Plasma omega 3 polyunsaturated fatty acid status and monounsaturated fatty acids are altered by chronic social stress and predict endocrine responses to acute stress in titi monkeys

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ARTICLE INFO

ABSTRACT

Disturbances in fatty acid (FA) metabolism may link chronic psychological stress, endocrine responsiveness, and psychopathology. Therefore, lipid metabolome-wide responses and their relationships with endocrine (cortisol, insulin, and adiponectin) responsiveness to acute stress (AS) were assessed in a primate model of chronic social stress (CS). Compared to controls (not exposed to CS), CS increased ($P \leq 0.05$) circulating triacylglycerol (TG) and phosphatidylethanolamine (PE) n-6/n-3 and reduced ($P \leq 0.05$) cholesterol ester (CE) 16:1n7 and phosphatidylcholine (PC) 18:1n7, suggesting lower omega-3 FA status and stearoyl-CoA desaturase activity, respectively. Cortisol responses to AS positively correlated with TG n-6/n-3 ($r=0.93$; $P=0.007$), but only in CS monkeys. The adiponectin response to AS inversely correlated with CE n-6/n3 ($r=-0.89$; $P=0.045$) and positively with TG 16:1n7 ($r=0.98$; $P=0.004$), only in CS monkeys. Our results are consistent with previously reported FA profiles in stress-related psychopathology and suggest that compositional changes of specific lipid FAs may form new functional markers of chronic psychological stress.

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1. Introduction

Chronic psychological stress and enhanced stress reactivity are linked to the development of CNS disease [1–3], which has been proposed to be related to dysregulation in the hypothalamic–pituitary–adrenal (HPA) axis [1]. Repeated or chronic exposure to psychological stress commonly results in the acute-stress-induced hyper-responsiveness of the HPA axis (measured as delta cortisol) [4]. Hyper-responsiveness of the HPA axis or increased cortisol reactivity is also typical of persons suffering from major depression and heightened anxiety, particularly in the context of social inhibition and vulnerability to social evaluative threat [5,6]. This regulatory shift in the responsiveness of this hormone to stress may in part explain the link between chronic stress and chronic diseases like depression. Furthermore, variability in the magnitude and direction of stress responsivity may in part explain individual differences in disease risk. While the underlying basis for this

functional change in endocrine responsivity remains unknown, we previously proposed that shifts in metabolic function, particularly in fatty acid metabolism, influence central mechanisms that regulate responsiveness in individuals undergoing chronic psychological stress [7].

Neuropsychiatric and cognitive diseases have poorly understood etiologies. Fatty acid dysregulation and deficiency may be linked to the development of these central nervous system (CNS) diseases. CNS diseases ranging from mood disorders to attention deficit and hyperactivity disorder have been shown to be associated with fatty acid deficiencies [8] and with alterations in specific fatty acid metabolites [9] [10]. For example, depression has been associated with increased plasma ratios of arachidonate:eicosapentaenate (AA:EPA) and n-6:n-3 fatty acid ratios, and lower EPA and C22:6n-3 docosahexaenoic acid (DHA) in circulating phospholipids and cholesterol esters [11–13]. Social anxiety disorder (SAD) has been associated with decreases of DHA and EPA in circulating phospholipids of red blood cells [14], and DHA and AA have been reported to be lower in the red blood cell phospholipids of schizophrenic patients [15]. In addition to the link between endogenous fatty acid metabolism and CNS diseases, fatty acids consumed exogenously have been shown to modulate symptoms

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of CNS disease. Dietary fish oil and DHA have been shown to exert anti-stress effects [16,17] and reduce depressive symptoms [18], suggesting that intake of n-3 fatty acids, particularly EPA and DHA, may have protective effects in mood disorders like major and bipolar depression [19]. However, some studies have failed to find such protective effects of consuming n-3 PUFA, further testing is required (e.g., [20]).

In providing a physiological basis for the associations between fatty acid metabolism and CNS diseases, it has been suggested that fatty acid dysregulation and deficiency may lead to abnormal brain function and health by decreasing neuronal membrane stability [21,22], altering membrane composition (e.g., n-6/n-3 fatty acids in membrane phospholipids) [22], and disrupting secondary messenger activity and neuropeptide trafficking (e.g., dopamine, serotonin, CRF) [23,24]. However, the factors leading to alterations in fatty acid metabolism and balance in the first place remain unknown. Although dietary and genetic factors likely play a role, other factors such as chronic psychological stress may significantly contribute to linking alterations in fatty acid balance and the development of CNS disease.

Recently, Lamaziere et al. [25] demonstrated the utility of a lipidomic approach to examining in rats omega 3 incorporation in the brain. In this project, a lipidomic approach was used to: (1) assess lipid metabolome-wide effects of chronic social stress in a non-human primate model (titi monkey (*Callicebus cupreus*)); (2) determine whether chronic social stress results in fatty acid metabolite profiles (e.g., lower omega 3 status) parallel to those seen in CNS diseases like depression; (3) test whether omega 3 status and concentrations of other plasma fatty acid metabolites explain variation in HPA responsiveness to acute stress; and (4) examine the stress response of the metabolic hormones insulin and adiponectin, which have both been proposed to link chronic stress with metabolic dysfunction (e.g., metabolic syndrome) and depression [26].

2. Methods and materials

2.1. Subjects and housing conditions

All experimental procedures were approved by the Animal Care and Use Committee of the University of California, Davis, and complied with National Institutes of Health ethical guidelines as set forth in the Guide for Lab Animal Care. All twelve male titi monkeys (*C. cupreus*) were laboratory-born and raised in stable family groups until they reached reproductive maturity (18 months). At random, 6 subjects were separated (chronic psychosocial stressor) from their families while the other 6 remained with their families (control). Animals were housed according to standard laboratory protocol that includes feeding twice daily (0700 and 1300 h) with water available ad libitum. All monkeys were provided the same diets which consisted of monkey chow (LabDiet 5045), cottage cheese, marmoset jelly (LabDiet 5041), apples, raisins, and baby carrots. Chow and all of the other food items were offered together, ad libitum, twice a day. The fatty acid composition of the total diet was of 34.4% saturated, 35.1% monounsaturated, 27.9% of n-6 polyunsaturated and 2.6% n-3 polyunsaturated fat as a percent of total fatty acids. Animals were maintained on a 12 h/12 h light dark cycle, with lights on at 0600. Skylights provide additional exposure to sunlight and natural variation in day-length. All blood draws were taken during the light cycle between 10:00 and 11:00 AM.

2.2. Experimental design

Chronic stress was introduced by capturing all family members from 6 randomly selected subjects. These chronically stressed
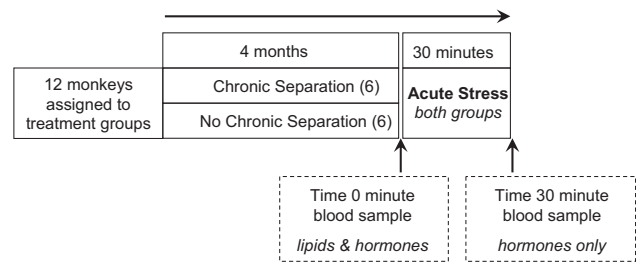

Fig. 1. Schematic of the study design.

monkeys were moved and singly housed for 4 months in new cages within the same colony room. The 6 control monkeys were moved to a new cage in the colony room and remained with their parents for 4 months. Four months after remaining in isolation, an acute stress was introduced to both chronically stressed and control monkeys. Starting at 10:00 AM, each subject was captured and removed from their respective cages followed by a baseline blood draw. After the baseline blood sample, monkeys were exposed to acute stress which involved placing each individual into transport cages as solitary confinement for 30 min at which time a second blood draw was taken (Fig. 1: the diagram of the study design). Immediately after the second blood draw, all monkeys were returned to their experimental home cages. Blood samples were collected at a designated and private location in the colony room within 3 min of entering the monkey's cage. One to two milliliters of blood was collected at each of the two collection times.

2.3. Biochemical analyses

Blood was collected from all participants into EDTA evacuated tubes, centrifuged immediately (1300g, 10 min, 20 °C), portioned into aliquots, and stored at −80 °C until analyzed. Plasma cortisol concentrations were determined using a standard RIA kit (Diagnostics Products Corporation [27]). Plasma insulin was assayed using an ultra sensitive insulin ELISA kit having broad species cross reactivity, including human (Crystal Chem, Inc.), and plasma adiponectin concentrations were determined using a standard RIA kit (Millipore, Inc; previously developed by Linco, Inc.) designed to assess human adiponectin, but routinely used for non-human primates [28]. All plasma hormones were measured at 4 months just prior to acute stress (time 0) and 30 min after acute stress.

2.4. Analysis of the fatty acid composition of plasma lipids

Fatty acid analyses of circulating lipid classes were determined by high-throughput methods developed by Lipomics Technologies, Inc. (West Sacramento, CA). The lipids from plasma (200 µL) were extracted using a modified Folch extraction in chloroform:methanol (2:1 v-v) [29] in the presence of a panel of quantitative authentic internal standards. Extracted concentrated lipids were analyzed by HPLC for phospholipid separation, TLC for non-polar lipid classes. Lipid classes were trans-esterified in 3 mol/L methanolic HCl in sealed vials under a nitrogen atmosphere at 100 °C for 45 min. The resulting fatty acid methyl esters were extracted from the mixture with hexane separated and quantified by capillary gas chromatography using an Agilent 6890 gas chromatograph (Santa Clara, CA) equipped with a 30-m DB-88 capillary column (Agilent Technologies) and a flame-ionization detector [30]. Fatty acids of each lipid class were determined quantitatively (µmol/L) and expressed as a % of total fatty acids within that class (mol%). Fatty acids in which 20% of the data were missing or below the limit of quantification were dropped from the analyses and considered not determined in the results section. Lipid classes were abbreviated in

the following way: Cholesterol Ester (CE); Free Fatty Acid (FFA); Triacylglycerol (TG); Phosphatidylethanolamine (PE); Phosphatidylcholine (PC); Plasmalogen (dm).

2.5. Statistical analyses

Statistical procedures were conducted using SPSS version 16.0 for Windows (SPSS, Chicago, IL). Means $\pm$ SD are reported for plasma hormones at time 0 and 30 min. Plasma fatty acids in each lipid class were treated and statistically analyzed as described in detail [31]. In short, due to high variation in abundance among circulating lipid classes, only fatty acids with a mean abundance of 1.0% or greater were used in each stepwise regression. All variables were analyzed for normality and appropriately normalized in order to conduct parametric statistical analyses. Data that could not be normalized were analyzed by a comparable non-parametric test.

Independent t-tests were performed to determine the effect of chronic stress on changes in plasma hormones in response to the acute stress with an alpha set at 0.05. Variables that were found significantly different by independent t-tests were re-analyzed using Cook's distance in general linear model ANOVA to confirm the significance was genuine. Data points with larger D-values than the rest of the data were considered highly influential and deleted. The models with deleted observations with large D-values were analyzed and compared to ensure the model was statistically relevant and not a product of one highly influential data point. For variables that could not be transformed, Kruskal Wallis test was performed in lieu of an independent t-test.

Stepwise linear regression was used to generate predictive models between baseline plasma fatty acids of each lipid class and 3 hormonal responses to the acute stress: delta cortisol, delta insulin, and delta adiponectin (Tables 1 and 2). Stepwise regressions were conducted for three conditions: all monkeys ($n=12$), only the chronically stressed monkeys ($n=6$), and only control monkeys ($n=6$). The ratios of circulating n-6/n-3 fatty acids were used as surrogates for omega-3 status in all lipid classes. For each stepwise regression, the F-statistic probability was set at an alpha between 0.05 and 0.10. Normality for each stepwise regression model was determined by generating normal probability plots of the regression standardized residual. Equal variance for each regression model across each dependent variable was determined by plotting the standardized predicted dependent variable by the standardized residuals. Outlying cases that strongly influenced each stepwise regression model were tested by Cook's distance (D) as mentioned above. Multi-collinearity between baseline lipids selected by stepwise regression was checked by a Variance Inflation Factor of ≤ 4.0. If variables demonstrated a Variance Inflation Factor greater than 4.0, they were dropped from the final regression model.

3. Results

3.1. Effect of chronic and acute stress on plasma hormones

There were no significant differences in baseline plasma cortisol, insulin and adiponectin between chronically stressed and control groups. However, in response to the acute stress, the reduction in plasma insulin was significantly greater in the chronically stressed (-31%) compared with the control group (-7%) $P=0.05$ (Table 1). Cortisol was significantly ($P<0.05$) elevated 30 min after the initiation of acute stress, but this cortisol response (HPA responsivity) did not differ between control (71%) and chronically stressed (82%) monkeys. Delta plasma adiponectin was not different between chronically stressed and control groups in response to acute stress.

Table 1
Plasma hormones.[a]

Variable	N	Sample time (min)	Control	Chronic stress
Cortisol (μg/dl)	6	0	23.0 ± 9.4	22.6 ± 5.7
	6	30	39.3 ± 13.9[b]	41.1 ± 10.6[b]
Δ Cortisol	6		16.3 ± 6.0	18.5 ± 7.9
Insulin (ng/ml)	6	0	2.1 ± 2.3	2.4 ± 1.3
	6	30	1.9 ± 2.4	1.6 ± 1.6
Δ Insulin	6		-0.16 ± 0.4	-0.73 ± 1.4[c]
Adiponectin (μg/ml)	5	0	14.0 ± 9.2	8.1 ± 4.1
	6	30	12.9 ± 8.0	9.0 ± 3.5
Δ Adiponectin	5		-1.1 ± 1.5	0.54 ± 0.76

$N=12$ monkeys.

[a] Starting at 10:00 AM, each monkey was captured and removed from his cage followed by a baseline blood draw. Monkeys were then placed into transport cages and remained in solitary for 30 min. (acute stressor) at which time a second blood draw was taken. Blood was collected within 3 min of entering the monkey's home and transport cages.

[b] Within experimental groups, acute stress significantly ($P<0.05$) increased plasma cortisol concentrations.

[c] Compared to controls, chronic stress significantly ($P=0.05$) reduced plasma insulin concentrations.

Table 2
Specific sets of predictor variables used in stepwise regression to generate predictive models for changes in plasma hormones in response to an acute stress.[a]

Models	Specific variables
CE[b]	16:0, 18:0, 16:1(n-7), 18:1(n-9), 18:1(n-7), 18:2(n-6), 20:4(n-6), n-6:n-3
FFA[b]	16:0, 18:0, 16:1(n-7), 18:1(n-9), 18:1(n-7), 18:2(n-6), 20:4(n-6), n-6:n-3
PC[b]	16:0, 18:0, 18:1(n-9), 18:1(n-7), 18:2(n-6), 20:3(n-6), 20:4(n-6), 22:6(n-3), n-6:n-3
PE[b]	16:0, 18:0, 18:1(n-9), 18:1(n-7), 18:2(n-6), 20:3(n-6), 20:4(n-6), 22:5n-3, 22:6(n-3), dm 16:0, dm 18:0, dm 18:1(n-9), total dm, n-6:n-3
TG[b]	16:0, 16:1(n-7), 18:0, 18:1(n-9), 18:1(n-7), 18:2(n-6), 18:3(n-3), 20:4(n-6), n-6:n-3

[a] Each of the 5 sets of possible predictor variables were used in stepwise regression to predict changes in plasma hormones—change in cortisol, insulin and adiponectin.

[b] Circulating fatty acids of each lipid class as mol% and their ratios were included as possible predictor variables in corresponding stepwise regression models.

3.2. Effect of chronic stress on plasma lipid metabolites

Plasma CE 16:1n7 ($P<0.05$) and PC 18:1n7 ($P<0.05$) at time 0 were significantly lower in the chronically stressed vs. the control group (Fig. 2A). Plasma TG n-6/n-3 and PE n-6/n-3 were significantly higher in the chronically stressed vs. control group ($P<0.05$; Fig. 2B).

3.3. Correlations between products of lipogenesis and stearoyl-CoA desaturase activities and changes in plasma hormones in response to acute stress

Analysis by stepwise regression revealed that plasma lipid metabolites could not explain the variance in delta plasma adiponectin when both groups were combined. However, in only the chronically stressed group, plasma TG 16:1n-7 was highly and positively correlated with delta plasma adiponectin in response to the acute stress ($r=0.98$, $P=0.004$) (Fig. 3A and B).
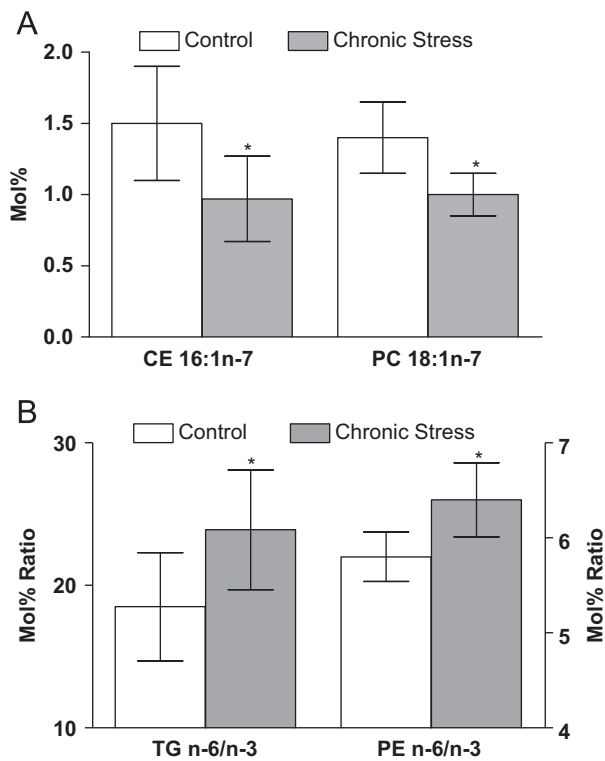
Fig. 2. (A) Mean plasma concentrations of CE 16:1n7 and PC 18:1n7 were lower in the chronically stressed compared with the control group (no social separation). (B) Mean TG and PE n-6/n-3 plasma concentration ratios (time 0) were higher in chronically stressed compared with the control (no social separation). Values represent means $\pm$ SD. *$P < 0.05$.

Fig. 3. Scatter plots of the relationships between baseline plasma TG 16:1n7 and the change (delta) in plasma adiponectin in response to an acute stress in chronically stressed (A) and control (B) monkeys.

3.4. Correlations between omega 3 status and changes in plasma hormones in response to acute stress

Analysis by stepwise regression revealed that plasma lipid metabolites could not explain the variance in delta plasma adiponectin or cortisol when both groups were combined. However, in the chronically stressed group, plasma TG n-6/n-3 was positively correlated ($r=0.93$, $P=0.007$) with delta plasma cortisol (HPA responsivity) in response to the acute stress (Fig. 4A and B). Furthermore, in only the chronically stressed group, plasma CE n-6/n-3 was negatively associated with delta plasma adiponectin in response to the acute stress ($r=-0.89$, $P=0.05$) (Fig. 4C and D).

3.5. Correlations between PE plasmalogens (dm) and changes in plasma adiponectin in response to acute stress

Analysis by stepwise regression revealed that plasma lipid metabolites could not explain the variance delta plasma adiponectin when both groups were combined. However, in the chronically stressed group, plasma PE plasmalogen (dm) 18:1n-9 was negatively correlated ($r=-1.0$, $P=0.0005$) with delta plasma adiponectin in response to the acute stress (Fig. 5A). Interestingly, in the control group, the reverse relationship was found between PE plasmalogen (dm) 18:1n-9 and delta plasma adiponectin ($r=0.88$, $P=0.02$) (Fig. 5B).

4. Discussion and conclusions

In this study, chronic stress (1) significantly altered plasma fatty acid products of lipogenesis and stearoyl CoA desaturase (SCD); (2) revealed associat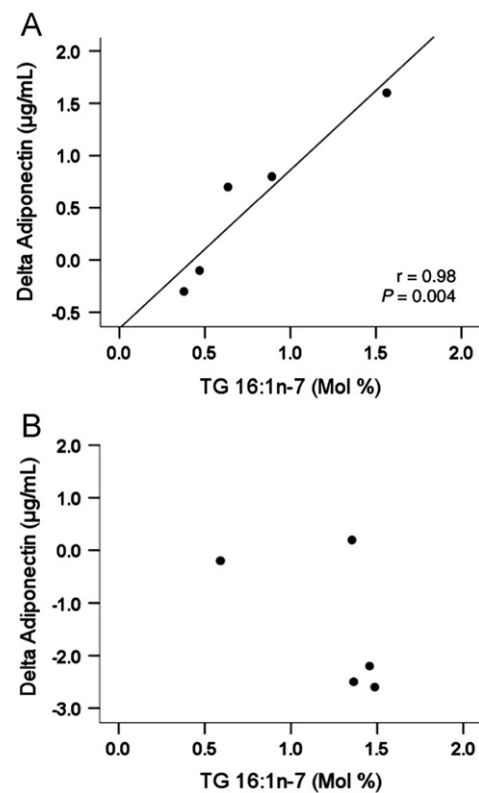ions between plasma n-6/n-3 ratio and stress-induced responsiveness of plasma cortisol and adiponectin; and (3) highlighted relationships between fatty acid products of SCD and ether lipids with the acute-stress-induced adiponectin response. Our study also suggests that the distribution of these fatty acids across different lipid classes (e.g., CE vs. TG) could reflect differential responses between lipid pools and endocrine responsivity in chronically stressed individuals. To our knowledge, this is the first report in which plasma lipids revealed a metabolic phenotype that predicts the effects of acute stress on endocrine responsiveness with and without a background of chronic psychosocial stress.

4.1. Effect of chronic stress on plasma lipid metabolites

Chronic stress reduced plasma CE 16:1n-7 and PC 18:1-n7 at time 0. These MUFAs are informative markers of metabolism because both are low in tissues and food supply [32,33]. Palmitoleate (16:1n-7) and its elongated product, vaccenic acid (18:1n-7), are products of SCD and markers of lipogenesis [32–35]. Reductions in 16:1n-7 and 18:1n-7 therefore suggest that this chronic stress model decreases lipogenic function, which is consistent with the report showing reduced lipogenic potential in chronically stressed mice [36]. Circulating concentrations of these fatty acids were also inversely associated with depression scores in depressive patients [37]. Although this study was not designed to measure the relationship between fatty acid metabolism and depression, previous work in the rat suggests that reduced lipogenic activity in the liver predicts higher expression of neuropeptides (e.g., CRF) [38] which mediate depression and anxiety [39]. Regardless, because psychological stress increases risk for depression and other psychiatric diseases [1–3], our findings do suggest that alterations in this enzyme system and
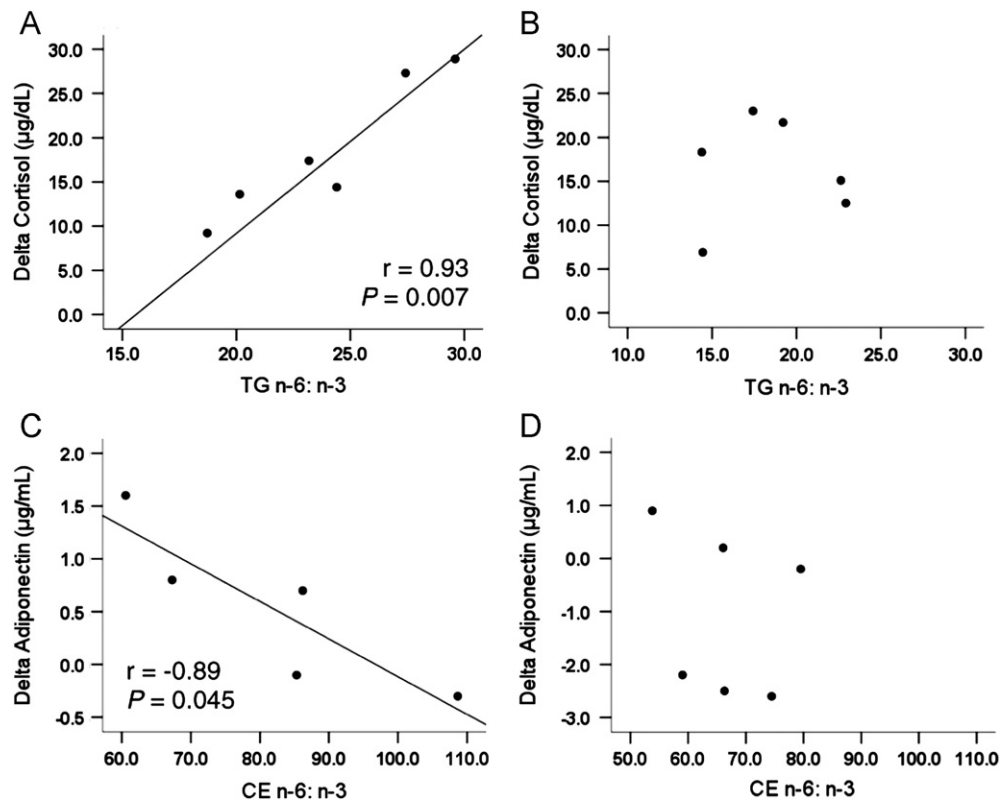
Fig. 4. Scatter plots of the relationships between baseline plasma lipid metabolites and changes (deltas) in plasma cortisol (A, B) and adiponectin (C, D) in response to an acute stress. Relationship between circulating baseline TG n-6/n-3 and changes in plasma cortisol in chronically stressed (A) and control (B) monkeys. Relationship between circulating baseline CE n-6/ n-3 and changes in plasma adiponectin in chronically stressed (C) and control (D) monkeys.

these fatty acids may play a role in and possibly predict risk for certain stress-related CNS diseases.

Chronic stress was also associated with higher circulating TG and PE n-6/n-3 ratios. These data are supported by large cross-sectional studies which found inverse relationships between concentrations of plasma phospholipid n-3 fatty acids and risk for psychological distress in Cree Indians [40] and Canadian Eskimo populations [41]. This relationship was proposed to result from lower fish consumption by individuals with psychological distress [40,41]. Although dietary intake was not assessed in these studies, because a single measurement of serum phospholipids has been shown to predict intake of marine origin n-3 PUFA, low levels of plasma phospholipid n-3 fatty acids in this group was most likely attributed to diet [42]. In the current study, monkeys consumed their diets ad libitum which was provided as monkey chow, cottage cheese, marmoset jelly, apples, raisins, and baby carrots. Because food intake was not quantified, and plasma concentrations of EPA and DHA of phospholipids were not significantly different between the two groups, it is unknown if chronically stressed monkeys preferentially selected foods lower in n-3 fatty acids.

Differences in plasma n-6/n-3 ratios between the two groups might also stem from the influence of chronic stress and related hormones on metabolism of dietary fatty acid substrates (linoleic and alpha linolenic acids), including their conversion into long chain PUFAs; e.g., preferential catabolism through β-oxidation and/or esterification in tissues as triacylglycerols. Hepatic microsomal delta-5 and delta-6 desaturase activities were decreased in chronically stressed rats [43], and acute IP injection of epinephrine increased plasma and liver linoleic acid and suppressed arachidonic acid [43] and conversion of 1–14C linoleic acid to γ-linolenic acid. The β blocker propranolol blocked these effects of epinephrine [44]. Injections of the chronic stress hormones, glucocorticoids, reduced hepatic conversion of 1–14C linoleic acid to gamma-linolenic acid

and 1–14C dihomo-γ-linolenic acid to arachidonic acid [45]. Glucocorticoids can also elevate fatty acid oxidation in liver [46] and heart [47], and fatty acid transport and TG accumulation in the heart [47]. The question remains, are omega-3 fatty acids selectively oxidized by, transported into, and/or re-esterified in tissues during states of chronic stress? It is not known if plasma TG n-3/n-6 and PE n-3/n-6 reflect endogenous metabolism, diet or both.

4.2. Correlations between plasma fatty acids and changes in plasma adiponectin in response to acute stress

Adiponectin, which is reduced in depression [48], is expressed in and secreted from adipose tissue [49]. Adiponectin facilitates peripheral glucose homeostasis by increasing tissue uptake [50] and may counter exaggerated hyperglycemia [50]. Plasma TG 16:1n-7 was positively associated with the change in adiponectin in response to acute stress, but only in chronically stressed monkeys. Plasma TG 16:1n-7 reflects lipogenic and SCD activities in liver [32] and adipose [35]. Moreover, a strong positive relationship was reported between SCD and adiponectin expression in human adipose tissue [51]. Unfortunately, the relationship between SCD activity in different tissues and stress hormones have been inconsistent [45,52–55]. However, our correlational findings together with our results showing chronic stress to depress 16:1n-7, suggest a link between chronic stress and SCD and lipogenic activities.

A previously conducted clinical trial found a strong positive association between basal circulating adiponectin and plasma n-3 fatty acids [56]. In the present study, higher plasma CE n-6/n-3 composition predicted lower adiponectin responses to acute stress, but this was specific to the chronic stress condition. Therefore, these findings suggest that chronic stress may trigger adaptive mechanisms that physiologically link n-6/n-3 CE composition and
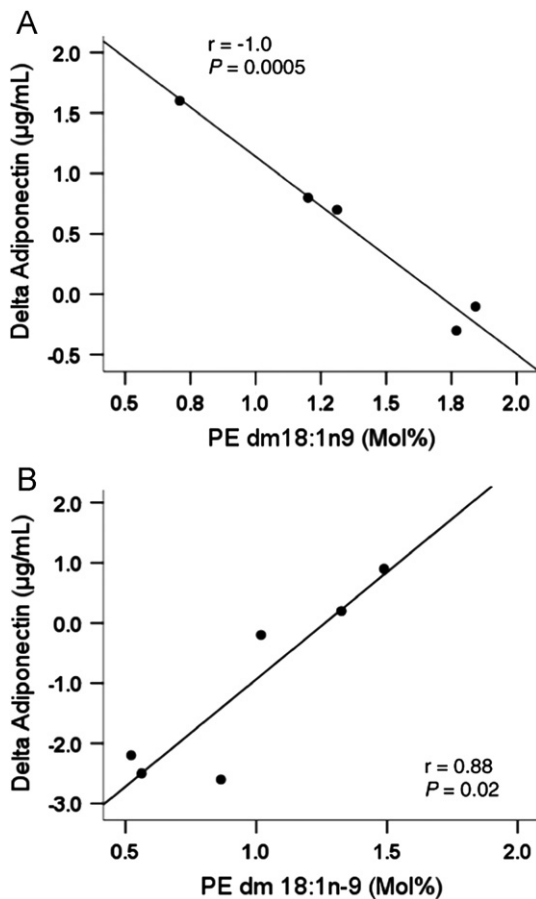
Fig. 5. Scatter plots of the relationships between baseline plasma PE plasmalogen (dm) 18:1n-9 and the change (delta) in plasma adiponectin in response to an acute stress in chronically stressed (A) and control (B) monkeys.

adiponectin responsivity. Although we cannot assume a relationship between our results and findings in CNS disease, it is worth noting that depression, which is commonly preceded by major episodes of acute stress, particularly in those with a history of chronic stress [57], is associated with increases in the n-6/n-3 lipid composition [12] and lower plasma adiponectin [48].

In chronically stressed monkeys, adiponectin responses to acute stress were negatively associated with plasma PE plasmalogen (dm) 18:1n-9. In controls, the converse relationship was observed. Plasmalogens are ether-linked phospholipids containing a vinyl aldehyde in the first position and an ester-linked fatty acid in the second position of the glycerol backbone [58]. They are found in neuronal membranes [59] and synthesized by peroxisomes [60] and endoplasmic reticulum [59]. Their physiological functions are undetermined, but PE plasmalogens were negatively correlated with Alzheimer's disease and age [61]. Interestingly, PE but not PC plasmalogens were positively correlated with statin-induced anti-inflammation, such that the higher baseline levels of PE plasmalogens, the greater the reductions in CRP with simvastatin treatment [58]. While little is known about plasmalogen functions, our data suggest that environment (stress vs. no stress) influences the relationship between these metabolites and changes in adiponectin.

4.3. Correlations between plasma fatty acids and changes in adrenocortical responsiveness to an acute stress

Chronic psychological stress and enhanced glucocorticoid reactivity are linked to the development of CNS disease [1–3], but

mechanisms for this relationship remain uncertain. In this study, we investigated whether certain fatty acids might explain variation in adrenocortical responsiveness. Plasma TG n-6/n-3 was positively associated with the plasma cortisol response to acute stress, which is consistent with a previous report showing inhibitory effects of consuming fish oil on the cortisol response to acute mental stress in humans [16]. Our results suggest that changes in TG n-6/n-3 concentrations may predict cortisol responsiveness, but only in chronically stressed individuals. There is a possible physiological basis for this result. Increasing n-6/n-3 fatty acid composition of lipids, which we observed in chronically stressed monkeys, increases activity of biosynthetic pathways that produce PGE2 [62,63]. PGE2 is elevated in response to psychological stress [64], mediates increased activity of the HPA axis [65] and, along with cortisol and elevated n-6/n-3 status, is increased in major depression [66,67]. Therefore, elevation in the n-6/n-3 status during states of chronic stress may increase the responsivity of the adrenocortical system to acute stressors.

Since chronic psychological stress, particularly of social origin, commonly precedes the onset of stress-related CNS diseases, our titi-monkey stress model led to the findings that support an etiological role of altered fatty acid status in neurological diseases. Furthermore, our findings are the first to possibly expose specific fatty acid markers of chronic stress and show a possible link between fatty acid composition and responsivity of key metabolic and neurobehavioral hormones, adiponectin and cortisol. Future studies on larger populations coupled with mechanistic validation to elucidate the direct role of lipid metabolism on chronic stress and CNS diseases are warranted.

Conflicts of interest

All authors have no conflicts of interest.

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