4. Discussion

The present study explored the association between BACE1 activity, which is regarded as the rate-limiting factor of Aβ production, and the concentrations of several AD markers in CSF. Our findings partly confirm the results of previous research but they also add new evidence to the existing literature, e.g. by demonstrating a positive correlation between BACE1 activity and SORL1 concentration in CSF.

4.1. BACE1 and tau

In the present study BACE1 activity correlated positively with tau concentrations in the AD group. This is a challenging observation at first glance, which is nevertheless in line with three previous individual reports (16, 17, 43) and a meta-analysis (17). Tau is a marker of axonal degeneration, which may enhance BACE1 shedding resulting in higher CSF levels and activity of BACE1 in AD (44). Alternatively, since both tau and BACE1 are primarily located in neurons, their correlation may indicate that increased BACE1 activity in CSF is associated with protein release from decaying neurons.

4.2 BACE1 and markers of APP metabolism

We also found a positive correlation between BACE1 activity and sAPPβ. This association was expected since sAPPβ is a direct product of APP cleavage by BACE1 (9). BACE1 activity did not correlate with the CSF levels of sAPPα in our study; this was also an expected result since there is no direct association between BACE1 and sAPPα, which is a product of α-cleavage rather than of β-cleavage (3). In contrast to our findings, an association between sAPPα and BACE1 activity in CSF

was observed in a previous study (16). The authors argued that this surprising finding might be explained by the strong correlation between sAPPα and sAPPβ in CSF suggesting tightly linked regulating processes, or alternatively by the fact that sAPPα may reflect overall APP levels. The expected correlation between BACE1 activity and $A\beta_{1-42}$ was probably obscured in our study by other factors influencing Aβ deposition in senile plaques, which is thought to be mirrored by decreased $A\beta_{1-42}$ concentrations in CSF.

4.3 BACE1 and SORL1

We also report a positive correlation between BACE1 activity and SORL1 concentrations in CSF. This finding is consistent with in-vitro studies showing a direct interaction between BACE1 and SORL1 (24). SORL1 was found to be reduced in the Golgi apparatus and early endosomal compartments in AD (45-47), allowing or promoting APP processing by BACE1 and α-secretase (23, 24, 48). The employed ELISA determines the soluble form of SORL1, which consists of the extracellular domain of the membrane-spanning SORL1 protein (40). This extracellular fragment seems to be less efficient than full-length SORL1 in mediating APP transport through the Golgi-apparatus (24) since SORL1 fragments have altered binding capacities in comparison to the full-length SORL1 receptor (49, 50). Taking into account that AD pathology is associated with increased BACE1 activity it can be hypothesized that the intracellular decline of full-length SORL1 levels in AD is caused by an elevation in the endoproteolytical cleavage of SORL1, resulting in increased concentrations of the less efficient soluble SORL1 that we measure in CSF. However, it has to be mentioned that no causalities can be derived from a study reporting associations between CSF proteins and that the validity of our argumentation will have to be tested in future studies.

4.4 Limitations

The present study should be viewed in the light of a number of limitations. The size of the control group was relatively small and the healthy controls were younger than the patients with AD. As a consequence we were not in the position to explore differences in BACE1 activity between physiological aging and AD. Furthermore, although not very likely, some patients with causes for cognitive impairment other than AD might have been included despite the rigorous diagnostic assessment. No pathological verification of diagnoses was available, but current diagnostic criteria for AD have been shown to be very accurate for populations recruited at specialized centers. Further research on larger samples with age-matched control groups is needed to replicate our findings on the one hand; on the other hand, genetic variants of SORL1 will also have to be considered in future analyses. The so far inconclusive findings on SORL1 in CSF [30, 31] might probably be partly explained by the genetic association of four other VPS10P-domain receptors with sporadic AD [24], which may dilute the effect of any individual marker including SORL1.

4.5 Conclusion

Our study provides a further piece of evidence pointing to the associations between BACE1 on the one hand and relevant CSF markers of AD on the other hand, including the soluble form of the APP sorting receptor SORL1, the first product of APP cleavage by BACE1 (sAPPβ), and a marker of axonal degeneration (tau). Although our investigation was not designed to establish any diagnostic validity of the studied CSF proteins, it still strongly supports the relevance of BACE1 and SORL1 in CSF for AD and their potential benefit as AD biomarkers and therapeutic targets.

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Table 1. Characteristics of the study groups

Variable	Control group	AD group
N	12	63
Age, years*	47.50 (13.70)	66.87 (9.39)
Age at onset, years*	na	62.83 (9.09)
Men : women	6 : 6	34 : 29
MMSE score*	30 (0.00)	22.54 (3.27)
BACE1 activity, FU/μL*	7468.43 (1966.75)	8757.01 (2636.36)
$A\beta_{1-42}$, ng/L*	708.33 (378.17)	540.48 (232.99)
Tau, ng/L*	125.58 (57.29)	605.21 (361.99)
sAPPα, ng/mL*	265.19 (218.35)	263.83 (145.58)
sAPPβ, ng/mL*	746.35 (519.92)	864.95 (405.522)
SORL1 ng/mL*	10.36 (2.61)	11.83 (4.74)†

* mean (SD); † N=40; na: not applicable; nd: not done; AD: Alzheimer's disease; MMSE: Mini-Mental-State Examination; FU: fluorescence units; Aβ: amyloid β; sAPP: soluble amyloid precursor protein; BACE1: β-site amyloid precursor protein-cleaving enzyme 1; SORL1: sortilin-related receptor with A-type repeats

Figure 1. Scatterplots between cerebrospinal fluid BACE1 activity and the concentrations of (A) $A\beta_{1-42}$, (B) tau, (C) sAPPα, (D) sAPPβ, and (E) SORL1 in the AD group