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ORIGINAL ARTICLE

Absence of attenuation in oxidative stress response with repeated lipid-rich feedings

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Abstract

Background: The study of postprandial oxidative stress has received considerable attention in recent years. Excess production of reactive oxygen and nitrogen species (RONS) in response to high fat feeding can lead to oxidative stress. However, repeated exposure to the same stressor may lead to attenuation in the oxidative stress response, possibly via an up-regulation in antioxidant enzyme activity.

Objective: To determine if repeated exposure to lipid-rich meal ingestion leads to a lower oxidative stress response over time, possibly due to an increase in antioxidant enzyme activity.

Methods: Sixteen healthy men consumed 10 high fat milkshakes over a 3+ week period. Blood was taken from subjects on the first day of each week (before and for 4 hours after milkshake ingestion) and analyzed for oxidative stress and antioxidant biomarkers.

Results: The oxidative stress response to repeated lipid-rich feeding was not different over time, as indicated by similar changes in plasma malondialdehyde and hydrogen peroxide, as well as superoxide dismutase, catalase and glutathione peroxidase activity.

Conclusion: These data indicate that RONS production is likely similar with repeated exposure to lipid-rich meals and does not induce an adaptive response within the blood antioxidant defense system in a way that is protective to cells.

INTRODUCTION

A recent PubMed search (May 1, 2014) using the term "postprandial oxidative stress" returned 459 results, demonstrating the interest in this area of investigation. Oxidative stress occurs when the production of reactive oxygen and nitrogen species (RONS) overwhelms antioxidant defenses and involves oxidative damage to lipids, proteins, DNA, and other macromolecules [1] in ways that impair cell function [2]. As a result, oxidative stress is known to be a major contributor to many chronic diseases, as well as to the aging process [3]. The production of RONS is a component of normal cell metabolism [2, 4] and serves multiple vital roles in human physiology (*e.g.*, cell signaling, apoptosis, and immune function). However, this can be problematic when RONS are produced in excess.

Likely the most prevalent factor in Western society known to increase RONS production is the consumption of food [5, 6]; specifically, food that is high in saturated fat and simple sugar. Postprandial oxidative stress describes a state in which RONS production surpasses the body's antioxidant defenses following meal consumption. RONS production has been shown to be greater after lipid-rich meals as compared to protein- or carbohydrate-rich meals, with protein causing the least oxidative insult [6]. It has also been noted that as the lipid or carbohydrate load is increased, the oxidative stress response is increased [5], suggesting either increased RONS generation and/or decreased antioxidant defense. High-fat meals and the associated oxidative stress have also been reported to impair endothelium-dependent vasodilation [7], which may contribute to the development of cardiovascular disease.

In many investigations, postprandial oxidative stress is compared before and following an intervention, such as dietary modification [8], nutritional supplementation [9], or chronic exercise [10]. In some instances, postprandial oxidative stress is noted to be lower following the intervention as compared to before the intervention. However, it is possible that the magnitude of response is simply blunted as a function of the individual become "familiar" with the meal; in such a way that their body learns to process nutrients more efficiency and may experience an up-regulation in antioxidant defense as a result of the repeated exposure to RONS. This process may occur in accordance with the principle of hormesis [11]; a phenomenon that is well-described for chronic exercise and results in a significant blunting or elimination of the oxidative stress response [12].

As investigators focused on the study of postprandial oxidative stress, it was our intention to determine if repeated exposure to lipid-rich meals resulted in a differing oxidative stress response over time. These findings would then serve to guide future study designs involving pre and post- intervention assessments of postprandial oxidative stress. That is, if a blunting of the response was observed with repeated exposure, perhaps one or more "familiarization" meals would be required in future designs before "pre" assessment data collection was conducted.

METHODS

Subjects

Sixteen healthy men between the ages of 19-43 years participated in this study. Considering our use of a cross-over design, our sample of 16 subjects was more than adequate to address our research questions. Subjects were physically active, with all subjects participating in both aerobic (*e.g.*, running, cycling, team sports) and anaerobic (*e.g.*, resistance training) exercise, with the exception of one subject who participated solely in aerobic exercise. The mean exercise involvement of our subjects exceeded six hours per week.

All subjects were also consuming a "healthy", low- or moderate-fat diet prior to enrolling. Specifically, their diet did not include routine (*i.e.*, daily) ingestion of high-fat foods, in particular those rich in saturated fat. A detailed interview was conducted with potential subjects to determine eligibility, in a similar manner as with using a food frequency questionnaire. All participants were non-smokers with no known cardiovascular or metabolic diseases. Subject characteristics are provided in Table 1. Subjects were advised to refrain from antioxidant supplementation at least two weeks prior to the start of the study, as well as during the study. Women were prohibited from participation in this study to allow for a more homogeneous sample due to the potential influence of estradiol on antioxidant activity and oxidative stress. Recruitment of subjects took place at the University of Memphis via flyers, e-mail, and word of mouth.

Initial lab visit

Eligibility was determined via interview and the completion of questionnaires pertaining to health history, physical activity, and medication and dietary supplement use. Each subject was informed of all procedures, potential risks, and benefits associated with the study in both verbal and written form. All study procedures were approved by The University of Memphis Institutional Review Board for Human Subjects Research. Subjects were required to provide written informed consent prior to being enrolled in the study.

Table 1. Characteristics of 16 healthy men consuming high-fat meals over the course of a 4 week period (mean ± SEM)

Variable	
Age (years)	24.9 ± 1.6
Height (cm)	176.3 ± 1.6
Body weight (kg)	80.3 ± 2.5
Body mass index ($kg \cdot m^{-2}$)	25.9 ± 0.7
Total body fat (%)	17.2 ± 6.7
Trunk body fat (%)	17.9 ± 1.8
Fat mass (kg)	14.1 ± 1.5
Fat free mass (kg)	66.2 ± 1.6
Waist circumference (cm)	85.7 ± 1.9
Hip circumference (cm)	101.6 ± 1.5
Waist to hip ratio	0.8 ± 0
Resting heart rate (bpm)	71.9 ± 3
Resting systolic blood pressure (mmHg)	120.8 ± 2.7
Resting diastolic blood pressure (mmHg)	76± 2.8
Total fasting cholesterol (mg/dl)	159.9 ± 3.9
Fasting HDL cholesterol (mg/dl)	51.4 ± 3.9
Fasting VLDL cholesterol (mg/dl)	23.2 ± 3.4
Fasting LDL cholesterol (mg/dl)	85.3 ± 2.8
LDL:HDL	1.8 ± 0.1
Total:HDL	3.3 ± 0.2
Weekly aerobic training (hrs)	3 ± 0.6
Aerobic training history (yrs)	6.2 ± 1.8
Weekly anaerobic training (hrs)	3.8 ± 0.7
Anaerobic training history (yrs)	6.1 ± 1.5

After consent was provided and eligibility determined, subjects were asked to void and rest for 10 min in a seated position. Following the rest period, two technicians assessed heart rate (via 60 second palpation of radial artery) and blood pressure (via auscultation). These measurements were used for descriptive characteristics, along with height, weight, body composition, body mass index (BMI), circumference measurements, and dietary intake (described below). Subjects' height was measured using a stadiometer, and their body weight was measured using a calibrated scale. BMI was calculated as bodyweight (kg) divided by height squared (m^2). Waist and hip circumferences were measured using a tension-regulated tape. Body composition was determined via dual energy x-ray absorptiometry (Hologic QDR-4500W) using a 4-min fan array. All above information was used for descriptive purposes.

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Test days

Within two weeks of the initial lab visit, subjects returned to the lab for the first of 10 meal (milkshake) visits. Of these 10 meal visits, only four were actual "test" visits in which blood was collected. Specifically, the "test" visits in which blood was collected, occurred on the Monday of each week. Additional meals (Wednesday and Friday of each week) were consumed in the lab during the morning, but no blood was collected on these days. All 10 meals were identical for each subject. Table 2 outlines the schedule for milkshake consumption and blood collection

The meal consisted of a milkshake made with whole milk, ice cream, and heavy whipping cream adjusted for body mass. One half of subjects were randomly assigned to consume a high-calorie/high-fat milkshake (1 g carbohydrate/kg; 0.8 g fat/kg; 0.25 g protein/kg), while the remaining subjects were assigned to consume a moderate-calorie/moderate-fat milkshake (one half of the amount noted above). This was done in an attempt to provide two different levels of stress. The composition of the milkshake is the same as we have used in our recent studies of postprandial oxidative stress. Moreover, both milkshakes deliver kilocalorie loads similar to what are provided within "medium" and "large" milkshakes available in many commercial establishments and are well-tolerated by subjects.

Subjects reported to the lab in a 10 hour fasted state on the morning of each test meal day (again, a total of 4 of the total 10 meal days). Blood was collected prior to meal ingestion (following a 20 min rest period), and at 2 and 4 h post meal ingestion. This time frame has been verified as appropriate in our prior work, in particular when using healthy men as subjects. No other food was allowed during the 4 h postprandial period; however, water was provided *ad libitum*.

Blood collection and biochemistry

Venous blood samples were taken from the subjects via needle and Vacutainer™. Blood samples that were collected in tubes containing EDTA were immediately separated via centrifugation at 1500g for 15 min at 4°C for collection of plasma. Blood samples that were collected in tubes containing no additives were allowed to clot at room temperature for 30 min and then separated by centrifugation at 1500g for 15 min at 4°C for serum collection. Blood samples were immediately stored in multiple aliquots at -70°C until analyzed for the variables indicated below.

A standard blood lipid panel was performed using fasting samples obtained from all subjects on day 1. This was done to further characterize subjects. Triglycerides (triacylglycerol, TAG) were analyzed in serum following standard enzymatic procedures as described by the reagent manufacturer (Thermo Electron Clinical Chemistry). Malondialdehyde (MDA) was analyzed in plasma using reagents purchased from Northwest Life Science Specialties (Vancouver, WA, USA). Hydrogen peroxide (H_2O_2) and catalase (CAT) activity were analyzed in plasma using the Amplex Red reagent method as described by the manufacturer (Molecular Probes, Invitrogen Detection Technologies; Eugene, OR, USA). Trolox equivalent antioxidant capacity (TEAC) was analyzed in serum according to the procedures outlined by the reagent provider (Sigma Chemical; St. Louis, MO, USA). Serum superoxide dismutase (SOD) activity was measured using enzymatic procedures as described by the reagent provider (Cayman Chemical; Ann Arbor, MI, USA), where 1 unit of SOD is the amount of enzyme needed to exhibit 50% dismutation of the superoxide radical. Plasma glutathione peroxidase (GPx) activity will be measured using enzymatic procedures as described by the reagent provider (Cayman Chemical). Values for GPx were calculated using the nicotinamide adenine dinucleotidephosphate (NADPH) extinction coefficient and are presented in nanomoles per minute per milliliter where 1 unit is defined as the amount of enzyme needed to oxidize 1 nmol of NADPH to NADP+. Samples for all outcome measures were analyzed in duplicate on first thaw. Blood samples were collected on each test day (milkshake meals 1, 4, 7, and 10; as indicated in Table 2) before and at 2 and 4 hours following meal ingestion.

Dietary records and physical activity

All subjects were instructed to maintain their normal diet during the study and were asked to record all food and drink consumed during the three days prior to each test meal (meals 1, 4, 7, and 10). Records were analyzed for total kilocalorie, macro- and micro-nutrient composition using Food Processor SQL version 9.9 (ESHA Research; Salem, OR, USA). Subjects were asked to maintain their usual activities of daily living throughout the study, but not to perform any strenuous activity during the 48 h prior to each test meal (meals 1, 4, 7, and 10).

Table 2. Study schedule for milkshake consumption and blood collection

Day of week	Test day	Milkshake	Blood collection
Monday	1	Yes	Yes
Wednesday		Yes	No
Friday		Yes	No
Monday	2	Yes	Yes
Wednesday		Yes	No
Friday		Yes	No
Monday	3	Yes	Yes
Wednesday		Yes	No
Friday		Yes	No
Monday	4	Yes	Yes

Statistical analysis

All biomarker data obtained before and following milkshake ingestion were analyzed using a 4 (milkshake) x 3 (time) repeated measures analysis of variance (ANOVA). Significant effects were analyzed further using Tukey's post hoc tests. A one-way ANOVA was used to analyze dietary intake prior to each test meal. All analyses were performed using JMP statistical software version 4.0.3 (SAS Institute; Cary, NC, USA). Statistical significance was set at $P < 0.05$.

RESULTS

A total of 16 subjects completed all aspects of this study. Subject characteristics are presented in Table 1. Three of the subjects reported taking nutritional supplements prior to enrolling in the study in the form of multivitamin and fish oil. We do not believe that the use of these supplements prior to starting the study influenced the results.

The milkshakes were tolerated by all subjects without significant adverse effects. One subject noted gastrointestinal distress (*e.g.*, bloating and gas) after consuming the milkshake. Dietary data during 72 h prior to each test day were not different ($P > 0.05$). Data for dietary data are presented in Table 3.

Although subjects were assigned to two separate groups, either a high- or moderate-fat milkshake group, there were no interaction effects noted for any outcome ($P > 0.05$). In fact, the pattern of response across time was nearly identical for the high- and moderate-fat groups, for the days tested. Therefore, the data were pooled and presented as such within the figures.

No interaction ($P = 1$) or day effect ($P = 0.99$) was noted for TAG. A trend was noted for a time effect ($P = 0.09$), with values highest at 4 h post-meal ingestion. Data for TAG are presented in Fig.1.

No interaction ($P = 0.96$) or day effect ($P = 0.89$) was noted for MDA. A time effect ($P < 0.001$) was noted with values greater at 2 and 4 h post consumption compared to pre ($P < 0.05$). Data are presented in Fig.2.

No interaction ($P = 0.94$) or day effect ($P = 0.94$) was noted for H_2O_2. A time effect ($P < 0.001$) was noted with values greater at 2 and 4 h post consumption compared to pre ($P < 0.05$). In addition, a condition effect ($P = 0.008$) was noted with higher values in the high-fat group compared to the moderate-fat group ($P < 0.05$). Data are presented in Fig.3.

No interaction ($P = 0.38$) or day effect ($P = 0.18$) was noted for TEAC. A time effect ($P = 0.02$) was noted with values greater at pre compared to 2 h post ($P < 0.05$). Data are presented in Fig.4.

No interaction ($P = 0.72$) or day effect ($P = 0.61$) was noted for SOD. A time effect ($P < 0.001$) was noted with values greater at pre and 2 h compared to 4 h ($P < 0.05$). Data are presented in Fig.5.

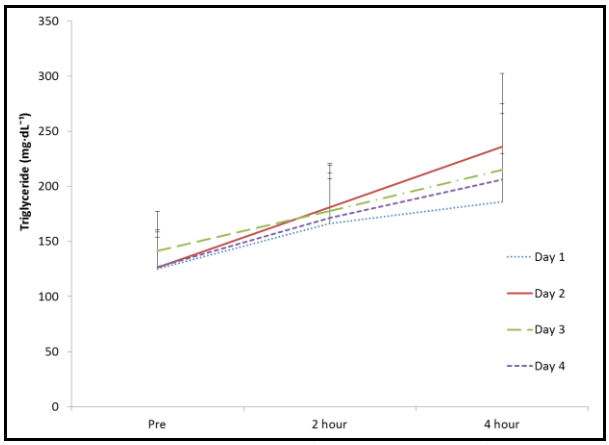

Figure 1. Blood triglyceride data of 16 healthy men before (Pre) and after (2 and 4 hour) consumption of a high-fat meal on four different occasions, separated by one week. Values are mean ± SEM. No interaction ($P = 1$), day effect ($P = 0.99$), or time effect ($P = 0.09$).

Table 3. Dietary data of 16 healthy men consuming high-fat meals recorded three days prior to each test day (mean ± SEM)

Variable	Day 1	Day 2	Day 3	Day 4	P value
Kilocalories	1930 ± 132	1728 ± 118	1678 ± 121	1814 ± 107	P = 0.47
Protein (g)	111 ± 7	92 ± 9	89 ± 9	97 ± 8	P = 0.26
Carbohydrate (g)	227 ± 18	202 ± 14	212 ± 19	205 ± 14	P = 0.71
Fat (g)	58 ± 5	58 ± 5	49 ± 4	65 ± 5	P = 0.17
Saturated fat (g)	20 ± 2	19 ± 2	17 ± 2	21 ± 2	P = 0.43
Cholesterol (mg)	333 ± 41	318 ± 35	207 ± 34	321 ± 43	P = 0.08
Vitamin C (mg)	69 ± 14	65 ± 11	85 ± 23	44 ± 7	P = 0.31
Vitamin E (mg)	7 ± 1	6 ± 1	5 ± 1	7 ± 2	P = 0.8
Vitamin A (RE)	621 ± 214	329 ± 75	269 ± 52	284 ± 92	P = 0.17
Selenium (µg)	66 ± 9	53 ± 8	47 ± 8	67 ± 13	P = 0.38

RE, retinol equivalents

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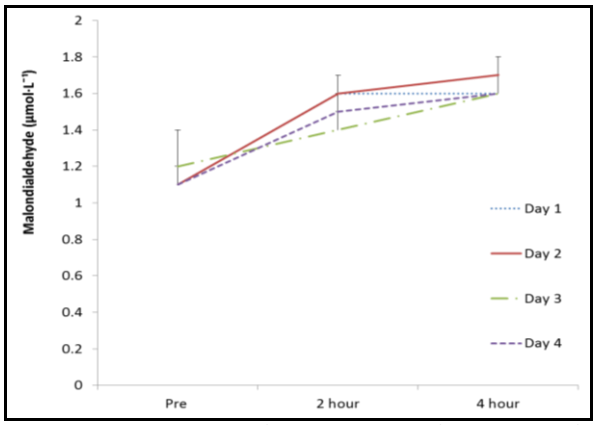

Figure 2. Blood MDA data of 16 healthy men before (Pre) and after (2 and 4 hour) consumption of a high-fat meal on four different occasions, separated by one week. Values are mean ± SEM. No interaction (P = 0.96) or day effect (P = 0.89). P < 0.001 for the time effect; 2 and 4 hour > Pre.

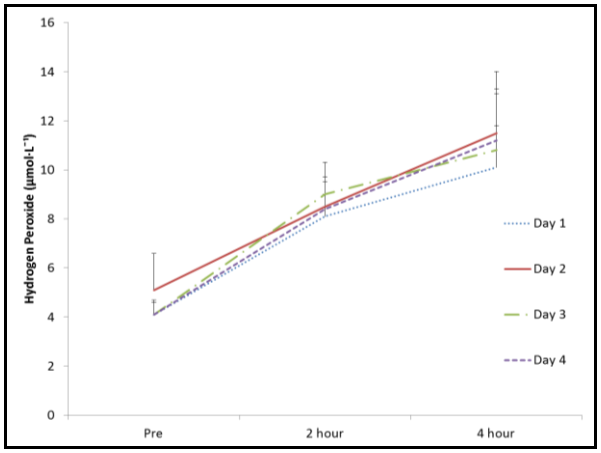

Figure 3. Blood H_2O_2 data of 16 healthy men before (Pre) and after (2 and 4 hour) consumption of a high-fat meal on four different occasions, separated by one week. Values are mean ± SEM. No interaction (P = 0.94) or day effect (P = 0.94). P < 0.001 for the time effect; 2 and 4 hour > Pre.

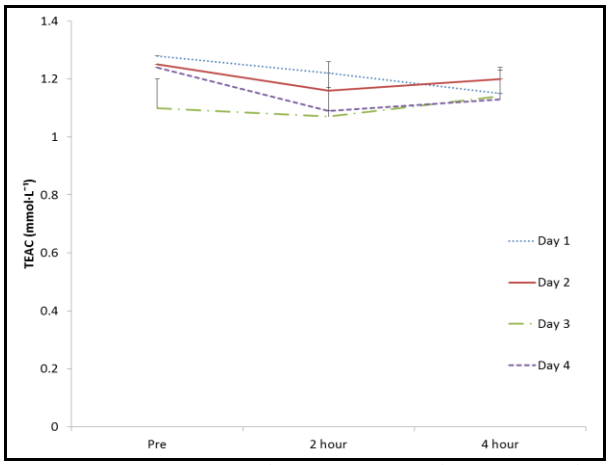

Figure 4. Blood TEAC data of 16 healthy men before (Pre) and after (2 and 4 hour) consumption of a high-fat meal on four different occasions, separated by one week. Values are mean ± SEM. No interaction (P = 0.38) or day effect (P = 0.18). P = 0.02 for the time effect; Pre > 2 hour.

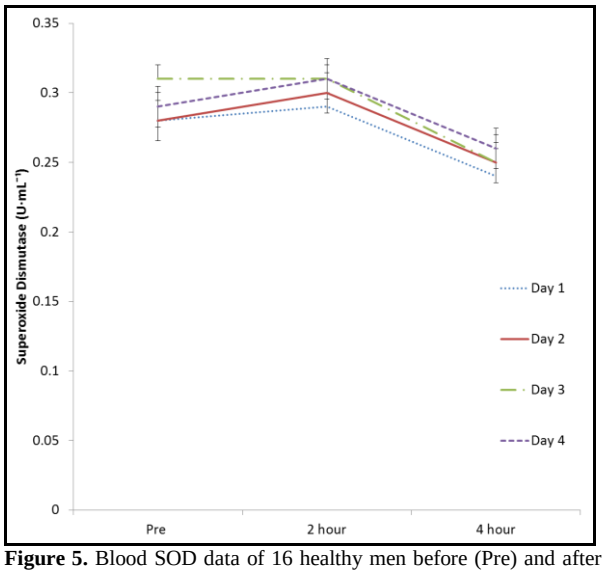

Figure 5. Blood SOD data of 16 healthy men before (Pre) and after (2 and 4 hour) consumption of a high-fat meal on four different occasions, separated by one week. Values are mean ± SEM. No interaction (P = 0.72) or day effect (P = 0.61). P < 0.001 for the time effect; Pre and 2 hour > 4 hour.

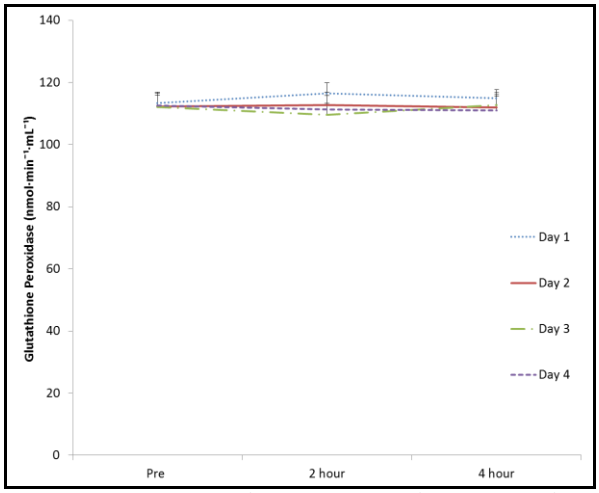

Figure 6. Blood GPx data of 16 healthy men before (Pre) and after (2 and 4 hour) consumption of a high-fat meal on four different occasions, separated by one week. Values are mean±SEM. No interaction (P = 0.95), day (P = 0.92), or time effect (P = 0.81).

No interaction (P = 0.95), day (P = 0.92), or time effect (P = 0.81) was noted for GPx. Data are presented in Fig.6.

No interaction (P = 0.98) or day effect (P = 0.94) was noted for CAT. A time effect (P < 0.001) was noted with values lower at 2 and 4 h compared to pre (P < 0.05). In addition, a condition effect (P < 0.001) was noted with lower values of CAT in the high-fat group compared to the moderate-fat group (P < 0.05). Data are presented in Fig.7.

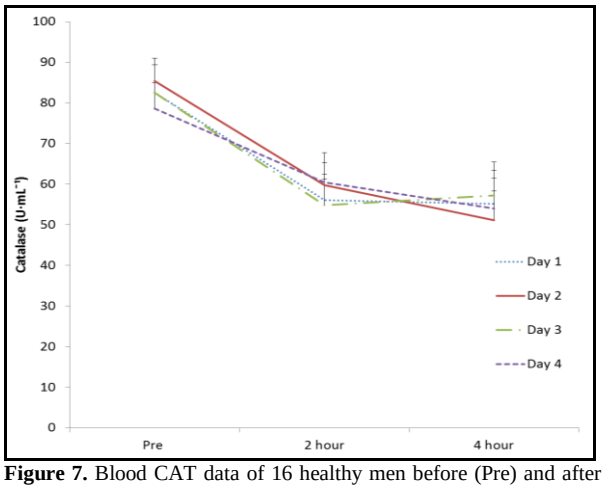

Figure 7. Blood CAT data of 16 healthy men before (Pre) and after (2 and 4 hour) consumption of a high-fat meal on four different occasions, separated by one week. Values are mean ± SEM. No interaction (P = 0.98) or day effect (P = 0.94). P < 0.001 for the time effect; 2 and 4 hour > Pre.

DISCUSSION

This was the first investigation, to our knowledge, to study the possible attenuation in postprandial oxidative stress following repeated ingestion of lipid-rich meals. Our main findings from this study are as follows: ***(1)*** the oxidative stress response is similar from one meal to the next, with minimal difference noted; ***(2)*** systemic antioxidant capacity is relatively unchanged over time; and ***(3)*** H_2O_2 and CAT were the only variables that were sensitive to differing meal sizes, with high-fat meals inducing a greater oxidative stress than moderate-fat meals (as evidenced by higher H_2O_2 and lower CAT).

As we have reported in several prior studies, oxidative stress is observed in response to high-fat feeding [5, 6, 8, 13-17] with values elevated for hours following meal ingestion. These findings may have implications for overall vascular and metabolic health over time, as increased postprandial oxidative stress is associated with endothelial dysfunction [17, 18] and metabolic dysfunction [19, 20].

We were interested to determine whether or not the oxidative stress response to moderate- and high-fat feeding was lowered following repeated exposure to the same lipid load. Such an answer is important in the design of future postprandial oxidative stress experiments. Our findings indicate that little to no differences are noted in the oxidative stress response to repeated lipid-rich feedings, confirming that no "familiarization" trials are necessary before collecting baseline postprandial oxidative stress data for use in intervention trials.

We were somewhat surprised by the lack of adaptive response in our subjects. This is particular true when considering the absolute magnitude of the oxidative stress experienced in response to lipid-rich feedings and the potential harm of such an oxidative stress over time. Considering that so many individuals consume lipid-rich meals regularly throughout the week, we believed that some attenuation in oxidative stress must be observed. If not, such individuals might be predisposed to a host of disease conditions, even more so than is seen in our society today.

We have the following for consideration regarding the lack of an observed difference in oxidative stress over time. First, our time frame of repeated RONS exposure may have been too short to provide for adaptation within the antioxidant defense system. Indeed, prolonged exposure to RONS may induce greater adaptation and this may be the case for individuals consuming frequent and routine high-fat meals as a part of their dietary intake. Second, the frequency at which we provided the meals may have been too low. That is, subjects only received a lipid-rich meal three days per week, when in actuality individuals might consume one or more such meals per day. It is possible that a more frequent protocol of high-fat feeding may be necessary to signal for an up-regulation in antioxidant enzyme activity, which may then be partly responsible for lowering the oxidative stress response to lipid-rich feeding. Indeed, animal studies that have noted an increase in antioxidant enzyme activity in response to high-fat feeding have provided increases in fat intake in small doses at each meal [21, 22]. For the purpose of the present study, it is clear that 10 or fewer exposures to lipid-rich meals at the calorie load provided here is inadequate to allow for differences to be noted in the oxidative stress response.

One additional consideration is the fact that the present study assessed oxidative stress biomarkers and antioxidant enzyme activity in blood samples only. It is possible that differing results may have been present in tissues unrelated to blood, such as skeletal muscle, liver, and heart. In support of this statement, Webster and colleagues studied oxidative stress in male rats exposed to hyperoxia over the course of a 5-day period [23]. The investigators measured SOD, CAT, and GPx activity in the liver, lung, and blood. SOD and CAT were significantly increased in both liver and lung tissue, but not in blood; whereas GPx was significantly increased in lung only. Similar findings for increased CAT expression have recently been reported within mouse cardiac mitochondria in response to high-fat feeding [21]. Conversely, Das and colleagues studied oxidative stress levels in the placental tissue and serum of pre-eclamptic women [24]. Significant increases in thiobarbituric acid reactive substances (TBARS) and SOD were noted in both tissue and serum, whereas glutathione (GSH) levels remained constant at both sites. These authors stated that that the stress levels

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measured in serum were a good indicator of what is occurring at the tissue level. While this may be the case in the specific design used by Das and colleagues [24], it may not hold true in designs such as ours in which healthy individuals are consuming high-fat loads with the expectation of increased oxidative stress. Clearly, it is possible that findings for oxidative stress and antioxidant biomarkers may differ across tissues being investigated and further research will be needed to more fully elucidate the potential changes in antioxidant activity in various tissues in response to high-fat feeding and other generators of RONS. Our failure to measure antioxidant activity and oxidative stress biomarkers in tissues other than blood should be considered a limitation of this work.

In conclusion, our results indicate that repeated moderate-to-high fat meals ingested over the course of a 3+ week period by healthy, active men promote a near identical oxidative stress response, without altering the antioxidant enzyme system. Individuals consuming such meals on a regular basis may experience a similar magnitude of elevated oxidative stress in response to each feeding, which may predispose them to ill-health and disease over time. Conversely, long-term exposure to lipid-rich meals may eventually lead to an adaptive response in such a way as to result in a blunting in postprandial oxidative stress. Future research inclusive of a much longer time frame of assessment, possibly involving both men and women spanning a wider age range (*e.g.*, 20-70 years), is needed to address this possibility.

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COMPETING INTERESTS

The authors declare no real or perceived conflicts of interest related to this work.

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