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Cholecystokinin and Alzheimer's disease: a biomarker of metabolic function, neural integrity, and cognitive performance

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ABSTRACT

Cholecystokinin (CCK) is a satiety hormone that is highly expressed in brain regions like the hippocampus. CCK is integral for maintaining or enhancing memory and thus may be a useful marker of cognitive and neural integrity in participants with normal cognition, mild cognitive impairment, and Alzheimer's disease (AD). Cerebrospinal fluid (CSF) CCK levels were examined in 287 subjects from the Alzheimer's Disease Neuroimaging Initiative. Linear or voxelwise regression was used to examine associations between CCK, regional gray matter, CSF AD biomarkers, and cognitive outcomes. Briefly, higher CCK was related to a decreased likelihood of having mild cognitive impairment or AD, better global and memory scores, and more gray matter volume primarily spanning posterior cingulate cortex, parahippocampal gyrus, and medial prefrontal cortex. CSF CCK was also strongly related to higher CSF total tau ($R^2 = 0.342$) and p-tau-181 ($R^2 = 0.256$) but not Aβ1-42. Tau levels partially mediated CCK and cognition associations. In conclusion, CCK levels may reflect compensatory protection as AD pathology progresses.

1. Introduction

Cholecystokinin (CCK) is a 33–amino acid satiety hormone secreted in the small intestines during digestion that binds to CCK-A receptors. CCK is secreted to allow the uptake of nutrients, most specifically fat uptake and metabolism of fatty acids (Pietrowsky et al., 1994). CCK is stimulated by fat and protein ingestion to signal the pancreas to release pancreatic enzymes into the duodenum and to signal the secretion of bile salts from the gall bladder into the duodenum. A main function of CCK is to slow gastric emptying to allow time for proper digestion. Patients with Alzheimer's disease (AD) have shown changes in their eating behavior, including both increased and decreased food intake, suggesting instability in weight regulation. Patients also manifest changes in food variety preferences and their eating patterns (Morris et al., 1989). Malnutrition is common and weight loss is seen in 40% of patients with AD (Wallace et al., 1995). Dietary changes, due to food preferences of patients with AD, tend to contain a higher proportion of carbohydrates and a reduced intake of proteins (Greenwood et al., 2005). Hyperphagia is also found in a third of all patients with AD (Morris et al., 1989). The reason for hyperphagia is unknown, but there may be a link to decreased satiety hormones or decreased sensitivity to these hormones (Adebakin et al., 2012). In concert, a decline in body mass index (BMI) is associated with an increased risk of developing AD (Buchman et al., 2005). This change in body mass could be due to muscle wasting (i.e., sarcopenia) or a result of decreased food uptake.

Interestingly, CCK receptors are found not only in the gut as CCK-A receptors but also in the brain as CCK-B receptors (CCKBR) (Pietrowsky et al., 1994). Fig. 1 illustrated the function of CCK peripherally and centrally. CCK is also the most abundant neuropeptide in the brain and selectively binds to CCKBR (Pietrowsky et al., 1994). Indeed, CCKBR are highly expressed in the

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hippocampus (Dockray et al., 1978; Innis et al., 1979; Zarbin et al., 1983), a brain region integral in memory formation that is adversely affected early in AD (Braak et al., 1993). Hippocampal injection or cell culturing with CCK agonists or antagonists, respectively, improves or impairs long-term potentiation and memory in rodents by acting on CCKBR (Sebret et al., 1999; Wen et al., 2014). Memory impairment in aged rodents also corresponds to less CCK expression (Croll et al., 1999). Furthermore, cerebral cortex has the highest concentration and CCK-specific binding in the brain (Saito et al., 1980), where endogenous CCK activity may produce long-term potentiation in medial prefrontal cortex akin to hippocampus (Liu and Kato, 1996). Thus, it is important to observe if metabolic biomarkers related to body weight and dietary regulation dynamics are associated with neural, cognitive, and other behavioral outcomes relevant to AD.

Despite a rich animal literature showing consistent enhancement or amelioration of memory by CCK-B activation, its role is virtually unknown in AD. AD-related changes in brain include progressive structural atrophy and decreased functional integrity (Klöppel et al., 2018), leading to forgetfulness and progressively worsening memory loss (Azuma et al., 2018). These changes occur in the presence of amyloid β (Aβ) plaques and hyperphosphorylated tau (p-tau) tangles, as observed in brain tissue at autopsy or antemortem through cerebrospinal fluid (CSF). Although CCKBR binding does not differ in cognitively normal (CN) versus AD patients (Löfberg et al., 1996), regional differences in postmortem CCK concentration suggest an AD-like pattern of decreased expression (Mazurek and Beal, 1991).

Thus, we examined if levels of CSF CCK were associated with onset and severity across the AD spectrum and determined if CCK was related to AD-like changes in cognition, neuroimaging, and classic AD biomarkers such as Aβ and tau.

2. Materials and methods

2.1. Participants

Data from late middle-aged to aged adults were obtained from the ADNI database (http://adni.loni.usc.edu/). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see http://www.adni-info.org. Written informed consent was obtained from all ADNI participants at their respective ADNI sites. The ADNI protocol was approved by site-specific institutional review boards. All analyses used in this report only included baseline data; however, measures were taken periodically for the database spanning a time of 90 months. Baseline CSF data for CCK was available for 287 subjects: 86 CN, 135 MCI, and 66 AD.

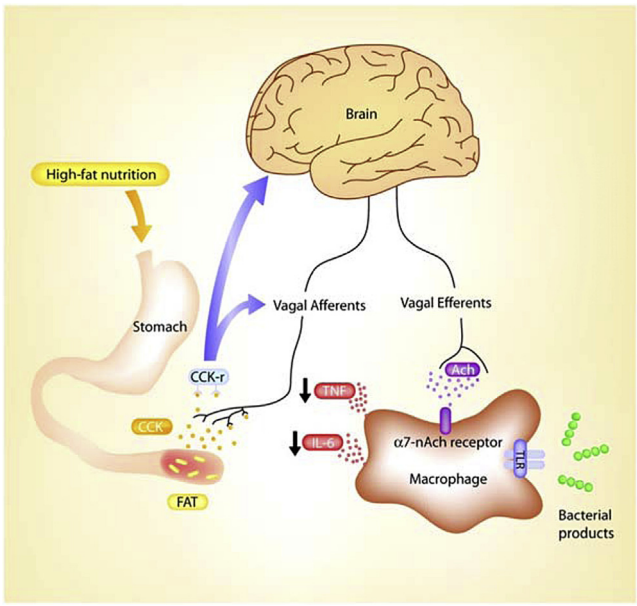

Fig. 1. Bidirectional CCK pathways in the periphery and brain. This diagram is reused with permission from the original publisher. Abbreviations: CCK-r, cholecystokinin receptor; IL-6, interleukin 6; TNF, tumor necrosis factor; TLR, toll-like receptors.

Participants with MCI had the following diagnostic criteria: (1) memory complaint identified by the participant or their study partner; (2) abnormal memory as assessed by the Logical Memory II subscale from the Wechsler Memory Scale-Revised, with varying criteria based on years of education; (3) Mini-Mental State Examination (MMSE) score between 24 and 30; (4) Clinical dementia rating of 0.5; (5) deficits not severe enough for the participant to be diagnosed with AD by the physician on site at screening. Participants with AD met similar criteria. However, they were required to have an MMSE score between 20 and 26, a clinical dementia rating of 0.5 or 1.0, and National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD.

2.2. Mass spectrometry and fasting glucose

Data were downloaded from the Biomarkers Consortium CSF Proteomics MRM data set. As described previously (Spellman et al., 2015), the ADNI Biomarkers Consortium Project investigated the extent to which selected peptides, measured with mass spectrometry, could discriminate among disease states. Briefly, Multiple Reaction Monitoring-MS was used for targeted quantitation of 567 peptides representing 221 proteins in a single run (Caprion Proteome Inc, Montreal, QC, Canada). Analyses for this report focused on CCK levels, which were assayed in the CSF proteomics panel, for which the peptide AHLGALLAR was chosen because it performed better in most analyses (data not shown).

2.3. Amyloid and tau CSF biomarkers

CSF sample collection, processing, and quality control of p-tau-181, total tau, and $A\beta_{1\text{-}42}$ are described in the ADNI1 protocol manual (http://adni.loni.usc.edu/) and (Shaw et al., 2011).

2.3.1. Apolipoprotein E ε4 genotype

The ADNI Biomarker Core at the University of Pennsylvania conducted apolipoprotein E (APOE) genotyping. We characterized participants as being "non-APOE4" (i.e., zero APOE ε4 alleles) or "APOE4" (i.e., 1 to 2 APOE ε4 alleles).

2.4. Neuropsychological assessment

ADNI uses an extensive battery of assessments to examine cognitive functioning with particular emphasis on domains relevant to AD. A full description is available at http://www.adni-info.org/Scientists/CognitiveTesting.aspx. All subjects underwent clinical and neuropsychological assessment at the time of scan acquisition. Neuropsychological assessments included The Clinical Dementia Rating sum of boxes (CDR-sob), MMSE, Auditory Verbal Learning Test, and AD Assessment Schedule—Cognition (ADAS-Cog). A composite memory score encompassing the Auditory Verbal Learning Test, ADAS-Cog, MMSE, and Logical Memory assessments

was also used (Crane et al., 2012). In addition, a composite executive function score comprising category fluency—animals, category fluency—vegetables, trails A and B, digit span backward, WAIS-R digit symbol substitution, number cancellation, and 5 Clock Drawing items were used (Gibbons et al., 2012). These composite scores were used in formal analyses to represent global memory and executive function among subjects.

2.5. Magnetic resonance imaging acquisition and preprocessing

T1-weighted magnetic resonance imaging scans were acquired within 10–14 days of the screening visit following a back-to-back 3D magnetization prepared rapid gradient echo scanning protocol described elsewhere (Jagust et al., 2010). Images were preprocessed using techniques previously described (Willette et al., 2013). Briefly, the SPM12 "New Segmentation" tool was used to extract modulated gray matter (GM) volume maps. Maps were smoothed with an 8 mm Gaussian kernel and then used for voxelwise analyses.

2.6. ^{18}F-fluorodeoxyglucose positron emission tomography

FDG-PET acquisition and preprocessing details have been described previously (Jagust et al., 2010). Briefly, 185 MBq of [18-153-F]-FDG was injected intravenously. After 30 minutes, six 5-minute frames were acquired. Frames of each baseline image series were coregistered to the first frame and combined into dynamic image sets. Each set was averaged, reoriented to a standard 160 × 160 × 96 voxel spatial matrix of resliced 1.5 mm^3 voxels, normalized for intensity, and smoothed with an 8 mm FWHM kernel. To derive the standardized uptake value ratio, pixel intensity was normalized according to the pons because it demonstrates preserved glucose metabolism in AD (Dowling et al., 2010). Normalization to the pons removed interindividual tracer metabolism variability. The Montreal Neurological Institute template space was used to spatially normalize images using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). A subset of subjects underwent FDG-PET scans and analyses included in this report.

2.7. Statistical analysis

All analyses were conducted using SPSS 23 (IBM Corp, Armonk, NY) or SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Binomial logistic regression was used to assess the odds ratio of a given participant being diagnosed as AD versus MCI or CN reference group. Linear mixed regression tested the main effect of CSF CCK on neuropsychological performance, modulated GM maps, FDG maps, and CSF biomarkers including A$\beta_{1\text{-}42}$, total tau, and p-tau-181. Covariates included age at baseline and sex in all models. Years of education was also covaried when analyzing memory and cognitive performance. For voxelwise analysis, 2nd-level linear mixed models tested the main effect of CCK on regional GM volume and FDG, controlling for age, sex, education, and baseline diagnosis. Based on the literature, contrasts tested if higher CCK was related to more regional GM or FDG. Statistical thresholds were set at $p < 0.005$ (uncorrected) and $p < 0.05$ (corrected) for voxels and clusters, respectively. Results were considered significant at the cluster level. As described previously (Willette et al., 2015), to reduce type 1 error, we used a GM threshold of 0.2 to ensure that voxels with <20% likelihood of being GM were not analyzed. For GM, Monte Carlo simulations in clusterSim (http://afni.nimh.nih.gov/afni/doc/manual/3dClustSim) were used to estimate that 462 contiguous voxels were needed for such a cluster to occur at $p < 0.05$ familywise error corrected. For FDG voxelwise analyses, Monte Carlo simulations in clusterSim were used to estimate that 224 contiguous voxels were needed for such a cluster to occur at $p < 0.05$ familywise error corrected.

3. Results

3.1. Data summary

Clinical, demographic, and CSF data for subjects with CSF CCK are presented in Table 1. Years of education, percent of APOE4 carriers, and age were not significantly different between participants diagnosed as CN, MCI, or AD. As anticipated for this ADNI subpopulation, cognitive function, observed using global cognitive tests, was significantly different across CN, MCI, and AD groups (all $p < 0.05$). CSF CCK levels were significantly lower in AD ($p < 0.001$) versus participants with MCI or CN.

3.2. Clinical characteristics and AD risk

Logistic regression was used to examine if higher CSF CCK expression predicted a decreased likelihood of being MCI or AD. The reference group was CN. The likelihood ratio statistic [$X^2 = 27.563$, $p < 0.001$] indicated that higher CSF CCK levels predicted a lower odds ratio for being MCI or AD [Wald = 13.437, $\beta = -1.039$, Exp(B) = 0.354, $p < 0.001$]. These results suggest that a per ng/mL increase in CSF CCK corresponded to a roughly 65% less likelihood of being diagnosed with AD versus CN or MCI. Higher levels of CSF CCK were not related to increased risk when comparing CN versus MCI, CN

Table 1
Demographic data for subjects with CSF CCK

Characteristic	CN (N = 86)	MCI (N = 135)	AD (N = 66)
Age (y)	75.70 ± 5.54	74.69 ± 7.35	74.98 ± 7.57
Education (y)	15.64 ± 2.97	16.00 ± 2.96	15.11 ± 2.96
Sex (% female)	48.8%	32.59%	43.9%
APOE status (% E4 carriers)	24.4%	52.6%	71.2%
Cholecystokinin (ng/mL)	13.48 ± 0.56	13.47 ± 0.53	13.23 ± 0.56
CSF total tau (pg/mL)	70.33 ± 27.64	102.99 ± 51.68	126.17 ± 60.69
p-tau-181 (pg/mL)	24.12 ± 11.97	35.25 ± 15.13	41.95 ± 20.60
Aβ 1–42 (pg/mL)	208.20 ± 56.05	161.21 ± 52.72	141.12 ± 37.39
CDR-sob	0.02 ± 0.11	1.56 ± 0.88	4.34 ± 1.56
MMSE	29.05 ± 1.02	26.91 ± 1.74	23.52 ± 1.85
ADAS-cog11	6.05 ± 2.90	11.72 ± 4.33	18.88 ± 6.71
Memory factor (Z-score)	0.98 ± 0.50	−0.15 ± 0.57	−0.90 ± 0.55

Values are mean ± SD. χ^2 analyses were conducted to examine differences between gender and APOE4 status. The ADNI memory factor values are Z-scored with mean 0 and a standard deviation of 1, based on 810 ADNI subjects with baseline memory data (Crane et al., 2012).
Key: ADAS-cog, AD Assessment Schedule–Cognition; AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein E; CSF, cerebrospinal fluid; CCK, cholecystokinin; CN, cognitively normal; CDR-sob, Clinical Dementia Rating sum of boxes; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SD, standard deviation.

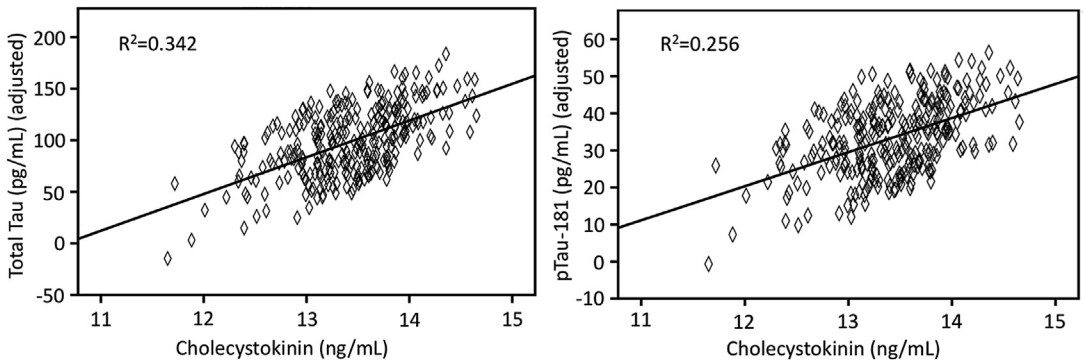

Fig. 2. The association between higher CSF CCK and higher CSF total tau and p-tau-181. Abbreviations: CSF, cerebrospinal fluid; CCK, cholecystokinin.

versus AD, or MCI versus AD individually. Among MCI participants, per unit increase in CCK was related to a 61.7% less likelihood (Wald = 6.708, $p = 0.010$) of progressing to AD (i.e., MCI-P) versus remaining stable with MCI (i.e., MCI-S).

3.3. AD CSF biomarkers

To examine the relationship between CSF CCK and AD CSF biomarkers, $A\beta_{1\text{-}42}$, p-tau-181, and total tau regression model analyses were performed with age, sex, BMI, baseline diagnosis, and APOE4 status as covariates. A significant association with $A\beta_{1\text{-}42}$ was not observed. However, as seen in Fig. 2, higher levels of CSF CCK were significantly associated with higher levels of CSF total tau ($\beta \pm SE = 37.857 \pm 4.799$, $F = 62.237$, $p < 0.001$) and CSF p-tau-181 ($\beta \pm SE = 10.046 \pm 1.630$, $F = 37.992$, $p < 0.001$).

3.4. Global cognition, memory, and executive function

As illustrated in Fig. 3, regression models showed that higher CSF CCK was related to better global cognition scores for CDR-sob, ADAS-cog-11, and MMSE. Similarly, higher CCK was associated with better memory factor and executive function factor ($\beta \pm SE = 0.156 \pm 0.077$, $p < 0.05$) scores.

3.5. Preacher-Hayes mediation of CCK and cognition outcomes

We also explored if CSF AD biomarkers modified associations between CCK and cognitive outcomes. For CDR-sob, no CSF markers mediated associations with CCK.

For ADAS-cog-11 and CCK (direct effect $\beta \pm SE = -3.110 \pm 0.585$, $p < 0.001$), higher total tau acted as a partial mediator, reducing the influence of CCK by 24% (indirect effect $\beta \pm SE = 0.735 \pm 0.063$, $p < 0.05$). For MMSE and CCK (direct effect $\beta \pm SE = 0.631 \pm 0.190$, $p < 0.001$), p-tau-181 acted as a partial mediator, reducing the influence of CCK by 26% (indirect effect $\beta \pm SE = -0.164 \pm 0.095$, $p < 0.05$).

For the memory factor and CCK, both total tau and p-tau-181 acted as partial mediators. Specifically, as indicated in Fig. 4, total tau reduced the influence of CCK on the memory factor by nearly half. In exploratory analyses, we examined if total tau mediation differed by baseline clinical diagnosis (CN, MCI, AD) or MCI

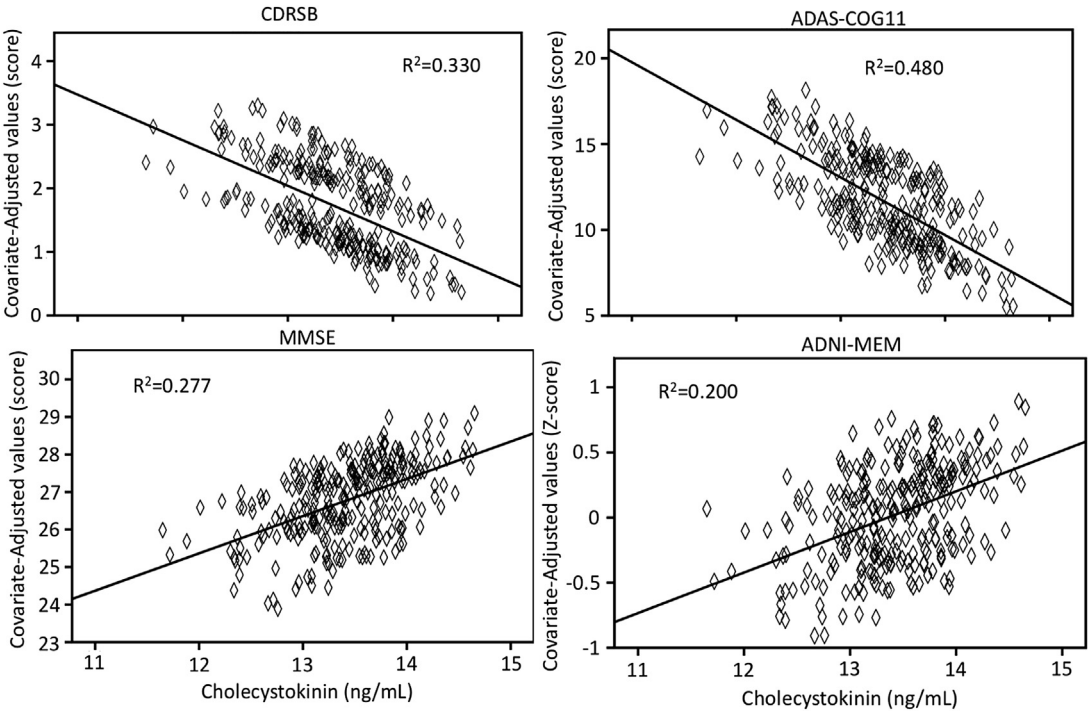

Fig. 3. The association between CSF CCK and cognitive scores, the Clinical Dementia Rating sum of boxes (CDRSB), Mini-Mental State Examination (MMSE), a composite memory score (ADNI-MEM), and AD Assessment Schedule–Cognition (ADAS-Cog). Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; CCK, cholecystokinin.

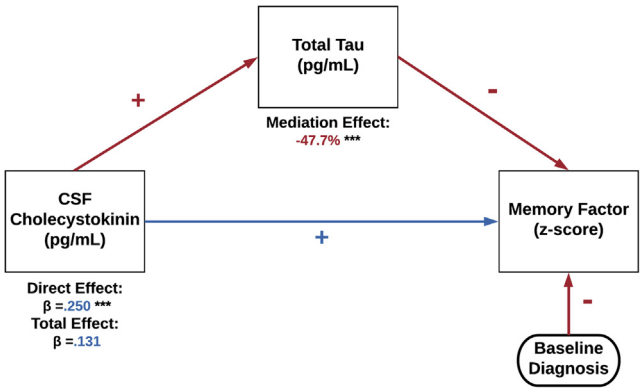

Fig. 4. Preacher-Hayes mediation of CSF CCK, total tau, and a composite memory score at baseline. Abbreviations: CSF, cerebrospinal fluid; CCK, cholecystokinin.

conversion (MCI-S, MCI-P). CN and AD showed no mediation effect, whereas for MCI, total tau continued to reduce the influence of CCK on the memory factor (direct effect $\beta \pm SE = 0.387 \pm 0.104$, $p < 001$) by 49.6% (indirect effect $\beta \pm SE = -0.192 \pm 0.054$). For MCI conversion, Supplementary Fig. 1 illustrates the direct effect of higher CCK levels, related to better memory scores for MCI-S ($\beta \pm SE = 0.533 \pm 0.174$, $p = 0.003$), which was reduced by 40.9% through total tau partial mediation ($p < 0.001$). By contrast, the direct effect for MCI-P was much weaker ($\beta \pm SE = 0.122$) and rendered nonsignificant by full mediation of total tau ($p < 0.001$).

In a separate model, p-tau-181 reduced the influence of CCK on the memory factor (direct effect $\beta \pm SE = 0.186 \pm 0.064$) by 36% (indirect effect $\beta \pm SE = -0.067 \pm 0.0263$). No effects were significant when stratifying by baseline diagnosis or MCI conversion. $A\beta_{1\text{-}42}$ was not a significant mediator for any cognitive measure.

Finally, for the executive function factor and CCK, both total tau and p-tau-181 acted as partial mediators. Specifically, total tau reduced the influence of CCK on the memory factor (direct effect $\beta \pm SE = 0.355 \pm 0.087$, $p < 0.001$) by 50% (indirect effect $\beta \pm SE = -0.178 \pm 0.041$, $p < 0.001$).

In a separate model, p-tau-181 reduced the influence of CCK on the memory factor (direct effect $\beta \pm SE = 0.315 \pm 0.082$, $p < 0.001$) by 47% (indirect effect $\beta \pm SE = -0.148 \pm 0.036$, $p < 0.001$). In exploratory analyses, no mediation analyses were significant when splitting by baseline clinical diagnosis or MCI conversion.

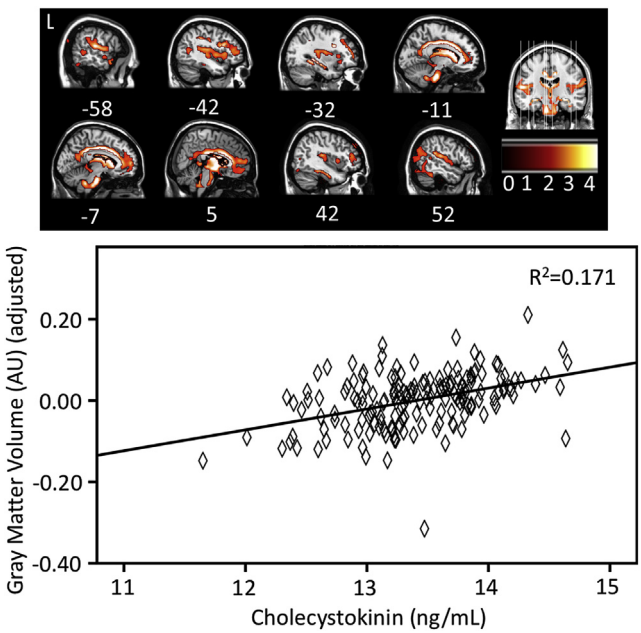

Fig. 5. The association between more CSF CCK and more regional gray matter volume. The graph depicts the relationship at a submaximum voxel in a sagittal cross section in midcingulate gyrus at 10, −27, and 38. Abbreviations: CSF, cerebrospinal fluid; CCK, cholecystokinin.

3.6. Regional gray matter volume

To determine the relationship between CSF CCK and regional GM volume, a voxelwise analysis was performed using SPM12 among a subset of 287 participants. Higher CSF CCK was significantly associated with greater GM volume in a large cluster of voxels (k = 11,962) primarily spanning cingulate cortex and parahippocampal gyrus, as well as thalamus, superior temporal sulcus, and medial prefrontal cortex (Fig. 5 and Supplementary Table 1).

3.7. Regional ^{18}F-Fluorodeoxyglucose positron emission tomography

Among 138 participants with FDG data, higher CSF CCK was not significantly associated with an increase in ^{18}F-fluorodeoxyglucose PET glucose uptake.

4. Discussion

In this study, we hypothesized that CCK may serve as a useful metabolic biomarker for predicting AD outcomes due to previous research looking at CCK-B and its role in maintaining or enhancing memory (Liu and Kato, 1996; Sebret et al., 1999; Wen et al., 2014). Although there was no statistically significant differences between groups when looking at Aβ, tau, or APOE4 carriers, clear trends were observed. We found that patients with AD had modestly lower CCK than CN or MCI. Per ng/mL increase in CCK, there was a roughly 65% decreased likelihood of having MCI or AD versus CN and a 62% decreased likelihood of MCI progression from MCI to AD. These results suggest that higher CCK levels are related to better cognitive outcomes. Postmortem tissue analysis has been mixed, with some groups noting no change (Perry et al., 1981; Ferrier et al., 1983) or decreased expression (Mazurek and Beal, 1991). Similarly, higher CCK was associated with better performance in memory, executive function, and global cognitive tests, which via mediation was partly mitigated by levels of CSF tau species but not $A\beta_{1\text{-}42}$. CCK has consistently been implicated as a protective or enhancing factor for memory formation. For example, in a rodent study that included CCK knockout mice, the mice without CCK performed worse on the Morris water-maze test compared to wild-type mice, while evincing similar locomotion and food intake, indicating that CCK was a factor in learning and memory (Lo et al., 2008). CCK administration is directly able to induce or curb long-term potentiation (Sebret et al., 1999; Wen et al., 2014), which is a well-established molecular process thought to underlie learning and memory.

We further observed that higher CSF CCK levels were also correlated with more regional GM volume in areas such as parahippocampal gyrus, hippocampus, posterior cingulate cortex, and superior and medial prefrontal gyri. The parahippocampal gyrus is part of the limbic system, which plays a crucial role in memory and is affected in AD with atrophy in GM (Köhler et al., 1998). Atrophy in the hippocampus and posterior cingulate cortex strongly track disease progression and underlie memory decline (Pengas et al., 2010). Medial prefrontal cortex is not only integral for memory retrieval but also executive function as well (West, 1996). These results suggest that as CCK levels increase, cognitive functions such

as memory may improve due to the protection of GM in memory-intensive regions of the brain.

In our study, we found no correlation between CSF CCK and Aβ; however, strong relationships were observed between higher CCK and higher tau levels. Although no existing work ties CCK to amyloid or tau to our knowledge, other studies have tested the relationship between AD markers and other satiety hormones. In a study conducted by Guo et al. (2016), Aβ was added to PC12 cells to reaffirm the fact that Aβ causes apoptosis due to cytotoxicity. However, when leptin, a satiety hormone released from adipose tissue, was added to the PC12 cells along with the Aβ, significantly less cell death was observed. This protective phenomenon of leptin may be due to increased activation of JAK2, used in the regulation of the phosphorylation of the tau protein. When JAK2 was inhibited in the presence of Aβ, there was an increase in phosphorylated tau regardless of whether leptin was present. Similarly, with leptin administration, there was more JAK2 activation which caused decreased GSK-3 activation and less damage caused by the presence of Aβ (Guo et al., 2016). GSK-3 is found in the brains of many patients with AD (Asuni et al., 2006) and is involved with the hyper phosphorylation of the tau protein. Thus, CCK may serve as a protectant against AD by suppressing expression of GSK-3 and increasing JAK2 activation. With increased CCK levels in patients with more severe pathology, it may be possible that CCK is, acting in a similar way to leptin, trying to protect the brain from neuronal cell death and not serving a pathogenic effect by directly increasing tau levels. At a certain point, GSK-3 levels may increase such that the compensatory function of CCK is overridden, leading to an increase in accumulation and phosphorylation of tau. Indeed, total tau and p-tau-181 levels partly mediate CCK and cognitive scores and strongly decrease such associations. Furthermore, the association between higher CCK and better memory scores was seen in MCI-S but not MCI-P due to full mediation by total tau. Therefore, CCK may not increase tau and p-tau-181 levels per se, but act as a protective response to the neuronal damage that is tied to tau accumulation, which may be mitigated by progressive neurodegeneration.

Limitations of this study should be addressed. Using data from ADNI, we were unable to obtain dietary data or other measures of body composition besides BMI. We were also unable to track changes in CCK over time, as this was only measured at baseline.

In conclusion, higher levels of CCK predicted better cognitive outcomes and more GM in memory-specific regions. Higher CCK was also related to more CSF total tau and p-tau-181. CCK may act as a protectant against AD by activated JAK2 and thus reducing the GSK-3 activation. We propose that as AD progression occurs, CCK levels increase in efforts to protect against further damage potentially induced by tau. Additional research would need to be done to further examine the relationship between CCK and tau over time. CCK levels may be a useful marker of cognitive and volumetric loss due in part to increased accumulation of tau, which may be useful for AD prognosis or a potential target to maintain memory in the face of AD pathology. In summary, CCK may be a useful biomarker for examining AD-related associations with GM atrophy, cognitive function, and especially tau deposition. CCK is not only an abundant neuropeptide but is also released as a response to the ingestion of primarily fat and proteins. Thus, future work should examine if dietary changes might increase CCK expression in CSF and if such changes are related to less AD-related pathology and cognitive decline.

Disclosure

The authors have no conflict of interest to report.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2019.01.002.

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