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 Alois 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,
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 Scopus 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. ABETA42 METABOLISM

3.1. Production of Abeta42

Abeta42 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 C99. sAPP-beta – just like sAPP-alpha – can be released into intracellular vesicles or extracellularly. C99 remains membrane-bound and is subsequently cleaved by gamma-secretase to produce Abeta42 or Abeta40 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, and for a small part at the plasma membrane. (26) Other proteases that have been reported to degrade 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) Fibillar 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 Abeta40 and Abeta42, 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 Abeta42

Abeta42 and Abeta40 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 Abeta42 and Abeta40 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. Abeta42 and Abeta40 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 Abeta40 when compared to Abeta42 (29, 31), probably related to Abeta40’s lower propensity to aggregate. Abeta42 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...
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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)

3.3.5. 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
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Table 1. Overview of arguments supporting or contradicting the hypothetical mechanisms that could explain the decreased CSF Abeta42 concentration in AD

<table>
<thead>
<tr>
<th>Hypothetical mechanism</th>
<th>Supporting arguments</th>
<th>Contradicting arguments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased production of Abeta42 (4.1.)</td>
<td>- Could be the result of a reduction in viable neurons due to neurodegeneration</td>
<td>- An increased brain Abeta42 load is found post-mortem - Abeta40 shares the same production pathway as Abeta42 but CSF Abeta40 is not decreased - Disorders with an increased production of Abeta have decreased concentrations of CSF Abeta42 - The production of Abeta42 in AD did not differ from controls in a labeling study</td>
</tr>
<tr>
<td>Decreased secretion of Abeta42 from neurons (4.1.)</td>
<td>- Intraneuronal Abeta aggregation has been described in Tg mice</td>
<td>- The typical Abeta plaques of AD are found extracellularly</td>
</tr>
<tr>
<td>Increased degradation of Abeta42 (4.2.)</td>
<td></td>
<td>- An increased brain Abeta42 load is found post-mortem - Increased degradation would probably affect Abeta40 as well, yet the CSF Abeta40 concentration is unchanged - Levels of neprilysin (one of the proteases involved in Abeta degradation) decrease with aging</td>
</tr>
<tr>
<td>Increased microglial uptake of Abeta42 (4.3.)</td>
<td>- Activated microglia are found in the vicinity of Abeta plaques</td>
<td>- An increased brain Abeta42 load is found post-mortem - Microglia become dysfunctional with aging</td>
</tr>
<tr>
<td>Increased clearance of Abeta42 from ISF to blood (4.4.1.)</td>
<td>- Expression of LRP (which promotes transport of Abeta from ISF to blood across the blood brain barrier) by perivascular cells increased in reaction to Abeta42</td>
<td>- Perivascular cells expressing LRP degenerated after uptake of Abeta - LRP expression is reduced in AD - No increase in plasma Abeta42 is found - An increased brain Abeta42 load is found post-mortem</td>
</tr>
<tr>
<td>Hampered transport of Abeta42 with ISF to CSF (4.4.2.1.)</td>
<td>- Dilated perivascular spaces may indicate obstruction of ISF flow</td>
<td>- Dilated perivascular spaces are often seen in the elderly and their clinical relevance is unclear - Other proteins (including Abeta40) still reach the CSF</td>
</tr>
<tr>
<td>Perivascular deposition of Abeta42 (4.4.2.2.)</td>
<td>- Abeta deposits are found perivascularly</td>
<td>- Perivascular Abeta deposits contain mostly Abeta40</td>
</tr>
<tr>
<td>Parenchymal aggregation and deposition of Abeta42 (4.4.2.3.)</td>
<td>- An increased brain Abeta42 load is found post-mortem - Abeta42 is more prone to aggregation than Abeta40</td>
<td></td>
</tr>
<tr>
<td>Increased clearance of Abeta42 from CSF to the blood (4.4.3.)</td>
<td></td>
<td>- Uptake of Abeta from CSF decreased with aging - No increase in plasma Abeta42 is found</td>
</tr>
</tbody>
</table>

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

is thus increased. (57, 58) However, the CSF concentration of Abeta42 is decreased in AD patients, while the CSF Abeta40 concentration is unaltered. (14, 48) We will focus on reasons why CSF Abeta42 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 Abeta42 production reduced?

Theoretically, a decreased concentration of Abeta42 in CSF could simply be the result of a decreased production of Abeta42, 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 Abeta42 load in the brain. Second, if the production of Abeta42 were decreased, the production of Abeta40 would probably be decreased as well, since Abeta42 and Abeta40 likely share the same production pathway. This should then lead to a decreased CSF Abeta40 concentration, which, however, is not observed in AD. Third, a decreased concentration of CSF Abeta42 is also found in familial AD and in Down syndrome, disorders in which overproduction of Abeta42 has been clearly demonstrated. (59-62) Decreased Abeta42 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 Abeta42 secretion from the cell is decreased, leaving less Abeta42 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 Abeta42 by the cell is unlikely to be the cause of the decreased CSF Abeta42 concentration.

Supporting these arguments against a decreased production or secretion of Abeta42 is a study showing that the production rate of Abeta42 and Abeta40, as measured in CSF using labeled Abeta42 and Abeta40, did not differ between controls and AD patients. (64)

4.2. Is Abeta42 degradation increased?

It can be hypothesized that an increase in proteolytic breakdown of Abeta42 leads to a decreased CSF Abeta42 concentration. However, an increase in proteolytic breakdown would clear the brain from not only Abeta42, but also from Abeta40 (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
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...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 Abeta42 increased?

An increased microglial uptake of Abeta42 could be hypothesized to lead to the decreased CSF Abeta42 concentration by leaving less Abeta42 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 Abeta42. (34, 70, 71) Thus, it is unlikely that microglial ability to degrade Abeta is increased in AD.

4.4. Is Abeta42 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 Abeta42 from ISF increased?

An increased clearance of Abeta42 from ISF to blood across the blood-brain barrier would leave a smaller amount of Abeta42 in the ISF that can be transported to the CSF and could thus explain the decreased CSF Abeta42 concentration. The primary transporter of Abeta across the blood-brain barrier is LRP. Even though LRP favors clearance of Abeta40 over Abeta42, it can be hypothesized that in AD, clearance of Abeta42 is upregulated while clearance of Abeta40 remains the same. In support of this hypothesis, expression of LRP by perivascular cells was increased in response to Abeta42 in vitro, while Abeta40 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 Abeta42 from ISF to blood-brain barrier and could actually lead to a reduced transport of Abeta42 out of the brain and an increased uptake of peripheral Abeta42 into the brain.

Another argument against an increased transport of Abeta42 across the blood-brain barrier is the lack of an increase in plasma Abeta42 concentration. Increased transport of Abeta42 to the blood should result in an increase in the plasma concentration of Abeta42 – assuming that the peripheral breakdown and elimination of Abeta42 are not increased in AD. Reports on the plasma Abeta42 concentration in AD patients are contradictory, but a clear increase has not been shown. (73, 74) Finally, enhanced clearance of Abeta42 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 Abeta42 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 Abeta42-containing ISF cannot reach the CSF or if Abeta42 is deposited before ISF reaches the CSF, the Abeta42 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 Abeta40 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 Abeta42 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 Abeta40, and to a lesser extent of Abeta42. (56) In clinically diagnosed cerebral amyloid angiopathy, a decreased CSF Abeta40 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 Abeta42 that is deposited in the cerebral vasculature is presumably insufficient to be the sole explanation for the decreased CSF Abeta42 concentration.

4.4.2.3. Parenchymal aggregation of Abeta

Aggregation of Abeta42 into insoluble deposits may be a reason why Abeta42 is decreased in CSF: less soluble Abeta42 is left for transport to the CSF, while the insoluble aggregates cannot be transported from ISF to the CSF. Abeta42 is much more prone to aggregation than Abeta40. (56, 80) Both diffuse and classic plaques contain Abeta42, but only the classic plaques, which are fewer in number, contain Abeta40. (54) Thus, much more Abeta42 than Abeta40 is deposited in AD. Considering that Abeta40 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 Abeta40 concentration. In contrast, the relative amount of Abeta42 that is deposited is much larger, which may explain why the CSF Abeta42 concentration is decreased.

4.4.3. Is CSF Abeta42 decreased because more Abeta42 is cleared from CSF?

Uptake of Abeta42 from the CSF was inferred from research in cell culture that used Abeta40 as a model compound for all Abeta species. (50) Theoretically, this process could be upregulated in AD, resulting in more Abeta42 to be transported from the CSF into the blood. Since the CSF Abeta40 concentration is unaltered, this upregulation should then selectively affect Abeta42 and not Abeta40. 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
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increase in the plasma concentration of Abeta42 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 Abeta42 from the CSF is the cause of the decreased CSF Abeta42 concentration in AD.

5. PERSPECTIVE

We have reviewed a number of possible mechanisms that could theoretically explain the typical observation of a decreased CSF Abeta42 concentration in AD. It appears very difficult to understand the decrease in CSF Abeta42 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 Abeta42 is accompanied by an unaltered CSF Abeta40 concentration. Furthermore, many of these theoretical mechanisms are contradicted by (often fragmented) findings from research. For example, a decreased production of Abeta42 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 Abeta42 is not supported, instead, a decrease in activity with aging is found. Increased clearance of Abeta42 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 Abeta42 concentration in CSF is Abeta42 aggregation. Abeta42 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. Abeta40 has different properties and is not as prone to aggregation, which may explain why less Abeta40 is found deposited in the AD brain, and why CSF concentrations of Abeta40 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 Abeta42 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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