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Selenium Species in Cerebrospinal Fluid and Hippocampal Volume among Individuals with Mild Cognitive Impairment

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Introduction

Selenium is an essential mineral that occurs naturally in soil-grown foods, though motorized traffic, tobacco smoke, and drinking water are additional sources of exposure.[1] Selenium is also found in multivitamins and is available as stand-alone supplements.[1] Animal[2–4] and epidemiological[4,5] studies indicate that some selenium species have neurotoxic properties. The extent to which selenium adversely affects the hippocampus, a key brain structure that predicts cognitive decline,[6] is, however, unclear.[3] In an earlier cohort study of ours,[7] higher cerebrospinal fluid (CSF) concentrations of selenate (inorganic selenium) in individuals with mild cognitive impairment (MCI) were associated with greater dementia risk. Herein, we assessed the association between baseline concentrations of selenium species in CSF and hippocampal volume in that cohort.

Methods

We used a subset of a previous cohort of individuals with an MCI diagnosis between 2008 and 2014.[7] Of the 56 cohort members enrolled at Modena University Hospital following Modena Ethics Committee approval (No. 84/2015) and who had undergone in-depth neurological examination and CSF sampling, we included the 33 individuals who had undergone high-resolution magnetic resonance imaging at baseline. Using administrative records, we abstracted data on age, sex, years of education (including primary school) and income. We used anion exchange chromatography and inductively coupled–plasma dynamic reaction cell–mass spectrometry to measure inorganic and organic selenium species in CSF as described in Vinceti et al.[7] In brief, CSF samples were analyzed on a Knauer 1100 Smartline high-performance liquid chromatography system and a NexIon 300D Perkin Elmer inductively coupled plasma-mass spectrometry. The limit of detection (LOD) was 0.02 ng/mL, and values below it were replaced with LOD/2.

Neuroimaging was based on high-resolution T1-weighted images all acquired on the General Electric Signa Architect 3T scanner, performing segmentation of the hippocampus based on an optimized deep learning technique.[6] We used SPHARM-PDM (version 1.4; https://www.nitrc.org/projects/spharm-pdm) to conduct a shape analysis, testing vector differences between groups based on a cut point, chosen based on spline regression, of CSF selenium species at every surface location.[8] We assessed the association between CSF selenium species and hippocampal volume with linear regression and restricted cubic splines, adjusting for age, sex, education.

Results

Sociodemographic characteristics of the 33 participants were similar to those of the larger cohort[7] (Table 1). Table 1 also shows CSF levels of total selenium and its species, demonstrating higher concentrations of organic species, especially selenoprotein P (Se-SELENOP) in comparison with selenium-carrying human serum albumin (Se-HSA) and inorganic species. Table 2 displays the linear regression coefficients for the association between selenium species and hippocampal volume in crude and multivariable analyses. Inorganic hexavalent selenium (selenate) was inversely associated with volume of left, right, and both hippocampi. Results from unadjusted and adjusted models were similar. Other inorganic selenium form (selenite), organic selenium species, and total selenium were not materially associated with hippocampal volume, apart from imprecise associations with selenocysteine (Se-Cys) (positive) and selenium-dependent glutathione peroxidase (Se-GPX) (negative) based on 7 (21.2%) and 12 (36.4%) of detectable values, respectively. Further adjustment for time since CSF sampling and intracranial volume, or income, had little effect on the results (https://git.unimore.it/creagen1/Supporting-information). In spline regression analysis, the inverse association between selenate and hippocampal volume emerged only at selenate concentrations above 0.2 ng/mL.

The results of the SPHARM-PDM computation by comparing two participant groups based on spline analysis, i.e., using a 0.2 ng/mL cut point (https://git.unimore.it/creagen1/Supporting-information), showed shape differences between the two groups, i.e., inward movement of vertices from participants with low selenate concentrations in the ventromedial region of the left hippocampus and in the frontal region of both hippocampi.

Discussion

We are not aware of previous human studies assessing associations of selenium and selenium species with hippocampal volume, either *in vivo* or *post mortem*. We observed an inverse association between hippocampal volume and one of the most toxic selenium species, selenate, but only at the highest exposure concentrations. This finding agrees with our previous study that indicated a positive association between selenate and dementia risk.[7] There was little evidence

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Table 1. Demographic characteristics, measured brain volumes, and cerebral spinal fluid concentrations of selenium for the considered population.

	Median	IQR	Range	$n <$ LOD (%)
Age (y)	65.23	(62.90–70.20)	(42.62–81.59)	—
Years of education	9.00	(5.00–13.00)	(4.00–17.00)	—
Annual income (€)	20,600	(12,400–26,600)	(0–85,700)	—
Sex	19 F (58%), 14 M (42%)	—	—	—
Race	33 White-Caucasian (100%)	—	—	—
Time from CSF sampling (months)	24	(18–36)	(6–120)	—
Intracranial volume (cm^3)	1,889	(1,846–1,925)	(1,578–1,990)	—
Left Hippocampus (cm^3)	4.03	(3.65–4.43)	(2.61–5.06)	—
Right hippocampus (cm^3)	4.20	(3.78–4.43)	(2.56–5.17)	0 (0.0)
Both hippocampi combined (cm^3)	8.13	(7.48–8.85)	(5.17–9.94)	0 (0.0)
Total selenium (ng/mL)	4.30	(3.72–4.87)	(2.18–7.28)	0 (0.0)
Inorganic selenium (ng/mL)	0.64	(0.43–0.76)	(0.01–1.17)	1 (3.0)
Se(IV) (ng/mL)	0.45	(0.33–0.63)	(0.01–0.77)	2 (6.1)
Se(VI) (ng/mL)	0.12	(0.10–0.23)	(0.01–0.41)	4 (12.1)
Organic selenium (ng/mL)	1.92	(1.38–2.41)	(0.28–3.99)	0 (0.0)
Se-SELENOP (ng/mL)	1.63	(1.16–2.11)	(0.20–3.33)	0 (0.0)
Se-Met (ng/mL)	0.16	(0.10–0.23)	(0.01–0.32)	2 (6.1)
Se-Cys (ng/mL)	0.01	(0.01–0.01)	(0.01–0.24)	26 (78.8)
Se-GPX (ng/mL)	0.01	(0.01–0.06)	(0.01–0.42)	21 (63.6)
Se-HSA (ng/mL)	1.65	(1.35–1.84)	(0.01–2.71)	1 (3.0)
Unknown selenium species (ng/mL)	0.25	(0.14–0.38)	(0.04–0.67)	0 (0.0)

Note:—, no data; CSF, cerebrospinal fluid; IQR, interquartile range; LOD, limit of detection; Median, 50th percentile; Se-Cys, selenocysteine; Se-GPX, Se-dependent glutathione peroxidase; Se-HSA, Se-carrying human serum albumin; Se-Met, selenomethionine; Se(VI), selenate; Se(IV), selenite; Se-SELENOP, selenoprotein P.

Table 2. Cerebrospinal fluid concentrations of selenium species (in nanograms per milliliter) and their association with hippocampal volumes (in cubic centimeters) among 33 patients with mild cognitive impairment.

Neuroimaging volume (cm^3)	β	Crude (95% CI)	β	Adjusted (95% CI)
Left hippocampus				
Total selenium	−0.17	(−0.36, 0.03)	−0.11	(−0.34, 0.11)
Inorganic selenium	−0.39	(−1.15, 0.37)	−0.30	(−1.06, 0.46)
Se(IV)	0.05	(−0.99, 1.08)	0.18	(−0.85, 1.20)
Se(VI)	−1.75	(−3.20, −0.30)	−1.65	(−3.07, −0.22)
Organic selenium	−0.15	(−0.39, 0.09)	−0.11	(−0.36, 0.14)
Se-SELENOP	−0.16	(−0.43, 0.11)	−0.12	(−0.40, 0.16)
Se-Met	−1.21	(−3.58, 1.16)	−0.58	(−3.14, 1.99)
Se-Cys	2.55	(−0.96, 6.06)	2.48	(−1.43, 6.39)
Se-GPX	−1.75	(−3.95, 0.45)	−1.42	(−3.66, 0.83)
Se-HSA	−0.04	(−0.43, 0.35)	0.06	(−0.33, 0.45)
Unknown selenium species	−0.30	(−1.44, 0.84)	−0.37	(−1.63, 0.89)
Right hippocampus				
Total selenium	−0.10	(−0.28, 0.08)	−0.11	(−0.32, 0.11)
Inorganic selenium	−0.38	(−1.08, 0.31)	−0.35	(−1.08, 0.38)
Se(IV)	−0.07	(−1.02, 0.89)	−0.02	(−1.01, 0.98)
Se(VI)	−1.47	(−2.82, −0.11)	−1.41	(−2.82, 0.00)
Organic selenium	−0.13	(−0.35, 0.10)	−0.13	(−0.37, 0.11)
Se-SELENOP	−0.12	(−0.37, 0.12)	−0.13	(−0.40, 0.14)
Se-Met	−0.82	(−3.02, 1.38)	−0.61	(−3.09, 1.87)
Se-Cys	1.49	(−1.81, 4.79)	1.48	(−2.38, 5.33)
Se-GPX	−2.05	(−4.03, −0.08)	−2.07	(−4.16, 0.02)
Se-HSA	0.07	(−0.29, 0.43)	0.11	(−0.27, 0.49)
Unknown selenium species	0.02	(−1.03, 1.07)	−0.17	(−1.40, 1.06)
Total hippocampus				
Total selenium	−0.27	(−0.62, 0.09)	−0.22	(−0.64, 0.19)
Inorganic selenium	−0.77	(−2.16, 0.61)	−0.65	(−2.08, 0.77)
Se(IV)	−0.02	(−1.92, 1.88)	0.16	(−1.77, 2.09)
Se(VI)	−3.21	(−5.87, −0.56)	−3.05	(−5.74, −0.37)
Organic selenium	−0.28	(−0.72, 0.16)	−0.24	(−0.71, 0.23)
Se-SELENOP	−0.28	(−0.77, 0.21)	−0.25	(−0.77, 0.27)
Se-Met	−2.03	(−6.38, 2.33)	−1.19	(−6.01, 3.63)
Se-Cys	4.04	(−2.45, 10.53)	3.96	(−3.45, 11.37)
Se-GPX	−3.81	(−7.77, 0.16)	−3.49	(−7.62, 0.64)
Se-HSA	0.03	(−0.68, 0.74)	0.17	(−0.56, 0.91)
Unknown selenium species	−0.28	(−2.37, 1.81)	−0.54	(−2.91, 1.84)

Note: Linear regression β coefficients and 95% CIs are from a multivariable model controlling for sex, age at baseline, and education as covariates. CI, confidence interval; Se-Cys, selenocysteine; Se-GPX, Se-dependent glutathione peroxidase; Se-HSA, Se-carrying human serum albumin; Se-Met, selenomethionine; Se(VI), selenate; Se(IV), selenite; Se-SELENOP, selenoprotein P.

of any association with the other selenium species, with the exception of an imprecise association with two organic selenium species whose biological relevance is difficult to assess due to high proportion of values below the LOD (i.e., Se-Cys and Se-GPX).

Our use of an *in vivo* central nervous system (CNS)-based exposure biomarker represents an improvement in exposure assessment because circulating blood concentrations of inorganic selenium species were shown to be uncorrelated with CNS concentrations,[9] and increased selenium concentrations associated with neurofibrillary tangle severity of Alzheimer's pathology in *post mortem* samples could have been a marker of disease progression.[10] Given the cross-sectional design, we acknowledge that reverse causation could have influenced our results if MCI status was associated with altered consumption of selenium-based foods or with abnormal selenium metabolism, which seems unlikely, or with alterations of the blood–brain barrier associated with both neurodegeneration and brain selenium concentrations. Another potential limitation is unmeasured confounding, because other factors associated with CSF content of selenium species could have influenced hippocampal volume. Finally, the small sample size yielded statistically imprecise estimates for some associations.

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Supporting information for this study can be found on GitHub at https://git.unimore.it/creagen1/Supporting-information.

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