Novel synaptic markers predict early tau pathology and cognitive deficit in an asymptomatic population at risk of Alzheimer's disease

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Abstract

Cognitive dysfunction in Alzheimer's disease (AD) correlates closely with pathology in the neuronal microtubule-associated protein tau. Tau pathology may spread via neural synapses. In a population of cognitively unimpaired elderly at elevated risk of AD, we investigated four cerebrospinal (CSF) markers of synaptic dysfunction and degeneration. Three of these (SYT1, SNAP25, and ADAM23) are derived from pre-synaptic structures, while ADAM22 reflects post-synaptic changes. All four markers correlated strongly with tau protein measures. In statistical models, SYT1 accounted for more than half the total variance in both total- and P(181)-tau levels. Observed correlations with CSF levels of Alzheimer amyloid-β (Aβ42) were somewhat weaker. In longitudinal data, baseline levels of ADAM22 and ADAM23 robustly predicted increase over time in both total- and P-tau. CSF SYT1 levels also correlated with PET image uptake of tau and (at a trend level) Aβ in areas of interest for early AD pathology. CSF SYT1 and SNAP25 levels correlated inversely with a global psychometric score and several of its domain subscales. In quantitative trait loci analyses, all four synaptic markers were associated with at least one AD genetic risk locus. Upon "staging" participants by their evidence of amyloid and tau pathology (A/T/N framework), the CSF synaptic markers were unexpectedly reduced in participants with CSF evidence of amyloid but not tau pathology. They were clearly elevated, however, in the CSF of persons with indications of both tau and amyloid pathology. These observations provide evidence for clear pre-synaptic degeneration in cognitively unimpaired persons with biomarker evidence of early AD pathology.

1. Introduction

Alzheimer's' disease (AD), the most common cause of dementia, represents a fundamental threat to the financial and social well-being of human populations [1]. Although some cases of atypical, early-onset AD can be provoked by single genes, the large majority of affected persons are older and have a disease with a strong polygenic predisposition [2]. Recently introduced anti-amyloid antibody treatments for AD afford only moderate benefit by slowing symptom progression in persons with mild cognitive impairment due to AD, or with mild AD dementia [3-5]. Development of preventive interventions for persons with still earlier-stage AD will require measurable biomarkers of pre-symptomatic disease progression, to identify and monitor effects on AD pathophysiology. Because synaptic dysfunction, degeneration and loss correlate strongly with cognitive decline in AD[6-8], measurable markers of synaptic pathology are of potential interest for this purpose, along with better-known indicators of amyloid and, especially, tau pathology. [9, 10] In this context, we take particular note of the recent observation that synapses in AD are packed with tau oligomers, most notably when persons with tau neurofibrillary pathology have substantial cognitive symptoms [11]. Hypothetically, synaptic oligomeric tau might be the very first stage of phosphorylated tau containing dystrophic neurites surrounding the amyloid plaques in AD. Furthermore, it appears that the association of Alzheimer amyloid (Aβ42) with tau pathology is significantly increased among persons with high CSF concentration of GAP-43, a well-established biomarker of presynaptic terminal damage[12]. Finally, in animal models, microglia and astrocytes engulf more synapses among mice with both amyloid and tau pathology [13-15]. Such tau-associated synaptic degeneration and engulfment are probably responsible for much of the characteristic cognitive deficits in AD, which, importantly, might be obviated if the synaptic degeneration could be prevented [13, 14, 16].

Synaptic dysfunction and degeneration can be studied by measuring cerebrospinal fluid (CSF) levels of synaptic proteins. These include two members of the A Disintegrin and Metalloprotease (ADAM) family. ADAM proteins are membrane-anchored proteins that are structurally related to snake venom disintegrins and have been implicated in several biological processes involving cell-cell and cell-matrix interactions including fertilization, muscle development, and neurogenesis. The genes *ADAM22* and *ADAM23* encode for ADAM22 and ADAM23, a pair of post- and pre-synaptic proteins that, unlike other members of the ADAM family, lack metalloprotease activity [17]. These genes are highly expressed in the human brain. Their protein products, together with leucine-rich glioma-inactivated protein 1 (LGI1), form a trans-synaptic complex, in which ADAM23 regulates the Kv1 potassium channel and ADAM 22 interacts intracellularly with PSD95, which links this complex to a stargazin, a regulatory subunit of the AMPA receptor. The resulting protein complex is essential for AMPA receptor-dependent excitatory synapse maturation and maintenance[18]. Prior work has shown that CSF ADAM22 is elevated in late stage AD patients[19], while plasma ADAM23 is related to AD risk factors [20].

Two other markers, synaptotagmin-1 (SYT1) and synaptosomal-associated protein 25 (SNAP25) have also been recently established as novel biomarkers for synaptic degeneration in AD [21, 22]. SYT1, a pre-synaptic protein, is a calcium sensor needed for synaptic vesicle exocytosis. It thereby mediates neurotransmitter release in hippocampal neurons, and it also promotes presynaptic clathrin-mediated endocytosis in interaction with membrane phospholipids and adaptor proteins[23]. The mostly pre-synaptic synaptosome associated protein 25 (SNAP25) is an essential part of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex that mediates synaptic communication by initiating the fusion of synaptic vesicles[24]. CSF levels of both SYT1 and SNAP25 are elevated in patients with AD dementia as compared with asymptomatic controls[21, 22]. We investigated AD pathophysiology and cognition in an aging human cohort at elevated risk of AD using cerebrospinal fluid (CSF) measures of four important synaptic proteins

2. Methods

All procedures were approved by the McGill University Faculty of Medicine Institutional Review Board and complied with the ethical principles of the Declaration of Helsinki.

2.1 Participants.

These studies were conducted among members of the Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer's Disease (PREVENT-AD) cohort. This longitudinal observational cohort enrolled cognitively unimpaired individuals over the age of 55, (mean age at entry 63.4 ± 5.0) who had a parent or multiple siblings diagnosed with AD dementia [25]. Participants have been followed-up annually with structural and functional magnetic resonance imaging (MRI), medical, and cognitive assessments. The cohort's 375 members donated blood at each visit, and a subset of 160 volunteered for at least one lumbar puncture (LP). Most of these were included in a sample of 129 participants who underwent brain positron emission tomography (PET) to assess Aβ and tau deposition. APOE genotype was determined using the PyroMark Q96 pyrosequencer (Qiagen, Hilden, Germany). DNA was amplified using PCR with primers with primers rs429358 amplification forward 5'-ACGGCTGTCCAAGGAGCTG-3', rs429358 amplification reverse biotinylated 5'-CACCTCGCCGCGGTACTG-3', rs429358 sequencing 5'-CGGACATGGAGGACG-3', rs7412 amplification forward 5'-CTCCGCGATGCCGATGAC-3', rs7412 amplification reverse biotinylated 5'-CCCCGGCCTGGTACACTG-3' and rs7412 sequencing 5'-CGATGACCTGCAGAAG-3'.

CSF from 112 subjects was analyzed by OLINK Proximity Extension Assay. Another 154 CSF samples from PREVENT-AD were analyzed by mass spectrometry by the Zetterberg, Blennow and Brinkmalm group in Sweden for synaptic protein concentrations as described below. Data for these studies were obtained from the PREVENT-AD Research Group data release 6.0 (https://prevent-alzheimer.net/?page_id=1760&lang=en). *A complete listing of PREVENT-AD Research Group can be found in the PREVENT-AD database:*

https://preventad.loris.ca/acknowledgements/acknowledgements.php?date=[2024-03-30].

2.2 CSF measurements

Lumbar punctures were performed following an overnight fast to obtain CSF samples, as previously described[26]. The CSF AD biomarkers p(181)*tau*, t-*tau*, and Aβ42 were measured using validated Innotest ELISA kits (Fujirebio, Sweden) following procedures from the Biomarkers for Alzheimer's Disease and Parkinson's Disease (BIOMARKAPD) consortium[27]. CSF ADAM22 and ADAM23 levels were measured using Olink's proximity extension assay system in its Neurology panel (Olink, Sweden). Immunoprecipitated SNAP-25 and synaptotagmin-1 SYT1 from CSF were analyzed using liquid chromatography/selected reaction monitoring mass spectrometry (LC-SRM/MS) (Agilent 6490 QQQ MS), as described by Brinkmalm et al.[28] and Öhrfelt et al.[22] For comparison purposes in the A/T/N stratification analysis, a subset of subjects (n=84) was measured at baseline for growth-associated protein 43 (GAP43) using the same MS method, as previously described.

2.3 PET image acquisition and processing

Aβ and tau deposition was quantified using ^{18}F-NAV4694 (Navidea Biopharmaceuticals, Dublin, OH, USA) and flortaucipir (^{18}F-AV1451; Eli Lilly & Company, Indianapolis, IN, USA). Amyloid and tau scans were acquired 40 to 70 and 80 to 100 minutes post-injection, respectively. T1-weighted structural MRI scans were obtained using a 3T Siemens Trio scanner at the Douglas Mental Health Research Institute (Montreal). Amyloid-beta positivity was determined as described recently.[29]. AD-related tau deposition was assessed by averaging flortaucipir standard uptake value ratio (SUVR) in the entorhinal cortex, fusiform, parahippocampal, and lingual gyri.[29, 30]

2.4 Genotyping and imputation

Automated DNA extraction from buffy coat samples was performed using the QIASymphony DNA mini kit (Qiagen, Toronto, Canada). Genotypes were determined with the Omni2.5 M-8 array (Illumina, San Diego, CA, USA). The PLINK tool set (http://pngu.mgh.harvard.edu/purcell/plink/) was used to filter gender mismatches, filter missingness at both the sample-level (<5%) and single-nucleotide polymorphism (SNP)-level (<5%), filter assess sample heterozygosity, and filter SNPs in Hardy-Weinberg disequilibrium ($P > .001$). Only post-imputed SNPs with an info score >0.7 were considered.

2.5 Cognitive testing

Participants' cognitive performance was measured annually using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS)[31]. This instrument evaluates five cognitive domains (immediate and delayed memory, attention, language, and visuospatial-constructional abilities) and yields a total summary score. Four equivalent test versions were administered in French or English as appropriate [31].

2.6 Pathological staging

Using the A/T/N criteria,[32] we used baseline CSF Aβ42 and total-tau measurements to stage 141 participants who also had at least one available CSF synaptic protein measurement. Disease status was classified as Stage 0 (normal CSF Aβ42 and t-*tau*; A-/T-), Stage 1 (low Aβ42, normal t-*tau*; A+/T-), Stage 2 (low Aβ42, elevated t-*tau*; A+/T+), and Suspected Non-Alzheimer Pathology (SNAP, high t-*tau* only; A-/T+). Because recent evidence suggests that increasing amyloid burden (*decreasing* CSF amyloid concentration) portends poorer clinical outcomes before typical thresholds are crossed [33-35], we applied a sensitive threshold value for Aβ42 abnormality at the 25th percentile value or <1028 pg/mL. Similarly, we applied a sensitive t-*tau* abnormality threshold at the 75th percentile, or >337pg/mL[36]. To increase contrasts between stages for these analyses, we excluded data from 23 individuals whose marker concentrations were within ±5% of either the Aβ42 or total-tau threshold.

2.7 Genotyping in the Quebec Founding Population (QFP) cohort

Quebec Founder Population (QFP) [37] descends in genetic isolation from a few thousand founders who emigrated to Eastern Canada from France in the 17th century. The demographic history of the QFP, which is characterized by a population bottleneck, a rapid population expansion and little admixture, makes it a valuable resource for genetic studies [38]. Indeed, the use of population isolates in order to map complex traits such as AD has been shown to reduce the genetic background noise and to allow the detection of rare population-specific signals[39]. Genomic DNA samples from Genizon and the Douglas—Bell Canada Brain Bank were extracted from blood or brain tissue using the DNeasy tissue kit (Qiagen, Toronto, Canada) and automated DNA extraction (NA-1000, AutoGen, Holliston, USA). Genotyping was performed with the Illumina 550k Human Quad array (Illumina, San Diego, USA) and quality controlled using PLINK as described in the previous paragraph.

2.8 Statistical analyses

We used Spearman's rank correlation tests to compare baseline demographic characteristics of cognitively unimpaired PREVENT-AD participants who were Aβ-positive vs. -negative, *APOE* ε4-positive vs, -negative, and tau-positive vs. -negative (Table S1). General linear models (GLM) tested for associations between CSF AD biomarkers (Aβ42, t-*tau* and (181)P-*tau*) and CSF synaptic proteins (ADAM22, ADAM23, SYT1, SNAP25) adjusting for age, sex, and *APOE* status. We used a similar approach to test for association between CSF synaptic protein levels with global cortical NAV4694 SUVR and flortaucipir retention in the entorhinal cortex area and in the fusiform, and lingual gyri, controlling for age, sex and *APOE* status. Likewise, we used GLM to test for associations between baseline CSF synaptic proteins and rate of change of AD biomarkers, CSF synaptic proteins at baseline and corresponding RBANS score as all using age, sex, *APOE* genotype and education as covariates. We conducted more linear regression analyses to examine the impact of AD risk genes on CSF synaptic protein expression levels, as well as cognitive performance assessed by polygenic risk score (PRS) of CSF synaptic proteins. We adjusted for sex, age, and APOE status. PRS is also adjusted for principal components of the synaptic proteins based on pQTL analysis. False discovery rate was applied to correct for multiple testing.

3. Results

3.1 Demographics

Table 1 summarizes the demographic characteristics of the PREVENT-AD cohort used to analyze the association of *APOE*-ε4 status with CSF synaptic protein levels and cognitive assessments. Consistent with the existing literature, *APOE* status affects CSF Aβ42 as well as PET amyloid and tau deposition. Sex showed an association with CSF Aβ42 and PET tau and, with total RBANS scores as well as language and immediate memory sub-scores (Table 1).

3.2 CSF synaptic proteins in relation to AD hallmark pathological protein biomarkers

At baseline level, the four CSF synaptic proteins (ADAM22, ADAM23, SYT1, SNAP25) were compared with AD classical pathological biomarkers (Figure 1) in asymptomatic PREVENT-AD participants. A significant positive correlation was found between all the synaptic proteins and the AD tau biomarkers, while the correlations with CSF Aβ42 were much weaker, and for post-synaptic ADAM22 and Aβ42 was not statistically significant. Especially notable was the correlation of tau (either t-*tau* or P-(181)*tau*) with presynaptic SYT1, where R^2 values >0.5 indicated that tau levels accounted for more than half the overall variance in the synaptic marker (or *vice versa*).

3.3 CSF synaptic proteins in relation to PET AD hallmark proteins.

Not surprisingly, we observed substantial deposition of Aβ and even tau in the PET scans of these high-risk but non-demented participants, even though levels were typically below conventional thresholds for Aβ or tau “positivity” (Figure 2). A meta-analytic SUVR for Aβ over regions of interest in early AD showed a suggestive association with CSF SYT1 that did not meet conventional criteria for statistical significance (Panel E). A stronger correlation was apparent between SYT1 and a meta-ROI assessment of tau deposition. Individual regional correlations were observed between PET tau with SYT1 and SNAP25 in the entorhinal area and lingual gyrus (Panels B and D), and with SYT1 in the fusiform area (Panel C); consistent with early Braak stage I-III deposition in prodromal subjects. On the other hand, presynaptic terminal protein GAP43 was significantly associated with all regional PET tau indices and global amyloid indices (R^2 = 0.107, p = 0.0453; Figure 3F).

3.4 CSF synaptic proteins in relation to cognitive performance

In linear regression analyses adjusted for age, *APOE* ε4 status, education, and sex, CSF synaptic proteins levels were assessed cross-sectionally in relation to RBANS total score (Figure 3A-D) and to each of its five cognitive domain scores (Figure 3E-T)). Here, individuals with multiple lumbar punctures contributed a data point for each time point of CSF donation. Higher CSF levels of presynaptic SYT1 and SNAP25 were found in persons with lower total RBANS scores (reduced cognition), while suggestive correlations were observed in several individual cognitive domains. Of possible note, we observed no association of CSF synaptic protein levels with the delayed memory subscale of the RBANS.

3.5 CSF synaptic markers and pathological staging.

Figure 4A shows how PREVENT-AD participants were assigned to four different quadrants using the AT(N) approach [32-36]. FDR-adjusted models revealed at least trend-level differences in all synaptic markers tested when comparing levels at Stage 0 (A-/T-) vs. Stage 1 (A+/T-), and again at Stage 1 vs. Stage 2 (A+/T+). Similar to observations described elsewhere for immune/inflammatory CSF markers[40, 41]; the observations show a consistent bidirectional pattern of association between the synaptic marker expression level and pathological stage, with reduced levels at Stage 1 and increased levels at Stage 2, when tau pathology emerges (Figure 4B).

3.6 Polygenic Risk Score of pQTL CSF ADAM22 and cognitive performance

Using pQTL analyses to identify genetic polymorphisms that affects synaptic proteins levels in the CSF, a polygenic risk score (PRS) was constructed for all synaptic proteins of interest and contrasted against baseline cognitive performance of participants using multiple linear models, adjusted additionally for educational years. Additionally, PRS was adjusted with age, sex, APOE ε4 status. Of all the synaptic proteins examined, only post-synaptic ADAM22 pQTL PRS was found to correlate with immediate memory subscale (Figure 5A, $R^2 = 0.143$, $p = 0.00397$), delayed memory subscale (Figure 5B, $R^2=0.0744$, $p = 0.00583$), visuospatial constructional memory subscale (Figure 5C, $R^2=0.275$, $p = 0.00735$), and total scale (Figure 5F, $R^2=0.227$, $p = 0.00701$). Conversely, ADAM23, SYT1, and SNAP-25, which are presymptomatic markers, did not show any associations with their corresponding polygenic risk score.

4.0 Discussion

In studies of synaptic involvement in the pathogenesis of early AD, we investigated two pre-synaptic (ADAM23, SYT1), one predominantly presynaptic (SNAP-25) and one post-synaptic (ADAM22) protein markers in the CSF of the PREVENT-AD cohort of initially unimpaired elderly persons at elevated risk of AD. A subset of PREVENT-AD subjects were analyzed to explore the suggested association between CSF GAP-43 and specific PET imaging markers mentioned in a recent report in AD[42]. We examined these proteins in relation to the classic CSF biomarkers of AD pathology, Aβ42 and total- and (181)P-*tau*, observing that all four synaptic proteins were strongly related to CSF levels of tau and, more modestly, Aβ42. The pre-synaptic marker SYT1 showed an especially strong association with total- and (181)P-*tau*. PET image analyses similarly revealed that CSF synaptic proteins are positively associated with tau deposition, especially in the entorhinal cortex, fusiform gyrus and lingual gyrus; consistent with early Braak stages I-III. Further, we observed an inverse association between the two pre-synaptic markers SYT1 and SNAP25 with global and domain-specific scores on a widely used neuropsychological battery.

Our results are consistent with recent findings that synaptic proteins co-localize with total- and p-*tau* in the microglia of the brain [11]. Microglia and astrocytes in tissue from AD patients have been shown to carry more oligomer-positive synaptic fragments, consistent with the fact that these glia are involved in the process of synaptic pruning and loss of synaptic connectivity that is characteristic of AD [11, 43]. This observation, combined with the presented results, implies that synaptic depletion is influenced by the progression of classical AD biomarkers in CSF as well as on PET imaging. Similar observations by others recently found association between another terminal-associated protein, GAP-43, and longitudinal PET-tau findings in ADNI participants with dementia [12]. Here, again, the associations of the CSF synaptic proteins with PET amyloid deposition were less impressive, in accord with the notion that earlier amyloid pathology may trigger both synaptic and tau pathology, either in parallel or sequentially (the order of the two changes being presently unknown). A correlation of tau biomarker pathology with cognitive decline is now widely accepted. Given the striking associations between CSF synaptic markers and tau described here, it is not surprising that the synaptic markers also showed a strong capacity to predict cognitive scores. It seems likely, but is unproven here, that synaptic dysfunction or degeneration, as indicated by the four CSF markers, accounts for much of the cognitive decline that is characteristic with the spread of tau pathology in AD.

Using pQTL analysis to identify polymorphisms that regulate CSF synaptic protein levels in the CSF in these asymptomatic subjects, we then constructed a polygenic risk score to examine the impact of regulating genetic variants on cognition (RBANS), including the five sub-domains. Although presynaptic SYT1, ADAM23 and SNAP-25 polygenic risk scores failed to show any association with the cognitive status, a highly significant positive correlation was observed between the post-synaptic ADAM22 PRS and total RBANS scale index scores; emphasizing the genetic connection between synaptic gene regulation and cognitive ability. The fact that ADAM22 PRS positively correlates with three of the five RBANS subscale is both interesting and intriguing. Intriguing because the association is positive and ADAM22 is a post-synaptic regulator of the glutamatergic AMPA and NMDA receptors activity. ADAM22-mediated NMDAR-dependent LTP results as a consequence of coincident depolarization and glutamate binding, calcium influx through NMDARs, which activates intracellular signaling cascades that ultimately are responsible for the altered synaptic efficacy[44]. As NMDA receptor-dependent long term potentiation (LTP) is believed to be the predominant type of LTP in the hippocampus[45] whereas transgenic models of AD pathology have been associated with disruption of NMDAR-dependent LTP and decreases of NMDARs[44, 46, 47], perturbation of the ADAM22 gene expression and/or catabolism by genetic polymorphisms included in the PRS suggested that a similar mechanism is at play early on in the disease process, years before the actual emergence of cognitive deficits.

While trying to understand the nature of relationship that synaptic proteins have with AD pathological markers, we found an interesting bi-directional relationship between CSF synaptic proteins and pathological stages defined according to the A/T/N criteria. Surprisingly, levels of all our CSF synaptic markers were reduced for participants whose biomarkers were positive for amyloid but negative for tau (A+/T-). Predictably, given our other findings, we found the opposite, an elevation in synaptic markers in CSF of persons with (A+/T+) biomarker status. Our earlier studies had detected a similar “chevron” pattern in PREVENT-AD participants’ CSF assays of the immune/inflammatory markers IL-8, IL-12, IL-15, and VCAM. [36] Our preferred interpretation of the latter observations is that a dearth of innate immune activation in some persons had created an environment that was permissive to the deposition of Aβ, so that amyloid pathology was inversely related to inflammatory marker levels. However, as tau positivity emerges in these subjects, the situation is reversed. Regarding the current findings, Franzmeier et al. have suggested that Aβ-related tau deposition is catalysed by high levels of the synaptic marker GAP-43 in the CSF [12]. We speculate that, at least early in the disease, increased levels of Aβ and of sAPP may actually be a part of an adaptive response that protects synapses from the degeneration[48] that appears once tau pathology is present. In this model, one could explain the sequence of Aβ deposition typically preceding tau pathology[49] by some effect of Aβ (or perhaps its progenitor molecular species) that is called upon to prevent impending synaptic and tau pathologies. That construct is consistent with animal and post-mortem data showing that tau spreads across synapses in a manner that is dependent on brain activity [50] but follows Aβ deposition [51].

In brief, CSF ADAM23, SYT1 and SNAP25 presynaptic proteins could serve as valid biomarkers for identifying those with a greater risk of MCI/AD conversion from a cohort of asymptomatic elderly. Supplementary figure 1 contains a summary heatmap of the study's overall results.

Considering the close relationship between synaptic function and cognition described here, these presynaptic markers could be used (in conjunction with the classical AD biomarkers) to monitor disease progression in absence of noticeable cognitive deficits in the prodromal phase of the disease. We demonstrated that increased levels of CSF synaptic proteins were associated with lower cognitive performance as measured in RBANS immediate memory subscale, language subscale, visuospatial constructional memory subscale, attention subscale and total scale (Figure 3). While these findings are also very consistent with others that CSF SYT1 and SNAP25 are elevated in cognitively impaired AD patients, as compared to controls [21, 22], our investigations provide further insight into the relationship between these CSF synaptic proteins and subscales of cognition in an at-risk cohort without dementia. Furthermore, although no previous study has examined the CSF protein level of ADAM22 and 23, the glutamatergic system and their impact on cognition, the functionality of these synaptic proteins in the prodromal phase of the disease warrant additional investigations.

Finally, the fact that many of the recently identified risk genes directly or indirectly affect synaptic physiology prompted us to examine in the PREVENT-AD cohort the relationship between the selected CSF synaptic proteins and the top 75 AD risk genes identified by GWAS [52]. As expected, several GWAS risk polymorphisms were found to significantly associates with the selected synaptic proteins discussed above (supplemental figure 2). Among the most significant associations, MME, also called neprilysin, is of special interest. It is known to act as a potent Aβ-degrading enzyme in the CNS[53]. Recent analyses showed that AD subjects displayed lower levels of MME gene expression in the frontal cortex [54] whereas cerebrospinal fluid (CSF) MME levels are also reduced in MCI and AD subjects and were correlated, in these patients, with lower MMSE scores as well as higher CSF tTau levels [55, 56]. In contrast, the negative correlation between the ACE polymorphism, the angiotensin converting enzyme, and synaptic markers SNAP25, SYT1 and ADAM23 is both intriguing and important. ACE and its mechanistic relationship to AD is complex. ACE is known for regulating blood pressure through the renin-angiotensin system, in which renin converts angiotensinogen to angI that is in turn cleaved by ACE1 to angII, a potent vasoconstrictor. Inhibition of ACE1 and angII signaling in the hippocampus enhances memory in rodents [57, 58], decreases memory deficits in mouse models of AD[57, 58], and reduces the incidence of AD in humans [59]. In the CSF of patients with AD, ACE1 positively correlates with tau, phosphorylated tau, Aβ, and late-onset AD risk (36, 37). ACE1 is increased in AD brain, correlating with Aβ and AD severity (38, 39). ACE1 could be up-regulated in response to Aβ because cell-based studies have shown that ACE1 degrades Aβ42 (40–42). It is thus tempting to link the association between ACE and MME variants and synaptic proteins to the amyloid metabolism however, in the pre-symptomatic phase, the most significant associations involved t-*tau* and to a lesser extent, Aβ42. One possible explanation could be that these risk variants can only enhance synaptic pathology when a given subject transits from the A+/T- stage 1 to the A+/T+ stage 2 status. This is consistent with the reported increased in neprilysin in the CSF in AD patients, with lower MMSE scores and higher CSF tTau levels [55].

4. Conclusion

Synaptic proteins appear to play an important role in the pathophysiology of sAD, and notably in the pre-symptomatic phase of the disease. Characterization and identification of pathways involved in synaptic degeneration are important for improved understanding of the stages of this disease where preventive interventions could have greatest benefit.

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Consent statement

All participants provided signed informed consent before their participation, and the protocol was approved by the ethics committee of McGill University.

Keywords

dementia; atrophy; apolipoprotein; *APOE* ε4; amyloid; blood; blood-brain barrier; phosphorylated; p-tau231; p-tau181; tau; bedtime; mild cognitive impairment; gray matter volume; accelerometry.

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