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Reviewing reasons for the decreased CSF Abeta$_{42}$ concentration in Alzheimer disease

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1. ABSTRACT

Cerebrospinal fluid (CSF) amyloid beta$_{42}$ (Abeta$_{42}$) concentrations are decreased in patients with Alzheimer disease (AD). Consequently, low Abeta$_{42}$ is considered a positive biomarker for AD. Surprisingly, the mechanisms that underlie the decrease in CSF Abeta$_{42}$ remain speculative. Better understanding of this biomarker is an essential step to unravel AD pathophysiology and to develop and evaluate treatment. Therefore, we systematically examined the possible reasons for the decreased CSF Abeta$_{42}$ concentration in AD. Under normal conditions, Abeta$_{42}$ can be degraded by proteases, taken up by microglia, or cleared from the brain interstitial fluid across the blood brain barrier. Alternatively, it can be transported to the CSF and be cleared from there. Aggregation of Abeta$_{42}$ appears the most likely cause for the decreased CSF Abeta$_{42}$ concentration in AD: the aggregated state inhibits Abeta$_{42}$ from being transported from the ISF to the CSF. Evidence for other possibilities such as a decreased production of Abeta$_{42}$, an increased proteolytic breakdown or microglial uptake of Abeta$_{42}$, or an increased clearance of Abeta$_{42}$ to the blood, is - at best - scarce or even absent.

2. INTRODUCTION

The characteristic plaques of Alzheimer disease (AD) were discovered by Aloïs Alzheimer in 1906, but it was not until the 1980s that it was demonstrated that these plaques consist of the amyloid beta protein (Abeta). (1-3) The realization that this protein was the same as the protein accumulating in brains of patients with Down syndrome led to the discovery of the amyloid precursor protein (APP), located on chromosome 21, as the precursor protein of Abeta. (4) Subsequently, pathogenic mutations in the APP gene were discovered in familial AD. (5-8) In the 1990s, Abeta could be measured in cerebrospinal fluid (CSF) for the first time. (9, 10) It was thereafter repeatedly shown that CSF Abeta$_{42}$ was decreased in AD. (11-14) Nowadays,

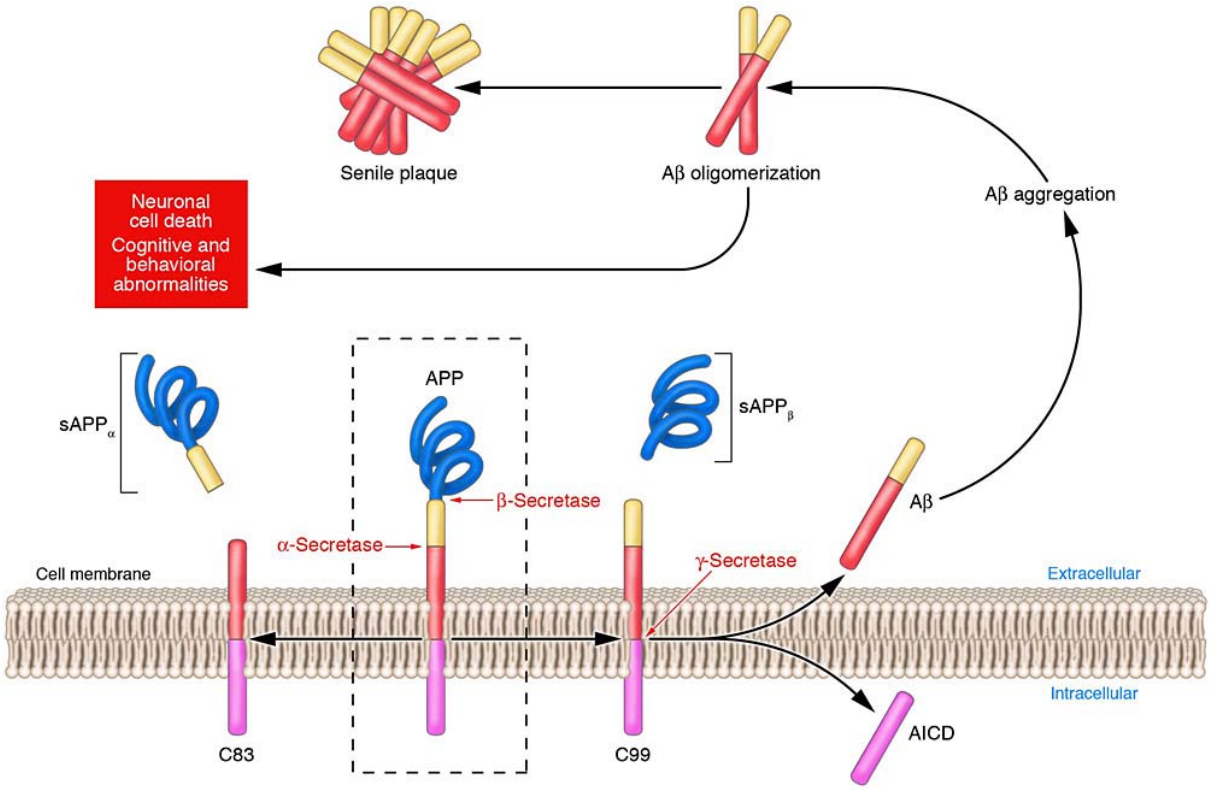

Figure 1. The non-amyloidogenic and amyloidogenic pathways of APP processing APP is cleaved by either alpha- or beta-secretase. Cleavage by alpha-secretase (the non-amyloidogenic pathway) generates sAPP-alpha and C83 (left). Cleavage by beta-secretase (the amyloidogenic pathway) generates sAPP-beta and C99 (right). C83 is cleaved by gamma-secretase, generating AICD and p3 (not shown). C99 is also cleaved by gamma-secretase, generating AICD and Abeta (right). (See text for abbreviations.) Republished with permission of the American Society for Clinical Investigation, from reference no. 22; permission conveyed through Copyright Clearance Center, Inc.

it is an accepted biomarker for AD (15, 16) that is frequently used in clinical practice. (17, 18) Surprisingly, the cause of its decrease has not yet been fully elucidated, although several explanations have been offered: changes in Abeta generation or degradation may affect the CSF concentration, or an alteration in the solubility of Abeta42 may diminish clearance of Abeta42 from the interstitial fluid (ISF) to CSF. (11-14) Determination of the CSF Abeta42 concentration in AD may be masked by its interaction with binding proteins, such as apolipoprotein J or E, or 11. E. Matsubara, B. Frangione and J. Ghiso, Characterization of apolipoprotein J-Alzheimer's Aβ interaction. J. Biol. Chem. 270 (1995), pp. 7563–7567. View Record in Scopus | Cited By in Scopuan increased clearance of Abeta42 from CSF might explain the diminished levels of Abeta42 in the CSF of AD patients. (14)

In spite of all these suggestions, the actual explanation for the decreased CSF Abeta42 in AD remains largely unidentified. Here, we will review the evidence for each of the proposed explanations to create a better understanding of the underlying mechanisms that lead to its recognition as an important AD biomarker.

3. ABETA$_{42}$ METABOLISM

3.1. Production of Abeta$_{42}$

Abeta$_{42}$ is produced by sequential cleavage of the amyloid precursor protein (APP) (Figure 1). APP is a membrane-bound protein whose function remains unclear, although a role in cell adhesion, cell growth and synaptogenesis has been suggested. (19, 20) APP can be cleaved by either alpha- or beta-secretase, and subsequently by gamma-secretase. Whether Abeta is produced from APP depends on which of these enzymes first cleaves APP.

Cleavage of APP by alpha-secretase at the plasma membrane or in the trans-Golgi network generates N-terminal fragment soluble APP-alpha (sAPP-alpha) and C-terminal fragment C83. (21) sAPP-alpha is released into intracellular vesicles or extracellularly. C83 remains membrane-bound and is cleaved by gamma-secretase to produce p3 (Abeta17-40 and Abeta17-42/43) and APP intracellular domain (AICD) (CT57-59). (22-25) The latter is released into the cytoplasm. This pathway is called the non-amyloidogenic pathway since no Abeta40 or Abeta42 is produced.

Cleavage of APP by beta-secretase, the amyloidogenic pathway, takes place in the trans-Golgi network and in endosomes (20, 26) and generates N-terminal fragment soluble APP-beta and C-terminal fragment C_{99}. sAPP-beta – just like sAPP-alpha – can be released into intracellular vesicles or extracellularly. C_{99} remains membrane-bound and is subsequently cleaved by gamma-secretase to produce $Abeta_{42}$ or $Abeta_{40}$ and AICD. (22, 23) Cleavage by gamma-secretase takes place in the endoplasmatic reticulum, trans-Golgi network, endosomes, and for a small part at the plasma membrane. (26) Other isoforms of Abeta have been identified as well, with heterogeneity either at the C- or N-terminus of the peptide, but for clarity this review will be limited to $Abeta_{42}$ and $Abeta_{40}$.

The amyloidogenic and non-amyloidogenic pathways are mutually exclusive. (22) APP molecules that are not cleaved at the cell membrane by alpha-secretase can be internalized by endocytosis and subsequently be cleaved by beta-secretase. (27) Redistribution of APP towards either the cell membrane or the cell interior can therefore influence the proteolytic pathway that APP undergoes. (22)

$Abeta_{42}$ and $Abeta_{40}$ are either retained in cells or secreted into the ISF that surrounds the brain cells. (23) The equilibrium between intra- and extracellular $Abeta_{42}$ and $Abeta_{40}$ is in part regulated by active transport via the receptor for advanced glycation end products (RAGE), (28) a multiligand receptor of the immunoglobulin family. (29)

3.2. Degradation of $Abeta_{42}$

3.2.1. Proteases

Several proteases can break down Abeta (both $Abeta_{42}$ and $Abeta_{40}$) *in vitro; in vivo* evidence stems mostly from animal studies. Insulin-degrading enzyme (IDE) and neprilysin have received most attention. IDE is a zinc-metalloproteinase present in the cytosol, in intracellular membranes and at the cell surface. (25, 30-32) It is secreted by neurons (32) and has also been found in CSF. (25) It can therefore degrade both intracellular and extracellular Abeta. IDE only degrades soluble, monomeric Abeta. (25, 30, 31) The cleavage products are not neurotoxic and are not prone to accumulate in plaques. (25) Neprilysin is an axonal and synaptic membrane-anchored protein with its catalytic site facing the cell exterior (31, 32) and is therefore primarily involved in the breakdown of extracellular $Abeta_{42}$. It can degrade monomeric as well as oligomeric Abeta. (32)

Other proteases that have been reported to degrade Abeta *in vitro* include matrix metalloproteinase-9, angiotensin converting enzyme, cathepsin D, plasmin and endothelin converting enzyme-1. (32, 33) Abeta aggregates can stimulate tissue-type and urokinase-type plasminogen activator to generate plasmin. Plasmin can degrade both monomeric Abeta and Abeta fibrils *in vitro*, although degradation of fibrils is far less efficient. Its role in degrading Abeta *in vivo* is unclear. (33)

3.2.2. Microglia

Microglia are the macrophages of the brain. They take up soluble Abeta by macropinocytosis and possibly by binding of Abeta to the low-density lipoprotein receptor-related protein (LRP). (34) Fibrillar forms of Abeta interact with the microglia cell surface and bind to the CD36 receptor expressed by microglia. CD36, a major pattern recognition receptor, mediates the microglial response to Abeta, leading to an intracellular signaling cascade that stimulates phagocytosis. (35) Ablation of microglia in mice led to an increase in soluble $Abeta_{40}$ and $Abeta_{42}$, but had no influence on number and size of Abeta plaques. (36) This would support the idea that microglia are inefficient in degrading fibrillar Abeta. (34) However, others have found that upon activation, for example by cerebral ischemia or after vaccination with Abeta specific antibodies, microglia can degrade fibrillar Abeta. (37-39)

3.3. Clearance of $Abeta_{42}$

$Abeta_{42}$ and $Abeta_{40}$ can also be cleared from the extracellular compartment. It can be cleared from the ISF across the blood-brain barrier towards the circulation, or it can be transported from the ISF to the CSF, and be cleared from there. Alternatively, Abeta can be transported with the ISF or CSF to the peripheral lymphatic system (Figure 2).

3.3.1. Active transport of Abeta from ISF to systemic circulation

Both $Abeta_{42}$ and $Abeta_{40}$ can be removed from ISF to the blood by crossing the blood-brain barrier. The blood-brain barrier is primarily formed by endothelial cells in brain capillaries that are closely connected via tight junctions which exclude the transfer of many macromolecules from ISF into blood. (40) Astrocytes and pericytes may also play a role in the control of transport across the blood-brain barrier. $Abeta_{42}$ and $Abeta_{40}$ are primarily transported across the blood-brain barrier by LRP. (29) LRP is a multiligand lipoprotein receptor that mediates endocytosis of secreted proteins. It provides a rapid transport of brain-derived Abeta into the blood. (41) LRP-mediated transport is more efficient for $Abeta_{40}$ when compared to $Abeta_{42}$ (29, 31), probably related to $Abeta_{40}$'s lower propensity to aggregate. $Abeta_{42}$ and $Abeta_{40}$ that is produced in the periphery can enter the brain ISF from the systemic circulation by active transport across the blood-brain barrier via RAGE, which is expressed on the luminal surface of brain vessels. (29)

3.3.2. Drainage of Abeta with ISF to lymphatics

One of the routes that ISF can follow is drainage along axonal tracts and through perivascular spaces. ISF travels along these perivascular spaces towards the surface of the brain and exits at the base of the skull, where it drains to regional lymph nodes in the neck. (42) The idea that Abeta is transported together with ISF along this pathway is supported by the fact that Abeta has been found in the basement membranes of capillary and arterial walls, but was not detectable further downstream in the walls of the carotid arteries. (43)

3.3.3. Transport of Abeta from ISF to CSF

Another route for ISF is towards the CSF, where it constitutes 10-30% to the total CSF production. (44) ISF mixes with CSF at the ventricles and presumably also in the subarachnoid compartment. (40, 44) Whether Abeta

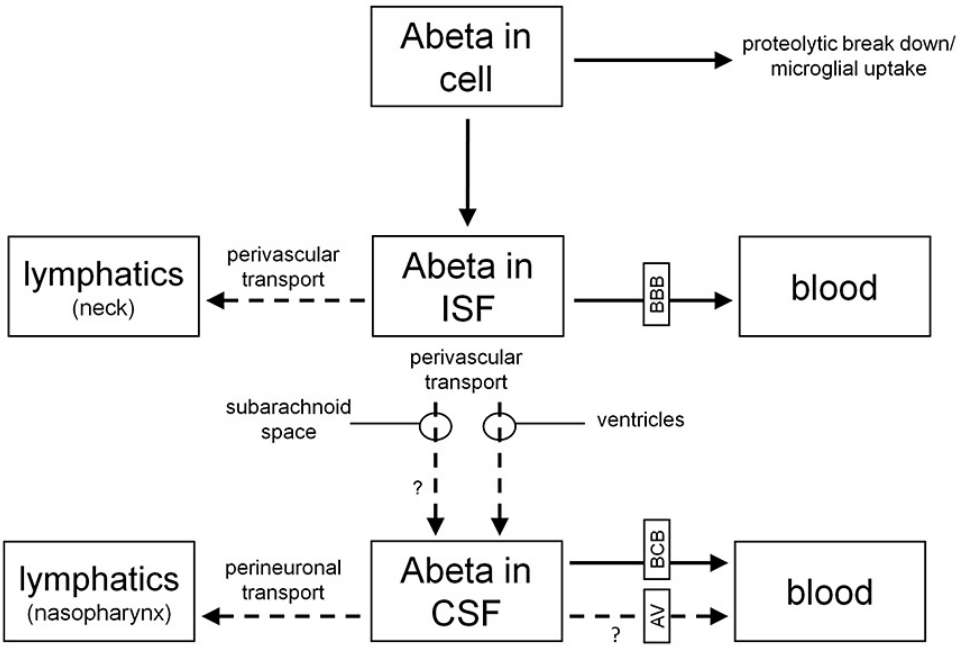

Figure 2. Schematic view of $Abeta_{42}$ and $Abeta_{40}$ clearance, Abeta can be $Abeta_{42}$ or $Abeta_{40}$. Solid arrows depict active transport of Abeta; dashed arrows depict passive transport of Abeta together with ISF or CSF.BBB = blood brain barrier, BCB = blood CSF barrier at choroid plexuses, AV = arachnoid villi

reaches the CSF via this route is uncertain. The glia limitans and the pia mater separate ISF from CSF in the subarachnoid space, however, the extent to which these layers block the passage of solutes and ISF into CSF is unknown. They may be fully permeable to fluid and small molecules, (29) but on the other hand, the presence of Abeta deposits in the glia limitans in AD suggests that transport of Abeta from ISF to CSF is limited in the subarachnoid compartment. (43)

The concentration of $Abeta_{40}$ in CSF is about 6-fold greater than the concentration of $Abeta_{42}$; (45-47) in AD, the decreased concentration of CSF $Abeta_{42}$ makes the CSF $Abeta_{40}$ concentration at least 10-fold that of CSF $Abeta_{42}$. (46-48)

3.3.4. Absorption of Abeta from CSF to systemic circulation

Labeled Abeta injected into CSF of rats was detectable in blood a few minutes after injection. (49) From cell culture research it was inferred that Abeta can be absorbed from CSF at the choroid plexuses. (50) The endothelium of the blood vessels within the choroid plexus is leaky, but the epithelium between blood vessels and ventricular CSF contains tight junctions and forms the blood-CSF barrier (which should not be confused with the blood-brain barrier). Small molecules can enter or leave the brain. (40) Uptake of Abeta peptides at the choroid plexus was rapid and occurred as a non-diffusional, yet unclear uptake process. Efflux of Abeta from CSF to blood was favored over influx from blood into CSF. (50) In addition to the blood-CSF barrier, CSF drains to blood in the subarachnoid compartment, where CSF drains into the major venous sinuses via arachnoid granulations. Tight junctions in these granulations prevent passage of proteins, (51) and it is therefore unclear whether Abeta can be cleared from CSF to blood in this way.

3.3.5. Drainage of Abeta with CSF to lymphatics

The perineural sheath along the olfactory nerve represents another pathway of CSF drainage. The olfactory nerve fibers enter the nasal mucosa in the roof of the nasal cavity. At this point CSF drains from the perineural subarachnoid space into the extracellular matrix, where it is absorbed by blind-ended lymphatic capillaries, and drained to the regional lymph nodes that serve the nasopharynx. (44, 51) CSF also flows along the perineuronal sheaths of the cranial and spinal nerves to regional lymphatics. (40, 51, 52) It seems plausible that Abeta is cleared together with CSF via this pathway, but studies to confirm this are currently lacking.

4. WHY IS CSF $ABETA_{42}$ DECREASED IN ALZHEIMER DISEASE?

Several morphological changes that are related to the fate of the $Abeta_{42}$ peptide have been observed in AD. Upon post-mortem examination, Abeta plaques are found: diffuse plaques that contain only $Abeta_{42}$, and classic plaques that consist of both $Abeta_{42}$ and $Abeta_{40}$. (53, 54) In most AD cases, at least a mild degree of cerebral amyloid angiopathy is found as well, that consists of Abeta deposits in the walls of leptomeningeal and cortical arteries and less frequently in capillaries. (55) In contrast to the plaques, these vascular deposits contain mostly $Abeta_{40}$. (56) The concentration of both $Abeta_{42}$ and $Abeta_{40}$ in the AD brain

Table 1. Overview of arguments supporting or contradicting the hypothetical mechanisms that could explain the decreased CSF $Abeta_{42}$ concentration in AD

Hypothetical mechanism	Supporting arguments	Contradicting arguments
Decreased production of $Abeta_{42}$ (4.1.)	- Could be the result of a reduction in viable neurons due to neurodegeneration	- An increased brain $Abeta_{42}$ load is found post-mortem - $Abeta_{40}$ shares the same production pathway as $Abeta_{42}$ but CSF $Abeta_{40}$ is not decreased - Disorders with an increased production of Abeta have decreased concentrations of CSF $Abeta_{42}$ - The production of $Abeta_{42}$ in AD did not differ from controls in a labeling study
Decreased secretion of $Abeta_{42}$ from neurons (4.1.)	- Intraneuronal Abeta aggregation has been described in Tg mice	- The typical Abeta plaques of AD are found extracellularly
Increased degradation of $Abeta_{42}$ (4.2.)		- An increased brain $Abeta_{42}$ load is found post-mortem - Increased degradation would probably affect $Abeta_{40}$ as well, yet the CSF $Abeta_{40}$ concentration is unchanged - Levels of neprilysin (one of the proteases involved in Abeta degradation) decrease with aging
Increased microglial uptake of $Abeta_{42}$ (4.3.)	- Activated microglia are found in the vicinity of Abeta plaques	- An increased brain $Abeta_{42}$ load is found post-mortem - Microglia become dysfunctional with aging
Increased clearance of $Abeta_{42}$ from ISF to blood (4.4.1.)	- Expression of LRP (which promotes transport of Abeta from ISF to blood across the blood brain barrier) by perivascular cells increased in reaction to $Abeta_{42}$	- Perivascular cells expressing LRP degenerated after uptake of Abeta - LRP expression is reduced in AD - No increase in plasma $Abeta_{42}$ is found - An increased brain $Abeta_{42}$ load is found post-mortem
Hampered transport of $Abeta_{42}$ with ISF to CSF (4.4.2.1.)	- Dilated perivascular spaces may indicate obstruction of ISF flow	- Dilated perivascular spaces are often seen in the elderly and their clinical relevance is unclear - Other proteins (including $Abeta_{40}$) still reach the CSF
Perivascular deposition of $Abeta_{42}$ (4.4.2.2.)	- Abeta deposits are found perivascularly	- Perivascular Abeta deposits contain mostly $Abeta_{40}$
Parenchymal aggregation and deposition of $Abeta_{42}$ (4.4.2.3.)	- An increased brain $Abeta_{42}$ load is found post-mortem - $Abeta_{42}$ is more prone to aggregation than $Abeta_{40}$	
Increased clearance of $Abeta_{42}$ from CSF to the blood (4.4.3.)		- Uptake of Abeta from CSF decreased with aging - No increase in plasma $Abeta_{42}$ is found

The numbers behind each mechanism refer to the corresponding section in the text.

is thus increased. (57, 58) However, the CSF concentration of $Abeta_{42}$ is decreased in AD patients, while the CSF $Abeta_{40}$ concentration is unaltered. (14, 48) We will focus on reasons why CSF $Abeta_{42}$ is decreased, while keeping in mind the other changes that occur in AD. Table 1 provides an overview of these reasons and the arguments supporting or contradicting them.

4.1. Is $Abeta_{42}$ production reduced?

Theoretically, a decreased concentration of $Abeta_{42}$ in CSF could simply be the result of a decreased production of $Abeta_{42}$, for example by a reduction in the number of viable neurons that produce Abeta. However, several arguments make this unlikely. First, a decreased production does not logically connect to an increased $Abeta_{42}$ load in the brain. Second, if the production of $Abeta_{42}$ were decreased, the production of $Abeta_{40}$ would probably be decreased as well, since $Abeta_{42}$ and $Abeta_{40}$ likely share the same production pathway. This should then lead to a decreased CSF $Abeta_{40}$ concentration, which, however, is not observed in AD. Third, a decreased concentration of CSF $Abeta_{42}$ is also found in familial AD and in Down syndrome, disorders in which overproduction of $Abeta_{42}$ has been clearly demonstrated. (59-62) Decreased $Abeta_{42}$ thus exists despite overproduction, which implies that factors other than production play a role in causing the decreased CSF concentration.

An alternative theory is that $Abeta_{42}$ secretion from the cell is decreased, leaving less $Abeta_{42}$ available in the ISF for transport to the CSF. Although intraneuronal Abeta aggregation has been described in triple transgenic mouse models, (63) Abeta predominantly accumulates extracellularly in human AD. This implies that the secretion of Abeta from the cell to the exterior is not diminished and that a decreased secretion of $Abeta_{42}$ by the cell is unlikely to be the cause of the decreased CSF $Abeta_{42}$ concentration.

Supporting these arguments against a decreased production or secretion of $Abeta_{42}$ is a study showing that the production rate of $Abeta_{42}$ and $Abeta_{40}$, as measured in CSF using labeled $Abeta_{42}$ and $Abeta_{40}$, did not differ between controls and AD patients. (64)

4.2. Is $Abeta_{42}$ degradation increased?

It can be hypothesized that an increase in proteolytic breakdown of $Abeta_{42}$ leads to a decreased CSF $Abeta_{42}$ concentration. However, an increase in proteolytic breakdown would clear the brain from not only $Abeta_{42}$, but also from $Abeta_{40}$ (65) and would preclude formation of plaques. Understandably, research has focused on finding defects in proteolytic degradation of Abeta rather than overactivity of these proteases to explain the elevated cerebral levels of Abeta. (32, 33) It appears that levels of

neprilysin decrease with aging (66) and that low levels of neprilysin make certain brain areas more vulnerable to Abeta deposition, (67, 68) suggesting that proteolytic activity is decreased rather than increased.

4.3. Is microglial uptake of $Abeta_{42}$ increased?

An increased microglial uptake of $Abeta_{42}$ could be hypothesized to lead to the decreased CSF $Abeta_{42}$ concentration by leaving less $Abeta_{42}$ available in the ISF for transport to the CSF. Activated microglia are found in the vicinity of compact Abeta plaques, (69) however, the very presence of these plaques shows that microglial uptake of Abeta is insufficient to lead to a lower-than-normal concentration of Abeta in ISF. On the contrary, it has been suggested that with age, microglia become dysfunctional and less able to clear $Abeta_{42}$. (34, 70, 71) Thus, it is unlikely that microglial ability to degrade Abeta is increased in AD.

4.4. Is $Abeta_{42}$ clearance affected?

Changes in the clearance of Abeta from either ISF or CSF (the solid arrows in Figure 1) can influence the Abeta concentration. An increased transport of ISF or CSF, containing Abeta, to the lymphatics will not affect the Abeta concentration.

4.4.1. Is clearance of $Abeta_{42}$ from ISF increased?

An increased clearance of $Abeta_{42}$ from ISF to blood across the blood-brain barrier would leave a smaller amount of $Abeta_{42}$ in the ISF that can be transported to the CSF and could thus explain the decreased CSF $Abeta_{42}$ concentration. The primary transporter of Abeta across the blood-brain barrier is LRP. Even though LRP favors clearance of $Abeta_{40}$ over $Abeta_{42}$, it can be hypothesized that in AD, clearance of $Abeta_{42}$ is upregulated while clearance of $Abeta_{40}$ remains the same. In support of this hypothesis, expression of LRP by perivascular cells was increased in response to $Abeta_{42}$ *in vitro*, while $Abeta_{40}$ had no such effect; however, uptake of Abeta resulted in degeneration of these perivascular cells. (72) It has also been reported that LRP expression was reduced in AD, while RAGE expression (which transports Abeta from blood to brain) was increased. (29) These changes do not support an increased clearance of $Abeta_{42}$ from ISF over the blood-brain barrier and could actually lead to a reduced transport of $Abeta_{42}$ out of the brain and an increased uptake of peripheral $Abeta_{42}$ into the brain.

Another argument against an increased transport of $Abeta_{42}$ across the blood-brain barrier is the lack of an increase in plasma $Abeta_{42}$ concentration. Increased transport of $Abeta_{42}$ to the blood should result in an increase in the plasma concentration of $Abeta_{42}$ – assuming that the peripheral breakdown and elimination of $Abeta_{42}$ are not increased in AD. Reports on the plasma $Abeta_{42}$ concentration in AD patients are contradictory, but a clear increase has not been shown. (73, 74) Finally, enhanced clearance of $Abeta_{42}$ from the ISF is incompatible with the increased Abeta load that is found in AD brains. In summary, it cannot be concluded that transport across the blood-brain barrier is increased.

4.4.2. Is transport of $Abeta_{42}$ from ISF to CSF hampered?

4.4.2.1. Hampered flow of ISF to CSF

ISF flows through the perivascular spaces, mixing with CSF in the subarachnoid compartment at the brain surface and at the ventricles. If $Abeta_{42}$-containing ISF cannot reach the CSF or if $Abeta_{42}$ is deposited before ISF reaches the CSF, the $Abeta_{42}$ concentration in CSF will be decreased. Dilated perivascular spaces may be interpreted as a sign that ISF cannot, or has difficulty to, reach the CSF. (75) However, dilated perivascular spaces are often seen in the elderly and are not AD-specific. (76) Their clinical relevance is unclear. The fact that $Abeta_{40}$ and other proteins can still reach the CSF in AD argues against an obstruction of transport between ISF and CSF.

4.4.2.2. Perivascular deposition of Abeta

Signs that $Abeta_{42}$ is deposited before it reaches the CSF are present: Abeta deposits are found in the walls of the cerebral vasculature and in the glia limitans in the subarachnoid compartment. (43, 77, 78) The deposits in the cerebral vasculature consist mostly of $Abeta_{40}$, and to a lesser extent of $Abeta_{42}$. (56) In clinically diagnosed cerebral amyloid angiopathy, a decreased CSF $Abeta_{40}$ concentration was found. (79) This suggests that perivascular Abeta deposition can indeed lead to a decreased CSF Abeta concentration. However, cerebral amyloid angiopathy found in AD is mostly mild to moderate, (55) and the amount of $Abeta_{42}$ that is deposited in the cerebral vasculature is presumably insufficient to be the sole explanation for the decreased CSF $Abeta_{42}$ concentration.

4.4.2.3. Parenchymal aggregation of Abeta

Aggregation of $Abeta_{42}$ into insoluble deposits may be a reason why $Abeta_{42}$ is decreased in CSF: less soluble $Abeta_{42}$ is left for transport to the CSF, while the insoluble aggregates cannot be transported from ISF to the CSF. $Abeta_{42}$ is much more prone to aggregation than $Abeta_{40}$. (56, 80) Both diffuse and classic plaques contain $Abeta_{42}$, but only the classic plaques, which are fewer in number, contain $Abeta_{40}$. (54) Thus, much more $Abeta_{42}$ than $Abeta_{40}$ is deposited in AD. Considering that $Abeta_{40}$ is the most abundant Abeta peptide in CSF, (81) the relative amount that is deposited in AD may be too little to induce a clear decrease in the CSF $Abeta_{40}$ concentration. In contrast, the relative amount of $Abeta_{42}$ that is deposited is much larger, which may explain why the CSF $Abeta_{42}$ concentration is decreased.

4.4.3. Is CSF $Abeta_{42}$ decreased because more $Abeta_{42}$ is cleared from CSF?

Uptake of $Abeta_{42}$ from the CSF was inferred from research in cell culture that used $Abeta_{40}$ as a model compound for all Abeta species. (50) Theoretically, this process could be upregulated in AD, resulting in more $Abeta_{42}$ to be transported from the CSF into the blood. Since the CSF $Abeta_{40}$ concentration is unaltered, this upregulation should then selectively affect $Abeta_{42}$ and not $Abeta_{40}$. Research to confirm this is currently lacking. In contrast, research in rats suggests that uptake of Abeta from the CSF decreases with aging. (82) Furthermore, the

increase in the plasma concentration of $Abeta_{42}$ that would be expected if upregulated efflux was the case (and peripheral elimination of Abeta was unaltered), has not been shown convincingly. (73, 74) Therefore it seems unlikely that an increased clearance of $Abeta_{42}$ from the CSF is the cause of the decreased CSF $Abeta_{42}$ concentration in AD.

5. PERSPECTIVE

We have reviewed a number of possible mechanisms that could theoretically explain the typical observation of a decreased CSF $Abeta_{42}$ concentration in AD. It appears very difficult to understand the decrease in CSF $Abeta_{42}$ found in AD. Based on simple but systematic reasoning, a number of theoretical mechanisms can be formulated, however, most of these do not concur with the premise that there is an increased Abeta load in the AD brain, and that the decreased CSF $Abeta_{42}$ is accompanied by an unaltered CSF $Abeta_{40}$ concentration. Furthermore, many of these theoretical mechanisms are contradicted by (often fragmented) findings from research. For example, a decreased production of $Abeta_{42}$ has not been shown: production rates were comparable between controls and AD patients. Increased proteolytic breakdown of Abeta is unlikely, since available evidence suggests a decrease in proteolytic activity rather than an increase. An increased microglial uptake of $Abeta_{42}$ is not supported, instead, a decrease in activity with aging is found. Increased clearance of $Abeta_{42}$ from either ISF or CSF has not been reported; rather, decreases in clearance have been suggested.

What, in our opinion, remains as the most plausible cause of the decreased $Abeta_{42}$ concentration in CSF is $Abeta_{42}$ aggregation. $Abeta_{42}$ is known to aggregate easily and once aggregates have been formed, transport of these aggregates from the ISF to the CSF may be seriously impaired. $Abeta_{40}$ has different properties and is not as prone to aggregation, which may explain why less $Abeta_{40}$ is found deposited in the AD brain, and why CSF concentrations of $Abeta_{40}$ are unaltered.

Until novel mechanistic insights with respect to the different steps in Abeta metabolism are obtained, this remains currently the most satisfying explanation for the observed Abeta changes in AD. Our systematic approach may have provided a framework against which the currently available knowledge from research can be laid out, as pieces of a puzzle. In this way, CSF $Abeta_{42}$ can be much more than a diagnostic test with an empirical cut-off value for use in clinical settings. Better understanding of this biomarker may be the key to a better understanding of the disease.

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