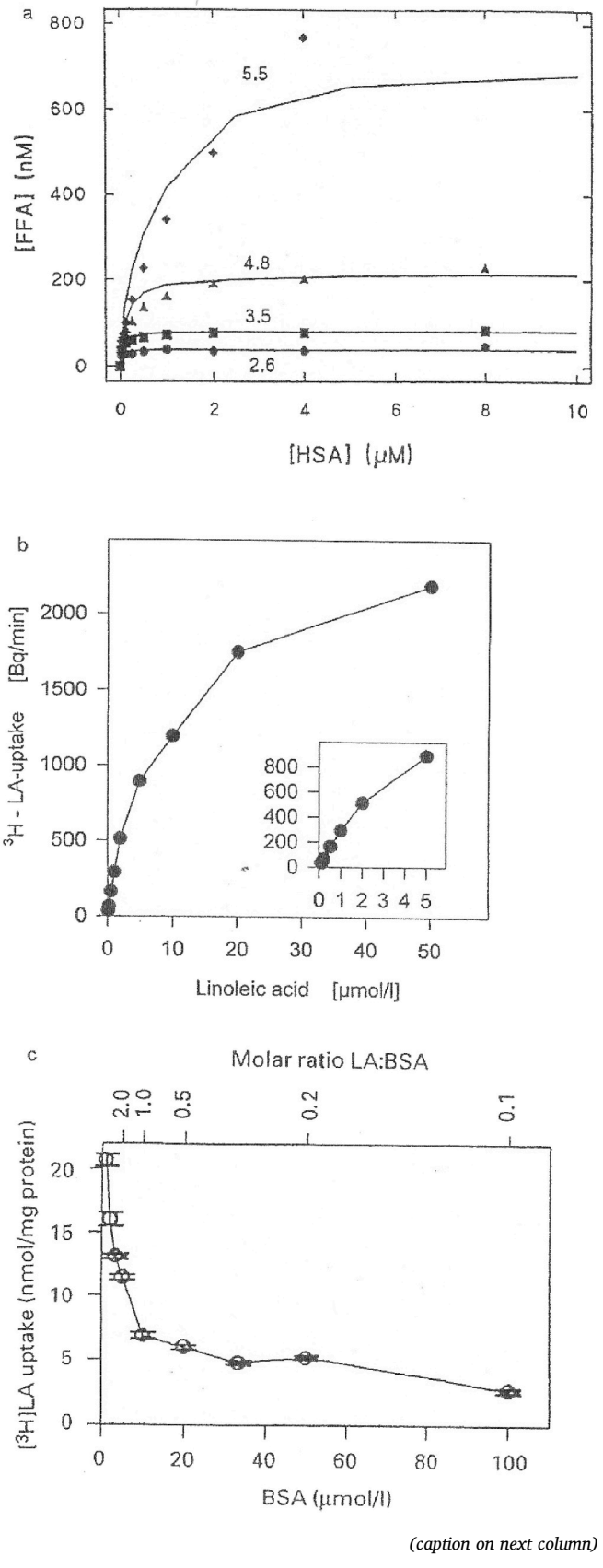

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Fig. 4. Significance of the mFAR for the cellular uptake of linoleic acid. a) Linoleic acid plus HSA at 37 °C in pH 7.4 buffer. The FFA_{H2O} concentration (ordinate FFA ≅ FFA_{H2O}) was measured at fixed mFAR values of 2.6; 3.5; 4.8; 5.5. At albumin concentrations near zero, the FFA_{H2O} concentration (ordinate) increases with both the mFAR and the concentration of the FFA/albumin complex (abscissa). At higher albumin concentrations, the FFA_{H2O} concentrations become solely a function of the mFAR (Richieri et al., 1993). b) Cellular uptake of linoleic acid of human eye lens epithelial cells (ordinate) as a function of the linoleic acid/albumin complex concentration at fixed mFAR = 1 (abscissa). Human lens epithelial cells were exposed for 2 min at 37 °C to increasing concentrations of ^{3}H-linoleic acid and equimolar concentrations of HSA in MEM (Iwig et al., 2004). c) Linoleic acid (LA) uptake as a function of the mFAR. Bovine lens epithelial cells were labelled with ^{3}H-linoleic acid at 37 °C for 30 min in MEM. The linoleic acid concentration was fixed at 10 µmol/l, with the BSA concentration, however, varying. **The fatty acid uptake increases slowly for mFAR (Molar ratio LA:BSA) between 0.1 and 1.0, but very strongly for mFAR>1** (Trimborn et al., 2000).

6 µmol/l albumin, corresponding to the concentrations in the aqueous humour of people with senile cataracts, an mFAR of 1.05:1 and 4.55:1 already caused inhibitions in the neutral red uptake of 20% and 50% (Iwig et al., 2004). This means that the age-dependent increase in the FFA/albumin complex concentration in the aqueous humour strongly impairs the mitochondrial activity of the lens epithelial cells.

4.4. Albumin rise in brain structures, mitochondrial dysfunction, and Alzheimer's disease

In recent years, several authors have argued that AD is a vascular disorder (Torre, 2009; Montagne et al., 2017). Miners et al. (2019) have shown that a dysfunction of the blood-brain barrier is related to the severity of the AD pathology. Orsucci et al. (2013) have stressed: "… recent evidence suggests that vascular wall cells, and especially their mitochondria, may be central targets for oxidative damage before the development of AD-pathology". It has been suggested that mitochondrial dysfunction is "an initial trigger for Aβ production" (Leuner et al., 2012), and may be the cause of the apoptotic loss of neurons and astrocytes during the progression of AD (Smale et al., 1995). Structural and functional changes of brain cell mitochondria are early and prominent features of AD, but the origin of the changes remains elusive (Swerdlow, 2018; Wang et al., 2020).

It has been revealed that the rise in albumin in the human cerebrospinal fluid is age-dependent and is significantly higher in patients with various types of dementia, including senile AD (Skillbäck et al., 2017; Musaeus et al., 2020). Furthermore, an age-related blood-brain barrier dysfunction with an increased uptake of albumin into the brain tissue precedes cognitive deficits and senile plaques in the Tg2576 Alzheimer's mice model (Ujiie et al., 2003). We suggest that slowly increasing concentrations of FFA/albumin complexes – especially complexes with increased FFA-loads – in the cerebrospinal fluid and in the interstitial spaces of brains affected by AD may causally be involved in the mitochondrial dysfunction of brain cells, similar to what has been described above for lens epithelial cells.

5. Lipotoxic damage of the vascular albumin barriers in the eyes and brain may link cataracts with Alzheimer's disease

Cataracts are closely related to senile and familial AD. Older people with newly diagnosed cataracts have a 1.43-fold increased risk of developing AD. The study was performed with 19,954 cataract patients, aged 65–84 years, and 19,954 controls over 5 years (Lai et al., 2014). The findings of Jun et al. (2012) suggest that genetic variations in delta-catenin, a component of the albumin barriers in the eyes and brain, cause both cortical lens opacities in midlife and future AD-related brain changes.

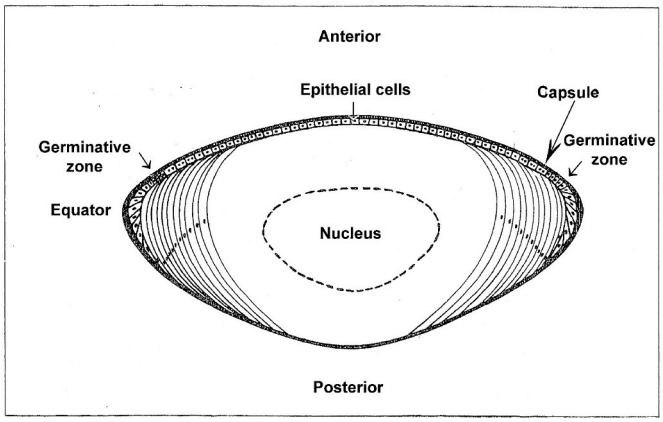

Fig. 5. Schematic representation of the vertebrate lens, see text. (According to Miller et al., 1997, modified).

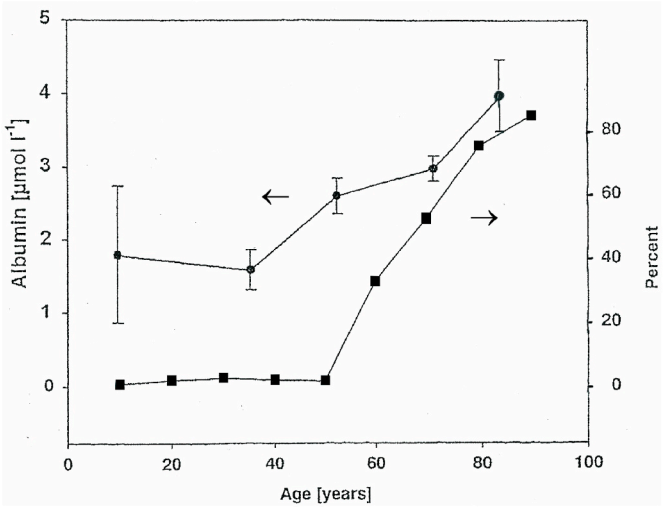

Fig. 6. The age-dependent rise of the albumin concentration in human aqueous humour correlates with the age-dependent lens opacification. Upper curve: Age-dependent rise of the albumin concentration in aqueous humour of 177 cataract patients (Iwig et al., 2004). Lower curve: Percent of lenses with opacities of 430 human post mortem lenses plotted against age (Harding and Crabbe, 1984).

5.1. Similarity of the albumin barriers in the eyes and brain

The blood-eye barriers as well as the blood-brain barriers are complex. However, the most effective barrier structures to albumin migration are the same in both systems: monolayers of vascular endothelial cells and vascular epithelial cells, each of them linked by tight and adherens junctions (Cole, 1984; Oldendorf, 1977; Rapoport, 1977). In young healthy people the barriers reduce the albumin concentration from around 650 µmol/l in blood to 1–2 µmol/l in the aqueous humour of the eyes (Fig. 6), and to 3 µmol/l in the cerebrospinal fluid (Seyfert et al., 2004), which, circulating in the subarachnoid space, is in close contact with the brain cells.

5.2. Increased mFAR in the blood in connection with C6-unsaturated FFA are risk factors for the vascular albumin barriers in the eyes and brain

Adipocytes are specialised cells for storing large amounts of FFA, mainly as triglycerides. However, other cells only have a limited capacity for storing long-chain FFA. Therefore, continuous exposure to excess FFA results in an accumulation of di- and triglycerides within the cells, causing cellular dysfunction and injury. This process, first revealed by Unger and colleagues using cultured pancreatic β-cells, has collectively been referred to as lipotoxicity (Lee et al., 1994; Unger, 1995). Cells of the vascular albumin barriers seem to be specifically impaired by the increased uptake of unsaturated FFA. Exposure to increased concentrations of the unsaturated oleic or linoleic acid increases the transfer of albumin molecules across cultured endothelial monolayers of porcine pulmonary arteries, whereas the saturated palmitic and stearic acids are ineffective (Hennig et al., 1984, 1990). Linoleic acid also interferes with the metabolism of proteoglycans, which have a key role in regulating the filtration barrier function of the vascular endothelium and basement membranes (Hennig et al., 1995).

Furthermore, linoleic acid activates vascular endothelial cells to produce TNF-α, vascular cell adhesion molecule 1 (VCAM-1) as well as the intracellular adhesion molecule 1 (ICAM-1) (Toborek et al., 2002), and stimulates macrophages to secrete the granulocyte macrophage colony-stimulator factor (GM-CSF) (Bahramian et al., 2004). Dysfunction of the vascular endothelial cells, diminished barrier function, increased production of pro-atherogenic factors such as TNF-α, VCAM-1, ICAM-1, and GM-CSF, are considered to be the first steps in the atherosclerotic process (Ross, 1999).

Linoleic acid (omega-6) and linolenic acid (omega-3) operate differently. Inflammatory mediators, induced by TNF-α in vascular endothelial cells, are amplified by cellular preenrichment with linoleic acid but are reduced or blocked by preenrichment with linolenic acid (Wang et al., 2008). These results correlate well with the anti-atherogenic effects of omega-3 fatty acids (Oh et al., 2010).

6. Chronically increased mFAR in the blood links aging and systemic diseases with senile cataracts, Alzheimer's disease, and mortality

In blood, long-chain FFA bind to albumin and other components, thereby buffering the concentration of the FFA_{H2O}-fraction. However, the buffering capacity of albumin greatly predominates that of any other component (Spector and Fletcher, 1978). In blood, therefore, the concentration of the FFA_{H2O}-fraction, which plays a key role in the FFA uptake of non-adipocytes, is principally a function of the mFAR, see Fig. 4a (Richieri et al., 1993). In the blood of healthy young adults, the mFAR is usually below 1. It will increase with decreasing concentrations of albumin, or with increasing concentrations of FFA, or with both. Fig. 4c demonstrates the strong effect of mFAR>1 on the cellular uptake of FFA. At mFAR≤1, the FFA are principally bound to the binding site with the highest affinity. At mFAR>1, binding sites with decreasing affinities are occupied too, which explains the exponential increase of the FFA_{H2O}-concentrations measured by Richieri et al. (1993), as well as the increased cellular FFA uptake and lipotoxicity, as demonstrated above for lens epithelial cells.

6.1. Aging, increasing mFAR, cataracts and AD

After maintaining a constant level of around 42 g/l (632 µmol/l) between 20 and 40 years of age, the plasma albumin concentration falls gradually at a rate of 0.05 g/l per year to approximately 39 g/l (586 µmol/l) at the age of 90 years (Campion et al., 1988). Furthermore, adipocytes become dysfunctional with aging leading to "… an elevation in systemic free fatty acids" (Pararasa et al., 2015). Aging is thus associated with an elevated mFAR in the blood. In a study on healthy males, all in excellent physical condition with no clinical abnormalities, Pickart (1983) determined an age-dependent progressively increasing rise of the plasma mFAR from 0.755 ± 0.061 in a group of men aged 20–29 years to 1.042 ± 0.165 in a group of men aged 60–69 years. Several factors may contribute to the pathology of senile cataracts and senile AD, but advancing age represents the greatest risk factor for both diseases. Lens opacification normally starts in people over 40 years of age (Fig. 6), and the individual risk of developing AD doubles every 5 years after the age

of 65 (Querfurth and Laferia, 2010). Besides aging, several systemic diseases, known to raise the mFAR of the blood, are especially associated with senile cataracts and senile AD.

6.2. Preeclampsia, increasing mFAR, cataracts, and AD

More females than males develop cataracts (Abraham et al., 2006) and AD (Pike, 2017). The frequency of cataracts increases with the number of children (Clayton et al., 1984). Characteristic features of preeclampsia are increased concentrations of FFA and decreased levels of albumin in blood plasma. The combined effects result in a clearly elevated mFAR. Endresen et al. (1992) found an mFAR of 0.61 in non-pregnant women, 0.86 in normal pregnancy, and 1.59 in the case of preeclampsia.

6.3. Diabetes mellitus, increasing mFAR, cataracts, and AD

Reaven et al. (1988) found chronically elevated plasma concentrations of FFA between 400 and 800 μmol/l in non-obese patients suffering from type 2 diabetes, compared with 160–520 μmol/l in control subjects. Yu et al. (2004) determined 364 μmol/l FFA in the blood plasma of controls, 675 μmol/l in diabetics without microalbuminuria and 1008 μmol/l in diabetics with microalbuminuria, resulting in an mFAR of 0.630, 1.210, and 1.769, respectively. Diabetes as a risk factor for cataracts has been established in numerous studies. However, type 2 diabetes is also a risk factor for vascular dementia and AD (Li and Huang, 2016).

6.4. Obesity, increasing mFAR, cataracts, and AD

Increased BMI has often been reported as a risk factor for cataracts (Abraham et al., 2006). In healthy people the fasting plasma levels of FFA usually range between 300 and 400 μmol/l and may temporarily increase to 800–1000 μmol/l only under extreme conditions. However, in obese individuals the plasma FFA are chronically elevated to around 600–800 μmol/l (Belfort et al., 2005). Obesity in midlife is associated with an increased risk of dementia and AD in later life (Kivipelto et al., 2005; Picone et al., 2020).

6.5. Cigarette smoking, increasing mFAR, cataracts, and AD

Immediately after smoking, increased lipase activity, decreased triglyceride concentrations and elevated levels of FFA are found in the blood plasma of smokers (Blache et al., 1992). On the other hand, cigarette smoking is associated with microalbuminuria (Barbato et al., 2019) and decreased plasma albumin levels (Shaper et al., 2004). Microalbuminuria has been shown to be directly related to the number of cigarettes smoked per day (Mustafa et al., 2017). Therefore, heavy cigarette smokers will have an elevated mFAR in the blood. Cigarette smoking is a major, consistently confirmed risk factor for cataracts (Ye et al., 2012), and a significantly increased risk factor for AD (Durazzo et al., 2014). Heavy smoking in midlife is a long-term risk factor for AD (Rusanen et al., 2011).

6.6. Artificially produced increasing mFAR, hypertension, cataracts, and AD

The sustained elevation of FFA, generated by “Intralipid” plus heparin infusion, is associated with a rapid and sustained increase in blood pressure, increased levels of inflammatory markers, and vascular endothelial dysfunction (Umpierrez et al., 2009). Hypertension increases the risk of cataracts (Yu et al., 2014) and has been described as the most detrimental vascular risk in the progression of AD (Thorin, 2015).

6.7. Increased mFAR of the blood and mortality

To our knowledge, there are no clinical studies which directly compare the mFAR in the blood with mortality. However, both parameters of an elevated mFAR, low plasma albumin levels (Akirov et al., 2017) and elevated plasma levels of FFA (Pilz et al., 2006), are independently associated with increased mortality. Furthermore, cataracts (Podgor et al., 1985; Williams et al., 2002) as well as AD (Ganguli et al., 2005) are significant predictors of increased mortality. Chronically increased mFAR of the blood in connection with C6-unsaturated FFA and oxidative stress may also explain the strong correlation between AD and cardiovascular diseases (Tublin et al., 2019). Globally, cardiovascular diseases are the leading cause of death (WHO updates 11 June 2021).

7. The lipotoxic cascade hypothesis

We propose a lipotoxic cascade hypothesis, explaining the as yet unexplained strong correlation between aging and AD, as well as the close correlation between aging, senile cataracts, AD, and mortality. Firstly, in humans over 40 years old, aging drives the increase of the mFAR in the blood by decreasing the plasma concentration of albumin and increasing the plasma concentration of FFA. Secondly, the elevated mFAR in connection with C6-unsaturated FFA causes an increased uptake of FFA, mitochondrial dysfunction and albumin barrier impairment of the vascular endothelial and wall cells. Thirdly, the vascular albumin barrier dysfunction causes enhanced concentrations of FFA/albumin complexes in the aqueous humour of the eyes as well as in the cerebrospinal fluid and in the interstitial spaces of the brain. Fourthly, increased concentrations of the FFA/albumin complexes, and especially complexes with increased mFAR, cause an increased uptake of FFA, mitochondrial dysfunction and apoptotic death of the lens epithelial and the brain cells. Fifthly, an enhanced mFAR in the blood in connection with an increased cellular uptake of *saturated* FFA, especially palmitic acid, may also be involved in organismic aging and mortality. The increased uptake of palmitic acid induces endoplasmic reticulum stress and apoptosis in pancreatic beta cells (Chu et al., 2010) as well as in cardiomyocytes (Haffar et al., 2015), and brain cells (Ortiz-Rodriguez et al., 2019; Vesga-Jiménez et al., 2022). The results reviewed herein support the hypothesis that “… a high molar ratio of FFA to albumin may lead to dysfunction of the cells which are directly exposed to the high FFA/albumin ratio” (Hostmark, 1995).

Doubts about the significance of the “lipotoxic cascade hypothesis” could arise from the fact that the development of cataracts as well as AD have very different causes. Recently, J. D. Rudge (2022) proposed a “Lipid Invasion Model” which also “… argues that AD results from external influx of free fatty acids (FFAs) and lipid-rich lipoproteins into the brain, following disruption of the blood-brain barrier (BBB).” With regard to more than 400 references from the literature, the author explains how very different risk factors, such as aging, apolipoprotein E4, hypertension, smoking, obesity, diabetes, chronic sleep deprivation, stress, and head injury may be involved in damaging the blood-brain barrier causing AD. Damage of the blood-aqueous and the blood-liquor barriers to FFA/albumin complexes are central to the “lipotoxic cascade hypothesis”.

8. Clinical implications and future research

Currently available AD-biomarkers in the eyes, cerebrospinal fluid, and blood present symptoms of the disease, ongoing for years (Fereshetian et al., 2021; Dubois et al., 2023; Hampel et al., 2023). However, according to the “lipotoxic cascade hypothesis” increased values of the mFAR>1 in the blood, are both: cause and one of the earliest biomarkers for physical aging, including the age-dependent development of cataracts and senile AD. Recent results of the AMBAR study have shown that the plasma exchange with a therapeutic albumin replacement leads to a

slower decline or stabilisation of cognitive and functional abilities of AD patients (Costa and Páez, 2021). Furthermore, treatment with nicotinic acid, known to diminish the plasma concentration of FFA (Carlson, 2005), has the potential to prevent cognitive decline across AD and vascular dementia (Campbell, 2022). Both results correspond with the assumption that increasing values of the mFAR>1 in the blood are involved in the development of AD. Up to now, the mFAR in the blood has rarely been considered in clinical studies. Future studies should research mFAR>1 as an early biomarker for aging-related diseases. Preventive and therapeutic treatments with diet, niacin, or blood plasma exchange could help to keep the mFAR<1.

Recently, Vesga-Jiménez et al. have thoroughly reviewed the possible role of palmitic acid in the development of neurodegenerative diseases, including AD (Vesga-Jiménez et al., 2022). Oleic acid and linoleic acid counteract the detrimental effects of palmitic acid to brain cells. Therefore, the authors propose using these fatty acids "as potential therapeutic approaches against neurodegenerative diseases". However, increased uptake of linoleic or oleic acid is strongly cytotoxic to lens epithelial cells (Glaesser et al., 1996; Trimborn et al., 2000; Iwig et al., 2004), while palmitic acid competitively inhibits the linoleic acid cytotoxicity (Trimborn et al., 2000). Again, future clinical studies should be focused on keeping the mFAR of the blood below 1.0, and not on therapies with "non-toxic" free fatty acids.

Declarations of interest

None.

CRediT authorship contribution statement

Dietmar Glaesser: Conceptualization, Writing – original draft. **Martin Iwig:** Validation, Writing – review & editing.

Data availability

No data was used for the research described in the article.

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