J Anal Res Clin Med, 2016, 4(1), 39-46.
doi: 10.15171/jarcm.2016.007, *http://journals.tbzmed.ac.ir/JARCM*

Original Article

Correlation of secretory phospholipase-A2 activity and fatty acids in cerebrospinal fluid with liver enzymes tests

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Article info
Article History:
Received: 12 July 2015
Accepted: 21 Oct 2015
ePublished: 29 Feb 2016

Keywords:
Liver,
Liver Enzymes Tests,
Cerebrospinal Fluid,
Fatty Acids,
Secretory Phospholipase-A2

Abstract

Introduction: The aim was to determine whether secretory phospholipase-A2 (sPLA2) activity and fatty acids in cerebrospinal fluid (CSF) are correlated with liver enzymes tests.

Methods: CSF and serum samples were collected from 49 patients (age 18-65) as part of routine diagnostic testing. Along with serum liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP), the fatty acid composition of CSF was measured by gas liquid chromatography. CSF enzyme activities of sPLA2 were measured using the standard assay with diheptanoyl thio-phosphatidylcholin as substrate.

Results: The saturated fatty acids (SFAs) including palmitic acid and stearic acid were positively, and the unsaturated fatty acids including oleic acid and linoleic acid were negatively correlated with liver enzymes tests. In regression analysis with adjustment for body mass index (BMI), the elevated liver enzymes tests were positively associated with activity of sPLA2 ($\beta > 0.31$, $P < 0.050$) and total SFAs ($\beta > 0.38$, $P < 0.010$) and negatively with total monounsaturated fatty acids (MUFAs) ($\beta < -0.40$, $P < 0.001$) contents of CSF.

Conclusion: CSF activity of sPLA2 and fatty acids may be linked to peripheral markers of liver function, suggesting an indirect impact of central fatty acids on hepatocytes function and metabolism.

Citation: Ghodoosifar S, Jafari-Rouhi AH, Pashapour A, Mehdizadeh A, Shaaker M, Darabi M. **Correlation of secretory phospholipase-A2 activity and fatty acids in cerebrospinal fluid with liver enzymes tests.** J Anal Res Clin Med 2016; 4(1): 39-46. Doi: 10.15171/jarcm.2016.007

Introduction

Over the last decade, a large number of studies have suggested that the physiological role of fatty acids extends beyond that of an energy source and includes the regulation of metabolic homeostasis likely via neural regulation of peripheral organs, such as adipose tissue,[1] liver,[2] and skeletal muscle.[3] Previous studies have shown the major role of the central nervous system (CNS) on

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glucose and energy homeostasis primarily via modulating expression profile of hepatic enzymes.[4] Interestingly, this observation may be attributed to hypothalamic sensing of fatty acids.[5] In particular, the levels of palmitic acid (16:0) and oleic acid (18:1n−9) in rat hypothalamus have been implicated as metabolic signals, where higher levels of these fatty acids were associated with relatively lower hepatic glucose production.[6] Clinical data also support an association of central fatty acids with energy metabolism. Jumpertz et al.[2] reported that fatty acids in the cerebrospinal fluid (CSF) are strongly correlated to peripheral insulin-mediated glucose utilization and thus lower blood glucose concentrations.

Secretory phospholipase A2 (sPLA2) is an established acute phase reactant that is associated with liver function[7] and is normally detectable in CSF.[8] Its activity leads to the formation of eicosanoids and platelet-activating factor from fatty acids that are essential in the growth regulation, differentiation, and inflammation.[9] Although sPLA2 and fatty acids have previously been reported as potential biomarkers and therapeutic target for neural and liver disorders, there has been no study to date specifically characterizing the physiological correlation between central fatty acids and liver function.

Human studies of fatty acids and liver health are currently being undertaken. Limited evidence exists about the correlation between central fatty acids with liver function. The objective of this study was to determine the correlation of CSF sPLA2 activity and fatty acid content with serum liver enzymes in an adult human population of subjects undergoing diagnostic lumbar puncture (LP). This study will add to the limited scientific knowledge regarding the central regulation of liver function and will bring clinical benefit to CNS-targeted treatment of patients with liver diseases.

Methods

This cross-sectional study was performed at the Tabriz University Hospital, Iran. The study was approved by the Ethic Committee of Tabriz University of Medical Sciences (IRB permission number 5.4.7624), and all patients provided written informed consent.

Subjects were recruited from a patient population scheduled for lumbar puncture (LP) between May 01, 2013 and November 30, 2014. These patients were suspected of CNS inflammation or infection and referred for CSF analysis as part of their emergency evaluation. In the present study, 49 patients (26 men and 23 women) were enrolled.

Figure 1 shows a flowchart of patient selection for the study. Patients over 65 years of age and those with a traumatic LP, history of smoking, meningitis, seizure, oncologic disease, chronic or acute hepatitis, cirrhosis, non-cirrhotic liver disease or diabetes that could influence liver metabolism were excluded to obtain a more homogeneous study population. Patients with abnormal CSF findings were also excluded from the study. The exclusion of persons with diabetes mellitus was based on self-reported diabetes as well as on fasting serum glucose > 125 mg/dl.

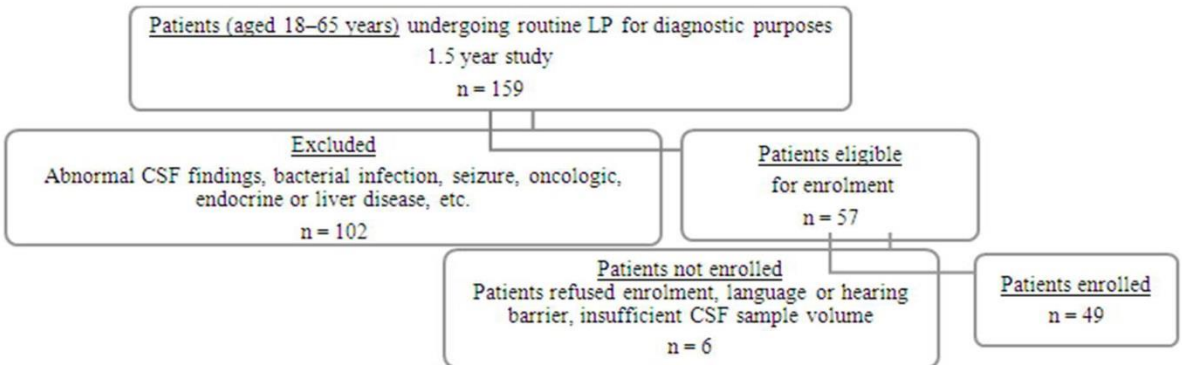

Figure 1. Patient selection flowchart
CSF: Cerebrospinal fluid; LP: Lumbar puncture

Venous blood for routine biochemistry and liver enzymes tests was collected following 12-14 hours fasting in the morning before LP. CSF sample was then obtained from patients in the fasting state by LP performed according to a standardized procedure, and all diagnostics were confirmed by biochemical and histopathologic examination. One set of CSF aliquots were centrifuged, and the supernatants were frozen at -70 °C until the analyses were performed.

Serum and CSF routine analysis of all patients were performed in the pathobiology laboratory at the university hospital. Quantitative determination of liver enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) was performed by standard commercial kits (Pars Azmoun, Tehran, Iran) on a BT 3000 autoanalyzer (Biotecnica Institute, Italy) with IFCC's kinetic method.

The activity of serum sPLA2 was determined by the standard assay with diheptanoyl thio-phosphatidylcholine as substrate (Cayman Chemicals, Windham, NH) using an Immunoscan model 310 microplate reader (Labsystems, Helsinki, Finland).

CSF lipids were extracted using the Bligh-Dyer method and were esterified with methanol during catalysis with acetyl chloride.[10] Fatty acid methyl esters were extracted and analyzed for fatty acid composition as described previously by us.[11] Briefly, fatty acid methyl ester derivatives formed by isolated CSF lipids were separated on a 60 × 0.25 mm Teknokroma TR-CN100 column using a Buck Scientific model 610 gas chromatograph (SRI Instruments, Torrance, USA) equipped with a split injector and a flame ionization detector. Tridecanoic acid (13:0) was used as the internal standard. Peak retention times were identified by injecting known standards.

Spearman correlation coefficients between serum liver enzymes and CSF sPLA2 and fatty acids were calculated. Scatter plots of the bivariate correlations were visually inspected to ensure outliers did not compromise the results of the correlations. For regression analysis, the values of serum liver enzymes and oleic to stearic acid (18:1n−9/18:0) were converted by logarithmic transformation to normalize distribution of the data. A regression analysis, controlling for body mass index (BMI), was then performed relating estimated serum liver enzymes and CSF fatty acids. A $P < 0.050$ was considered statistically significant. All analyses were carried out using SPSS software (version 11, SPSS Inc., Chicago, IL, USA).

Results

The clinical details and serum liver enzymes of the study subjects are presented in table 1. Table 2 shows the level of sPLA2 activity and fatty acids measured in the CSF samples. Palmitic acid was the major fatty acid in CSF, followed by stearic acid and oleic acid.

The correlation coefficient of demographic characteristics and serum liver enzymes with the fatty acid contents of CSF are shown in tables 3 and 4, respectively. Serum liver enzymes were inversely correlated with the total monounsaturated fatty acids (MUFAs) content of CSF ($r < -0.30$, $P < 0.050$). The saturated fatty acids (SFA) content of CSF was positively correlated with serum liver

Table 1. Clinical characteristics and serum liver enzymes in the 49 selected patients

Clinical characteristics	Mean ± SD (range)
Age (year)	40.29 ± 12.80 (18-65)
Gender (women) (%)	47
BMI (kg/m^2)	23.80 ± 1.78 (19.14-26.45)
AST (IU/L)	25.70 ± 8.74 (9-40)
ALT (IU/L)	28.20 ± 13.83 (9-55)
ALP (IU/L)	112.78 ± 26.62 (52-171)

SD: Standard deviation; BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase, ALP: Alkaline phosphatase

Table 2. Cerebrospinal fluid (CSF) secretory phospholipase-A2 activity and fatty acids in the 49 selected patients

Parameters	Mean ± SD (range)
sPLA2*	0.059 ± 0.019
14:0 (myristic acid)	1.74 ± 0.59 (0.63-3.56)
16:0 (palmitic acid)	36.12 ± 4.34 (28.46-44.55)
16:1n−7 (palmitoleic acid)	1.63 ± 0.43 (0.53-2.56)
18:0 (stearic acid)	25.99 ± 5.62 (12.29-34.75)
18:1t (trans oleic acid)	1.63 ± 0.79 (0.79-3.92)
18:1n−9 (oleic acid)	19.69 ± 6.62 (6.01-31.63)
20:0 (arachidic acid)	1.74 ± 0.80 (0.4-3.62)
18:2n−6 (linoleic acid)	6.79 ± 1.36 (3.39-9.86)
18:3n−9 (linolenic acid)	0.57 ± 0.25 (0.19-1.42)
20:4n−6 (arachidonic acid)	1.69 ± 0.53 (0.59-3.27)
20:5n−3 (eicosapentaenoic acid)	1.49 ± 0.63 (0.49-3.02)
22:6n−3 (docosahexaenoic acid)	0.92 ± 0.46 (0.17-2.07)
SFAs	65.59 ± 6.22 (53.12-80.61)
MUFA	21.32 ± 6.62 (7.29-32.92)
n6-PUFA	8.48 ± 1.46 (4.74-11.75)
n3-PUFAs	2.98 ± 0.93 (1.32-6.04)

*Expressed as units of µmol/min/ml.
SD: Standard deviation; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acids; sPLA2: Secretory phospholipase-A2

Table 3. Spearman's coefficient of correlation (rho) between secretory phospholipase-A2 activity and cerebrospinal fluid fatty acids and demographic characteristics

Characteristics	Age	P	BMI	P
sPLA2	0.15	0.310	0.31	0.060
14:0 (myristic acid)	-0.07	0.650	0.04	0.780
16:0 (palmitic acid)	-0.01	0.920	0.17	0.250
16:1n−7 (palmitoleic acid)	-0.07	0.630	0.09	0.550
18:0 (stearic acid)	-0.01	0.950	0.01	0.970
18:1t (trance oleic acid)	0.23	0.110	0.06	0.670
18:1n−9 (oleic acid)	0.05	0.710	-0.16	0.270
20:0 (arachidic acid)	0.04	0.800	-0.11	0.440
18:2n−6 (linoleic acid)	-0.10	0.480	0.21	0.140
18:3n−9 (linolenic acid)	-0.05	0.730	-0.07	0.640
20:4n−6 (arachidonic acid)	-0.13	0.370	0.05	0.720
20:5n−3 (eicosapentaenoic acid)	-0.13	0.370	-0.18	0.210
22:6n−3 (docosahexaenoic acid)	0.21	0.150	0.19	0.190
SFAs	-0.05	0.720	0.10	0.480
MUFA	0.06	0.700	-0.17	0.260
n6-PUFAs	-0.11	0.440	0.22	0.130
n3-PUFAs	0.05	0.720	-0.02	0.880

BMI: Body mass index; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acids; sPLA2: Secretory phospholipase-A2

enzymes ($r > 0.33$, $P < 0.050$). The level of CSF linoleic acid was inversely correlated only with AST ($r = -0.29$, $P = 0.040$). BMI was positively correlated with the level of all three serum liver enzymes, but the strongest correlation was with AST ($r = 0.38$, $P = 0.006$) (Table 5).

Because of BMI interrelation to serum liver enzymes, multivariate regression using BMI as a covariate were calculated to depict the independent association between sPLA2 and serum liver enzymes and the fatty acid contents of CSF samples. The activity of CSF sPLA2 ($\beta > 0.31$, $P < 0.050$), SFA ($\beta > 0.38$, $P < 0.010$), and MUFA ($\beta < -0.40$, $P < 0.001$) content of CSF were independently associated with the level of all three serum liver enzymes. The correlations of the stearic acid (18:0; $\beta = 0.20$, $P = 0.070$) and linoleic acid (18:2n-6; $\beta = -0.21$, $P = 0.090$) with the AST

were not independent of the level of BMI.

The ratio of 18:0/16:0 was calculated as an elongase activity index. The 18:1n-9/18:0 and 20:4n-6/18:2n-6 ratios were calculated as indices of stearoyl-CoA (SCD) and Δ6 desaturases activity, respectively. Only, the ratio of 18:1n-9/18:0 was correlated negatively with serum liver enzymes ($r < -0.32$, $P < 0.020$) (Figure 2). Although these correlations were independent of the level of stearic acid, the correlation of 18:1n-9/18:0 remained only significant with AST ($\beta = -0.35$, $P = 0.010$) in multivariate analysis. No significant correlations were found between sPLA2 and fatty acids determined in CSF, even after adjustment for BMI.

Table 4. Spearman's coefficient of correlation (rho) between secretory phospholipase-A2 activity and cerebrospinal fluid fatty acids and serum liver enzymes

Parameters	AST	P	ALT	P	ALP	P
sPLA2	0.21	0.130	0.19	0.150	0.25	0.130
14:0 (myristic acid)	-0.14	0.350	0.08	0.590	0.16	0.260
16:0 (palmitic acid)	0.45	< 0.010	0.54	0.010	0.16	0.270
16:1n−7 (palmitoleic acid)	0.01	0.980	-0.16	0.270	-0.09	0.550
18:0 (stearic acid)	0.38	0.010	0.22	0.130	0.30	0.050
18:1t (trans oleic acid)	0.20	0.180	0.17	0.250	-0.09	0.520
18:1n−9 (oleic acid)	-0.51	< 0.010	-0.45	< 0.010	-0.32	0.020
20:0 (arachidic acid)	-0.01	0.920	0.17	0.240	0.14	0.320
18:2n−6 (linoleic acid)	-0.29	0.040	-0.17	0.240	0.06	0.680
18:3n−9 (linolenic acid)	0.15	0.320	0.20	0.160	0.04	0.780
20:4n−6 (arachidonic acid)	0.10	0.510	-0.09	0.520	0.10	0.480
20:5n−3 (eicosapentaenoic acid)	-0.21	0.150	-0.20	0.160	-0.16	0.270
22:6n−3 (docosahexaenoic acid)	0.08	0.580	0.11	0.440	0.23	0.110
SFAs	0.57	< 0.010	0.49	< 0.010	0.33	0.020
MUFA	-0.54	< 0.010	-0.49	< 0.010	-0.33	0.020
n6-PUFAs	-0.23	0.120	-0.17	0.250	0.06	0.680
n3-PUFAs	-0.08	0.610	-0.04	0.780	-0.04	0.800

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acids; sPLA2: Secretory phospholipase-A2

Table 5. Spearman's coefficient of correlation (rho) between liver enzymes and demographic characteristics[1]

Characteristics	Age	P	BMI	P
AST	-0.01	0.970	0.38	< 0.010
ALT	0.10	0.500	0.30	0.040
ALP	-0.15	0.310	0.33	0.020

BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase

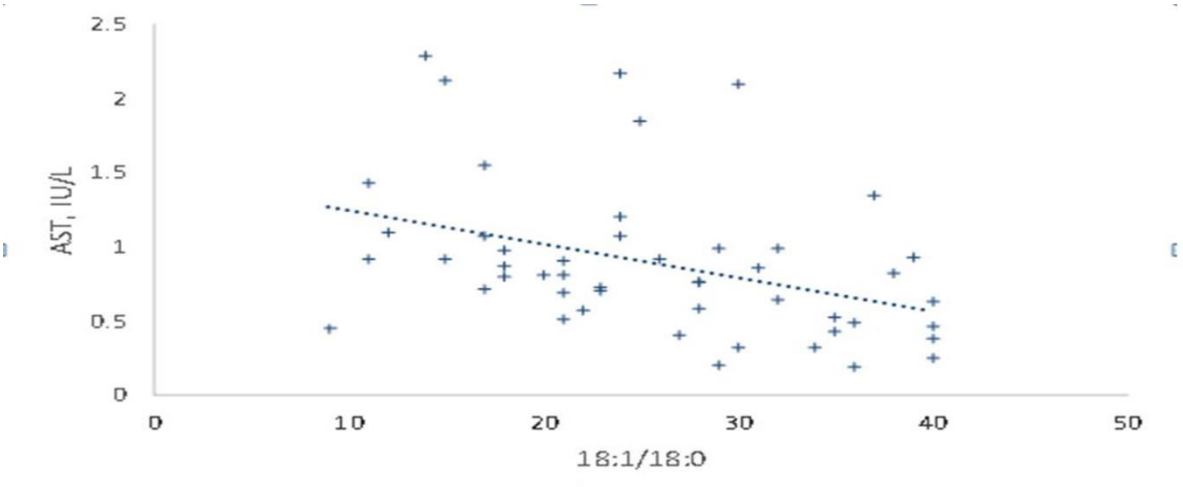

Figure 2. Correlation of cerebrospinal fluid oleic to stearic acid (18:1/18:0) with serum aspartate aminotransferase (AST)
Adjusted for the effect of body mass index (BMI) ($\beta = -0.35$, $P = 0.010$)

Discussion

In our study population, there was a significant interaction between BMI measure and all three hepatic enzymes. In consistent, a significant correlation has been shown between liver markers and BMI in population-based studies.[12,13]

Our findings showed that CSF total SFA was directly correlated with all serum liver enzymes. Multivariate analysis adjusting for BMI demonstrated the independent association of the activity of sPLA2 and total SFA with hepatic enzymes. CSF sPLA2 is a biomarker of CNS inflammation[14] and blood-CSF barrier permeability.[8] sPLA2 is known to play a significant role in induction of inflammation through enhancement of fatty acid conversion to eicosanoids. Notably, strong correlations were observed for ALT with the activity of circulating lipoprotein-associated PLA2 in healthy adults.[7,15] sPLA2 preferentially releases arachidonic acids from the sn-2-position of phospholipids.[9] However, the activity of this enzyme was not correlated with any type of CSF fatty acids, possibly because of further metabolism to bioactive compounds.

Specifically, the major SFA palmitic acid was positively correlated with AST. However, the stearic acid alone was not remained significant when adjusted for body weight. Some previous reports suggest that palmitic acid might be involved in the pathogenesis of liver disease. Since, in both animal and human models of high palmitic acid diet, liver failure is present together with the obesity phenotype,[16,17] it is to be expected that altered levels of CSF palmitic acid might be involved in liver function too. In contrast to MUFA, SFAs palmitic and stearic acids were accumulated in the hypothalamus upon high-fat feeding.[18] The possibility that high-fat feeding could reduce the activity of hypothalamic SCD has been proposed for this accumulation.[18] Consistent with this, our data showed a significant independent correlation between SCD activity index in CSF and serum AST. Altogether, it may be suggested that modulation of both sPLA2 and SCD contribute to central effects of fatty acids.

In this study, it was observed that central MUFA and oleic acid were inversely correlated with serum hepatic enzymes. Adjustment for BMI increased the strength of these correlations. On the contrast, oleic acid is known to induce hepatic steatosis. Teubert et al.[19] have shown that an increased oleic acid level in alcohol dependent patients is accompanied by an increase in serum liver enzyme and a decrease in linoleic acid. These data suggest that the biologic consequence of increased serum and CSF oleic acid on the liver function is not the same. In previous studies, nitric oxide (NO) signaling pathway and subsequent changes in parasympathetic nervous function have been linked to the effect of hypothalamic oleic acid on hepatic function.[2] The importance of the observed inverse correlation between CSF oleic acid and serum aminotransferases in hepatic diseases remain to be determined.

In this study, the level of CSF dietary essential fatty acid and linoleic acid was independently and inversely correlated with serum AST, a measure that represents liver functional capacity. This observation is in agreement with a previous clinical study that found an associations between n−6 polyunsaturated fatty acids (PUFAs) in CSF and peripheral glucose concentrations.[2] It is of note that no correlation was observed between CSF n−3 PUFA and serum liver enzymes.

Although previous research has shown the association between CSF fatty acids and peripheral glucose metabolism, this is the first study to examine the physiological relationship between sPLA2 activity and CSF fatty acids and circulating liver enzymes. Our findings along with the published mechanistic studies on central fatty acids point to a central role for fatty acids in the regulation of liver function. Findings in the present study are limited to patients referred for diagnostic lumber puncture and may not be representative of the general population. However, to minimize the potential effect of the non-physiological conditions, we included only patients who had normal CSF

and liver enzymes test as well as no co-existing disease at initial evaluation. Future studies investigating association of other metabolic parameters with CSF fatty acids would be valuable.

Conclusion

Several significant correlations among serum liver enzymes, the activity of CSF sPLA2 and some of the CSF fatty acids, including SFA and low MUFA were found in a group of adult patients undergoing diagnostic LP. Additional research is warranted to further elucidate associations of central fatty acids to liver disease in human.

Conflict of Interests

Authors have no conflict of interest.

Acknowledgments

This research was conducted as part of a Master's thesis project at the Tabriz University of Medical Sciences for the first author. This study was supported by a grant (No. 5.4.9705) from the Emergency Medicine Research Team at Department of Emergency Medicine, Tabriz University of Medical Sciences. Support was also provided by the Liver and Gastrointestinal Disease Research Center at Tabriz University of Medical Sciences.

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