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Depression and altered serum lipids in cynomolgus monkeys consuming a Western diet

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ABSTRACT

Research over the past 15 years has suggested a high comorbidity of depression and coronary heart disease (CHD). However the mechanisms responsible for this relationship are poorly understood. This study was designed to examine the relationships between depressive behaviors and concentrations of circulating lipids and lipid signaling molecules that may be common to both CHD and depression in a cohort of cynomolgus monkeys (*Macaca fascicularis*) consuming a 'Western' diet, enriched with saturated fat and cholesterol. Socially-housed adult female cynomolgus monkeys (n = 36) were fed the Western diet for 27 months and depressive behavior was recorded weekly. Body weight, body mass index and circulating cholesterol profiles were measured in all animals, and fatty acids (FA) and FA-based signaling molecules were measured in the 6 least and 6 most depressed monkeys. Monkeys consuming the Western diet exhibited a broad range of percent time spent in depressive behavior. The percent time spent depressed was positively correlated with total plasma and LDL cholesterol and negatively correlated with HDL cholesterol. Despite being leaner, depressed monkeys had higher concentrations of monounsaturated fats (C16:1 and C17:1), a higher ω6/ω3 polyunsaturated fatty acid (PUFA) ratio and higher concentrations of omega-6 (ω6) PUFAs, particularly C18:2ω6 and C20:3ω6. FA ratios suggest that stearoyl CoA desaturase 1 activity was increased in depressed monkeys. Depressed female cynomolgus monkeys had elevated concentrations of serum lipids and lipid signaling molecules that are typically associated with obesity, insulin resistance and cardiovascular disease, which may account in part for the comorbidity of depression and CHD.

1. Introduction

Dietary and lifestyle changes over the past three decades have dramatically increased the global burden of a number of chronic human diseases including obesity, type 2 diabetes and cardiovascular disease and depression [1,2]. By the year 2030, coronary heart disease (CHD) and major depression are expected to be two of the three leading causes of morbidity in developed countries [3,4].

CHD and depressive mood disorders are highly comorbid. CHD is caused by coronary artery atherosclerosis and its sequelae. Coronary artery atherosclerosis develops for decades before CHD symptoms first appear. Recently, studies suggest that depression may be associated with coronary artery atherosclerosis [5–7] but offer little in the way of mechanistic links. Perturbed lipid metabolism has been observed in depression that could impact CHD risk [8]. Increases in systemic inflammation have also been suggested to be a common mechanism of several chronic disorders including CHD [1]. While the link between CHD and inflammation has been established for some time, recent studies indicate that patients with major depression also exhibit systemic and central nervous system inflammation as shown by increases in inflammatory cytokines including tumor necrosis factor (TNF)-alpha, interleukin (IL)-1 and IL-6 as well as the acute phase protein, C-reactive protein (CRP) in peripheral blood and cerebrospinal fluid [9,10].

The ingestion of fats has long been linked to CHD and more recently to cognitive function and behavioral abnormalities. Long chain polyunsaturated fatty acids (LC-PUFA) are critical components for neural and immune cell membranes and serve as key signaling molecules necessary for healthy brain development and function. The brain dry matter is about 60% lipid, and the omega-3 (ω3) fatty acid docosahexaenoic acid (DHA) is the most abundant fatty acid in the

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brain, constituting 30–50% of the weight of a neuron's plasma membrane [11–13]. The ω6 LC-PUFA, arachidonic acid (AA) is also a major LC-PUFA found in the brain and its metabolic products are crucial to orchestrating immunity and inflammation [11,14].

Adoption of the modern Western diet has been accompanied by a large increase in the consumption of seed oils, containing ω6 PUFAs, at the expense of ω3 PUFAs [15]. Importantly, the lack of ω3 LC-PUFAs, or an imbalance between ω3 and ω6 fatty acids, has been associated with CHD as well as neurological and psychiatric disorders in both children and adults, including depression [16,17].

Fish is the main source of DHA and a bioactive precursor eicosapentaenoic acid (EPA). A large number of retrospective and prospective studies, as well as clinical trials, over the past three decades indicate that consumption of fish and fish oils rich in ω3 LC-PUFAs reduces CHD. Additionally, dietary enrichment with ω3 PUFA-enriched fish oil inhibits atherogenesis in macaque monkeys [18,19]. The effect of ω3 LC-PUFAs on depression is promising, but not yet proven. Several studies suggest that patients with clinical depression have either an elevated ratio of circulating long chain ω6:ω3 PUFAs [14,20,21], or just low circulating long chain ω3 PUFAs [22]. There is a 60-fold variation across countries in annual fish consumption and a strong inverse relationship between national per capita fish consumption and the prevalence of depression [21,23,24]. Early clinical trials suggest that dietary fish oils reduce signs and symptoms of depression in some, but not all patient populations [16,25–29].

A major challenge in exploring the relationship between diet and diseases such as depression and CHD in human studies is controlling for dietary, environmental and lifestyle factors. An appropriate animal model is often necessary because it allows for control of heterogeneity in many variables inherent to human populations. Female cynomolgus monkeys (*Macaca fascicularis*) are an established model of coronary artery atherogenesis [30,31]. We have also used these monkeys to develop a female nonhuman primate model of depression which has been reviewed in detail elsewhere [32–34]. Briefly, like people, monkeys may respond to the stress of low social status with depressive behavior accompanied by perturbations in hypothalamic–pituitary–adrenal (HPA) function, the autonomic nervous system, circulating cholesterol levels, ovarian function, neural serotonergic system function, hippocampal volume, and decreased activity levels, all of which are associated with exacerbated coronary artery atherosclerosis or increased risk of CHD [35]. Additionally, despite being leaner than their nondepressed counterparts, female cynomolgus monkeys that are depressed develop four times the coronary artery atherosclerosis [36]. In the current study, circulating atherogenic lipids and signaling molecules are examined in detail in female cynomolgus monkeys consuming a diet modeled after the Western diet to identify potential mechanisms by which depression may exacerbate coronary artery atherosclerosis in this model system.

2. Materials and methods

2.1. Animals and diet

Thirty-six adult female cynomolgus monkeys were obtained directly from Indonesia (Institut Pertanian Bogor, Bogor, Indonesia). All procedures involving primates were conducted using protocols approved by the Animal Care and Use Committee of Wake Forest University Health Sciences and were in compliance with all institutional, state, and federal laws for the usage of primates in laboratory settings.

The animals were part of an experiment to evaluate the comorbidity of depression and coronary artery atherosclerosis [36]. Thus, the animals consumed an atherogenic diet (Table 1) for 27 months that contained 0.28 mg cholesterol/cal (approximately equal to a human consumption of 500 mg/day), and 42.4% of calories as fat. The fatty acid composition of the diet, given in Table 2 (fatty acids measured as described below), resulted in a PUFA to saturated fatty acid ratio of 1:6 and a ω6:ω3 ratio of 25:1.

Table 1
Diet composition[a].

Ingredient	g/kg dry weight	kJ/kg dry weight
Casein	123	1859
Lactalbumin	120	1924
Dextrin	203.8	3424
Sucrose	200	3360
Alphacel	55.4	
Lard	90	3410
Beef tallow	70	2652
Butter, lightly salted	30	903
Safflower oil (linoleic)	20	743
Crystalline cholesterol	1	
Complete vitamin mix[b]	25	336
Mineral mix[c]	50	
Calcium carbonate	4.3	
Calcium phosphate	7.5	

[a] Diet composition (% of calories): 38.3% carbohydrate, 42.4% fat, and 19.4% protein with 0.28 mg/cal cholesterol.
[b] Complete vitamin mixture (BGSM formula) made by Harlan Teklad (Madison, WI).
[c] Modified #2 Ausman–Hayes Mineral Mix made by Harlan Teklad. All calcium phosphate tribasic and potassium phosphate dibasic were removed from the mineral mixture and replaced with potassium carbonate and dextrin.

2.2. Experimental design

During the first 12 months that the animal consumed the atherogenic diet they lived in single cages with visual, auditory, and olfactory contact with other monkeys. During the following 15 months, the monkeys lived in small social groups of four animals each in 3.05 m × 3.05 m × 3.05 m indoor enclosures with visual access to the outside. Social behavior was recorded throughout the 15 months the monkeys lived in social groups. After 11 months in social groups the monkeys were fasted overnight, and blood samples were collected for total plasma cholesterol (TPC) and high-density lipoprotein cholesterol (HDL-C) measurements (n = 34), as well as fatty acid determinations (n = 12) as described below. After 15 months in social groups, body weight (BW) and trunk length were measured, body mass index (BMI) was calculated (BW (kg)/trunk length (m^2)) as previously described [36], and blood samples were collected for glucose and insulin assay after an overnight fast.

2.3. Behavioral depression (Fig. 1)

The definition of depressive behavior includes three components: 1) a slumped or collapsed body posture; 2) a relative lack of responsiveness to environmental stimuli to which other monkeys

Table 2
Fatty acid composition of the diet.

Fatty acids	mg/monkey/day[a]	% total fatty acids
Total fatty acid	2734.50	100.00
Saturated fatty acids (45.1%)[b]	1627.35	59.51
Monounsaturated fatty acids (40.4%)[b]	826.06	30.21
Polyunsaturated fatty acids (14.4%)[b]	281.10	10.28
Total ω6	270.33	9.89
Total ω3	10.77	0.39
Arachidonic acid (AA, C20:4ω6)	4.31	0.16
Eicosapentaenoic acid (EPA, C20:5 ω3)[c]	0.00	0.00
Docosapentaenoic acid (DPA, C22:5 ω3)	0.54	0.02
Docosahexaenoic acid (DHA, C22:6 ω3)[c]	0.00	0.00

[a] Values are means from 4 samples; 2 fresh samples and 2 samples left at room temperature for 6 h since diet is generally consumed over several hours. The fatty acid profile of the diet was not altered by room temperature storage.
[b] Percent of fat in diet.
[c] EPA and DHA were present at levels below 0.01 mg.

	Non - depressed	Depressed	p ≤
%Time Depressed	2.05 ± 0.38	9.25 ± 0.72	0.0001
Body Weight (kg)	3.29 ± 0.14	2.81 ± 0.09	0.02
Body Mass Index	50.4 ± 2.32	42.2 ± 2.84	0.04
Glucose (mg/dl)	77.1 ± 3.06	79.5 ± 4.86	0.70
Insulin (uU/ml)	29.0 ± 2.25	25.9 ± 5.37	0.69

Fig. 1. Characteristics of the monkeys. An alert nondepressed monkey (left) and a monkey sitting in the depressed posture (right). Behavior was documented throughout the experiment. Monkeys that fell above the mean in percent time spent depressed (n = 15) were considered depressed, whereas those that fell below the mean (n = 21) were considered nondepressed. Weight (n = 36), BMI; (n = 36), fasting glucose and insulin (n = 31) are shown in the table. Data are mean ± SEM.

are attending; and 3) open eyes to distinguish this behavior from resting [37]. An example is depicted in Fig. 1. Time spent in the depressed posture was recorded for 15 min weekly for 15 months, counterbalanced for time of day, using a focal animal technique that has been described in detail previously [36,38]. This behavior is easily recognizable; interrater reliability, determined biannually, was ≥0.92 throughout the experiment. The average time spent depressed each month was calculated from these observations. Previously, we demonstrated that the number of months in which a monkey was observed in the depressed posture was highly correlated with the average time spent in the depressed posture throughout the experimental phase ($r = 0.84$, $p < 0.001$) [33]. Thus, time spent in the depressed posture was averaged over the entire 15 month phase for analysis. Monkeys that fell above the mean in percent time spent in depressed behavior (n = 15) were considered depressed, whereas those that fell below the mean (n = 21) were considered nondepressed [33]. While socially subordinate monkeys have been observed to exhibit more depressive behavior than dominants [37], there were no significant differences in social status between the 15 depressed and 21 nondepressed monkeys in this 15 month period [$t = 1.58$, $p = 0.12$; 33]. Behavioral and physiological characteristics of these depressed versus nondepressed monkeys have been described in detail previously [33].

2.4. Assays

TPC and HDL-C concentrations were measured using enzymatic methods on the COBAS FARA II analyzer (Roche Diagnostics Inc., Montclair, NJ, USA), with protocols and reagents supplied by Boehringer Mannheim. HDL-C concentrations were measured using the heparin–manganese precipitation procedure and as described in the Manual of Laboratory Operations of the Lipid Research Clinics Program [36]. LDL-C was determined by subtracting HDL-C from TPC. Glucose was determined using standard chemistries on the COBAS FARA II analyzer and insulin concentrations were determined by RIA. Glucose and insulin data were available from 13 of the depressed and 18 of the nondepressed females.

2.5. Fatty acid profiles

Blood was collected, and serum was prepared by centrifugation at 200 × *g* for 10 min within 1 h of collection and frozen and stored at −70 °C. For this pilot study, serum fatty acid profiles were determined in the 6 most and 6 least depressed monkeys. Prior fatty acid analyses suggested that this number would provide adequate power to detect a significant difference. The diet was also prepared and frozen at −20 °C. For analysis, lipids were extracted by the method of Bligh and Dyer [39] from 100 mg of diet; the internal standard diheptadecanoyl-*sn*-glycero-3-phosphorylcholine (25 μg) was added to the monophase. The fatty acids in the diet extracts and serum (50 μL; plus internal standard) were derivatized to fatty acid methyl esters and then analyzed by gas chromatography with flame ionization detection [40,41]. The desaturation indices using the product–precursor ratios of C16:1/C16:0 and C18:1/C18:0 were used as markers of stearoyl CoA desaturase 1 (SCD1) activity [42].

2.6. Statistical analysis

T-tests were used to determine group differences in cholesterol, BW, BMI and FA concentrations. Pearson r correlations were used to measure the strength of associations. The α-level was set at 0.05 and all reported p-values are from two-sided tests. The data are depicted as means ± SEM.

3. Results

3.1. Characteristics of depressed and nondepressed monkeys

Among the animal studied (n = 36), 42% (n = 15) exhibited depressive behavior. Depressed monkeys had significantly lower body weight ($t(34) = 2.47$, $p = 0.02$) and body mass index ($t(34) = 2.19$, $p = 0.04$) compared to their nondepressed counterparts (Fig. 1). In contrast, the circulating glucose ($t(29) = 0.38$, $p = 0.70$) and insulin ($t(29) = 0.40$, $p = 0.69$) concentrations in the fasted state were similar in the two groups of animals.

3.2. Correlations between depression and circulating cholesterol concentrations

Relationships between circulating cholesterol concentrations and time spent in the depressed posture are shown in Fig. 2. Total plasma cholesterol (TPC; Fig. 2A) was positively correlated with time spent in the depressed posture. HDL-C (Fig. 2B) was negatively correlated with time spent in the depressed posture. The direction of these correlations is reminiscent of the relationship of these lipids to CHD.

3.3. Profile of major and minor fatty acids in the plasma of nondepressed and depressed animals

Fig. 3 shows the concentrations of major fatty acids in the 6 least and 6 most depressed monkeys. Total fatty acids (Fig. 3A) were higher on average in depressed monkeys, although this difference did not reach significance ($t(10) = 1.94$, $p = 0.08$). There were no differences between depressed and nondepressed monkeys in saturated fatty acids (Fig. 3A) such as palmitic (C16:0; $t(10) = 1.44$, $p = 0.18$) or stearic acids (C18:0; $t(10) = 0.73$, $p = 0.48$). In contrast, circulating ω6 PUFAs were markedly higher in depressed monkeys. Although the precursors of arachidonic acid, linoleic acid (C18:2ω6; $t(10) = 2.95$,

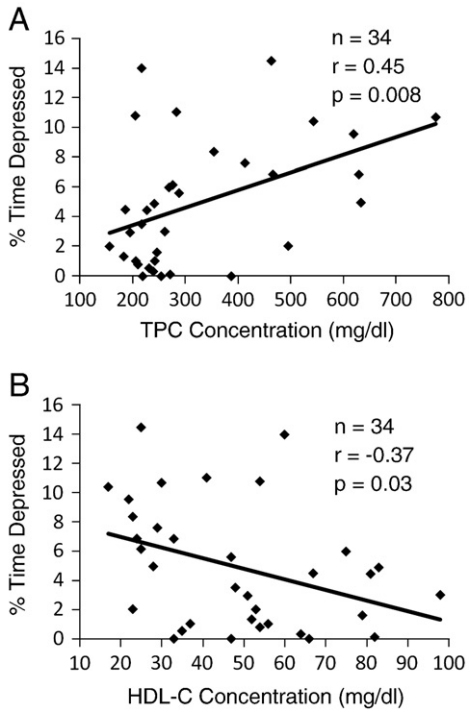

Fig. 2. Relationship between depressive behavior and plasma cholesterol concentrations in female monkeys (n = 34). TPC = total plasma cholesterol and HDL-C = high density lipoprotein cholesterol.

p = 0.01; Fig.3A) and dihomo-gamma-linoleic acid (C20:3ω6; t(10) = 2.38, p = 0.04; Fig. 3B) were both 42% higher in depressed monkeys, arachidonic acid (C20:4ω6; t(10) = 1.71, p = 0.12; Fig. 3B) was not different between the two groups of monkeys. Among the ω3 PUFAs (Fig. 3C), there were no significant differences between depressed and nondepressed monkeys in eicosapentaenoic (EPA: C20:5ω3; t(10) = 0.43, p = 0.67), docosapentaenoic (DPA: C22:5 ω3; t(10) = 0.42, p = 0.68), and docosahexaenoic acids (DHA: C22:6ω3; t(10) = 1.50, p = 0.16). These fatty acid concentrations resulted in a significantly higher ratio of ω6:ω3 PUFAs (t(10) = 2.76, p = 0.02) in the depressed animals (Fig. 3D). The ratio of circulating PUFAs to saturated fatty acids was also higher, on average, in depressed monkeys although this difference did not reach significance (t(10) = 2.07, p = 0.07; Fig. 3D).

3.4. Monounsaturated fatty acid concentrations and SCD1 activity in nondepressed and depressed animals

SCD1 activity and one of its primary metabolic products, palmitoleic acid, C16:1ω7 have been linked to obesity, peripheral insulin resistance, and enhanced lipid synthesis and accumulation [43]. SCD1 activity was inferred from the product–precursor ratios of C16:1ω7/C16:0 and C18:1ω9/C18:0 [44]. Total circulating concentrations of the major sixteen, seventeen, and eighteen carbon chain SCD1 products were analyzed in the 6 least and 6 most depressed monkeys. Fig. 4A shows the concentrations of circulating palmitoleic acid (C16:1ω7), heptadecenoic acid (C17:1), and oleic acid (C18:1) in nondepressed and depressed monkeys. Monkeys in the depressed group had higher concentrations of palmitoleic acid (t(10) = 2.22, p = 0.05) and heptadecenoic acid (t(10) = 2.34, p = 0.04) than their nondepressed counterparts. Oleic acid was higher, on average, in depressed monkeys but this difference did not reach significance (t(10) = 2.17, p = 0.06). The product–precursor ratios of C16:1ω7/C16:0 and C18:1ω9/C18:0, were 20% (t(10) = 2.75, p = 0.02) and 27% (t(10) = 2.88, p = 0.02) higher, respectively, in depressed animals (Fig. 4B), suggesting higher SCD1 activity.

4. Discussion

Depression has been suggested to be an independent risk factor for cardiovascular disease. However, among patients with depressive and cardiovascular disorders, the heterogeneities in lifestyles and diets make it difficult to design experiments that uncover mechanistic links between these complex diseases. Animal models suitable for testing

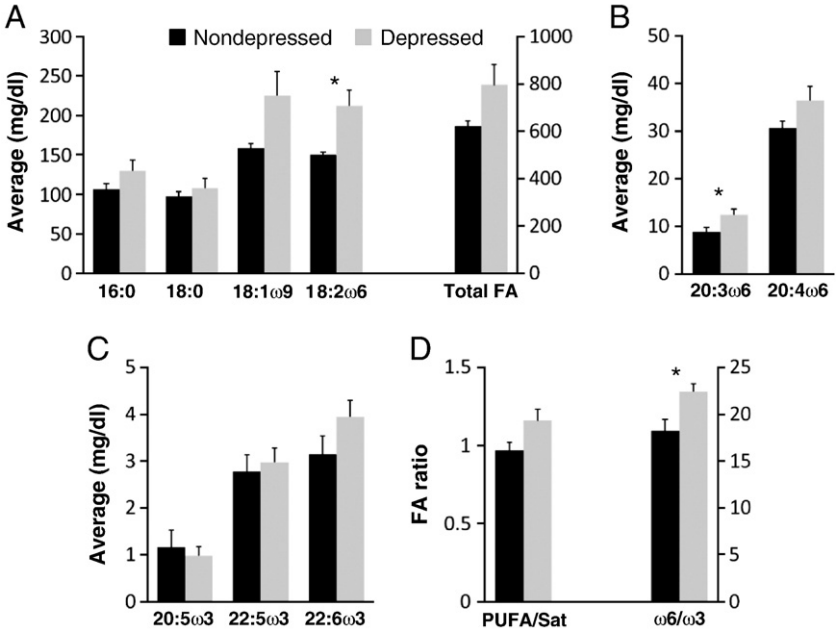

Fig. 3. Serum fatty acids (FA) and FA ratios in depressed (n = 6) and nondepressed (n = 6) monkeys. A. C16:0 (palmitic); C18:0 (stearic); C18:2ω6 (linoleic); and Total FA. B. C20:3w6 (dihomo-gamma-linoleic) and C20:4ω6 (arachidonic). C. C20:5ω3 (eicosapentaenoic); C22:5ω3 (docosapentaenoic); and C22:6ω3 (docosahexaenoic). Total and individual FAs are expressed as mg/dl serum. D. FA ratios in depressed and nondepressed monkeys. The PUFA/SAT ratio = the ratio of the sum of polyunsaturated to the sum of saturated fatty acids. ω6/ω3 = the ratio of the sum of ω6 to the sum of ω3 fatty acids. Data are mean ± SEM. Values from depressed monkeys significantly different (*p<0.05) from those from control animals are indicated.

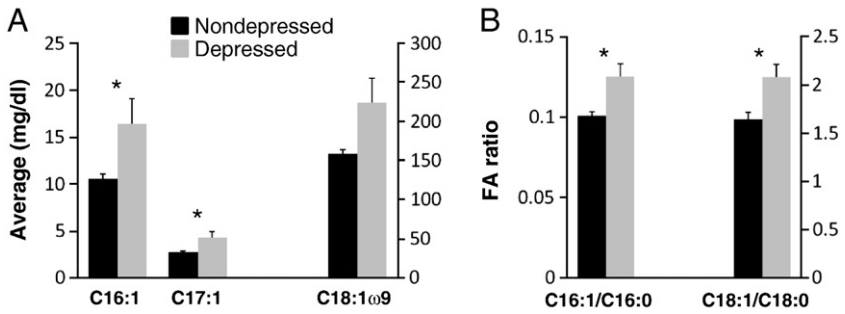

Fig. 4. Total circulating concentrations of the major sixteen, seventeen and eighteen carbon monounsaturated fatty acids and monounsaturated to saturated fatty acid ratios in depressed (n = 6) and nondepressed (n = 6) monkeys. A. C16:1 (palmitoleic); C17:1 (*cis*-10-heptadecenoic); and C18:1ω9 (oleic) acids are expressed as mg FA/dl serum. B. Ratio of monounsaturated to its corresponding saturated (precursor) fatty acid used as an estimate of SCD1 activity. Data are mean ± SEM. Values from depressed monkeys were significantly different (*$p<0.05$) from those from control animals are indicated.

such hypotheses are difficult to develop since an animal model of comorbidity requires the model to have pathophysiological characteristics critical to both diseases. Our laboratory has developed a primate model of adult depression using female cynomolgus macaques, a well established model of coronary artery atherosclerosis [36,45]. The current study reveals that a large proportion (42%, Fig. 1) of cynomolgus monkeys that were fed a high fat Western diet exhibit depressive behavior which is associated with profiles of circulating lipids and lipid signaling molecules that are linked to obesity and cardiovascular disease. These changes were evident in depressed monkeys despite the fact that all animals consumed the same diet and depressed animals had lower BMI and body weight compared to their nondepressed counterparts.

Specifically, alterations in three major lipid classes were associated with behavioral depression. First, depression was positively correlated with TPC and negatively correlated with HDL-C (Fig. 2). The relationship between depression and circulating cholesterol concentrations has been of particular interest in several studies over the past few years. Low TPC has been associated with depression in some human studies but not others [46–49]. The literature is also mixed in regard to the relationship between depression and HDL-C. However, three large studies report an inverse correlation between depression and serum concentrations of HDL-C in women, but not men [50–52]. Taken together these data suggest a relationship between mood and lipid metabolism, though the nature of that relationship remains to be understood.

The second major lipid perturbation observed in this model was a higher concentration of ω6 fatty acids and a higher ratio of ω6/ω3 fatty acids (Fig. 3). Elevated levels of linoleic acid (C18:2ω6) and dihomo-gamma-linolenic acid (C20:3 ω6) were the key factors that resulted in the change in the ω6/ω3 ratio (Fig. 3). With regard to the impact of linoleic acid on behavioral disorders, Hibbeln and colleagues demonstrated that greater consumption of linoleic acid correlated with higher rates of homicide mortality over a 20-fold range across countries [53]. More recently, dietary intake of seed oils, which are rich in linoleic acid, has been associated with depressive symptoms in an elderly population [54]. Additionally, a recent 10 years follow-up of a national cohort provides strong evidence that diet rich in linoleic acid may enhance the risk of depression among the general population [17].

A significant increase in circulating MUFAs was a third perturbation in circulating lipids. Stearoyl CoA desaturase (SCD1) is an enzyme that has been shown to produce MUFA signaling molecules. Certain MUFAs, in particular, palmitoleic acid (C16:1, Fig. 4A) has been demonstrated to influence energy metabolism leading to obesity, insulin resistance, diabetes and hyperlipidemia [42,43,55]. In fact, the SCD1 reaction product, palmitoleic acid, appears to be a key lipokine communicating with peripheral organs to regulate systemic metabolic homeostasis [56]. Recent observations from the CARDIA study provide strong evidence that depression promotes the development of visceral obesity, and thus metabolic syndrome, diabetes and CHD [57]. The elevated levels of palmitoleic acid and the product–precursor ratio (C16:1/C16:0 or C18:1/C18:0), which estimates SCD1 activity (Fig. 4), in depressed monkeys may be one mechanism by which this occurs.

Depression in human and nonhuman primates may be precipitated by social stressors and is accompanied by perturbations in multiple systems. In addition to many differences in the structure of the brain and the function of many neurotransmitter systems, depression is also accompanied by deleterious changes in the autonomic system, HPA axis, activity levels, reproductive system, immune system, and lipid metabolism, all of which are associated with increased CHD. Lipid metabolism has an enormous impact on CHD risk, thus lipid perturbations in depression are likely one of the mechanisms that contribute to increased CHD among depressed patients. In our nonhuman primate studies in which the monkeys consume a Western diet, about 40% exhibit depressive behavior. It may be that a Western diet increases depressive behavior among a subgroup of susceptible individuals. This hypothesis requires closer examination in future studies.

In summary, this study of female monkeys consuming a high-fat Western diet reveals associations between behavioral depression over a two-year period and circulating fatty acid concentrations. Cholesterol and fatty acid concentrations were not associated with body weight, BMI or fasting glucose and insulin concentrations. These data suggest that lipid dysregulation characteristics that are typically associated with obesity, diabetes and the metabolic syndrome are also associated with behavioral depression in a nonhuman primate model in which depressed monkeys develop more coronary artery atherosclerosis.

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University Health Sciences and to outside sponsors and are institutionally managed.

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