Metabolic Benefits of Marine n–3 Fatty Acids Demonstrated in Nonhuman Primates

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Rates of obesity, insulin resistance, and metabolic syndrome are increasing in many countries. Diet is an obvious factor that can contribute to the risk of these metabolic conditions, which, in turn, predispose one to type 2 diabetes and cardiovascular disease, major sources of morbidity, mortality, and health expenditure. The key dietary components involved in increasing metabolic risk are subject to much conjecture, but there is a view that increased intake of fructose as dietary sucrose and from high-fructose syrups is a major culprit. Recent work in rhesus monkeys demonstrated that a high-carbohydrate, high-fructose diet induced several features of human metabolic syndrome, including obesity, hypertriglyceridemia, and insulin resistance (2). In this issue of The Journal of Nutrition, an article reports on the effects of marine n–3 (ω–3) PUFAs in rhesus monkeys fed a high-carbohydrate, high-fructose diet (3). Marine n–3 PUFAs were shown to prevent the hypertriglyceridemia and insulin resistance induced by the high-carbohydrate, high-fructose diet. The animals were adult males aged 12 to 20 y and weighed an average of 15.6 kg at study entry. They were fed a grain-based primate diet providing 11% of energy as fat (>90% as n–6 FAs), 30% of energy as protein, and 59% of energy as carbohydrate, and additionally received 75 g of fructose daily in a 500-mL beverage. The intention of this dietary strategy was to induce metabolic syndrome, in particular obesity, insulin resistance, and dyslipidemia, as previously demonstrated (2). Half of the animals received a treat that included 4 g of fish oil (FO), whereas the treat given to the remaining animals, the control group, contained 4 g of safflower oil, which is rich in the n–6 essential FA linoleic acid. The treats used, which weighed 44 g, also provided unspecified amounts of fat and carbohydrate. The FO provided ~0.64 g EPA and 0.44 g DHA daily. The feeding period was 6 mo. The intention of supplementing the FO was to prevent the development of metabolic syndrome.

Over the 6-mo feeding period, the control group demonstrated increases in body weight (13%), total insulin AUC during a 60-min intravenous-glucose-tolerance test (89%), and concentrations of fasting plasma TGs (64%), apo C3 (25%), apo E (29%), fasting insulin (104%), and leptin (30%), and a decrease in concentrations of adiponectin (~21%). Thus, the dietary strategy achieved the aims of inducing insulin resistance and dyslipidemia, especially hypertriglyceridemia. Data on body composition are not presented, but the increase in leptin concentration might suggest increased fat mass in the control group.

What, then, was the effect of supplementation with FO? The animals that received marine n–3 PUFAs showed an average 9% increase in body weight, less than in the control group, although the increase in body weight was not significantly different between the 2 groups of animals. However, this lack of significant difference between weight gains of 13% and 9% may be due to the small number of animals in each group (9 in the control group and 10 in the FO group) rather than a lack of effect. Also, the difference in weight gain may have become more pronounced with a longer duration of feeding. In the FO-supplemented animals, plasma TGs declined by 8.5%, and this change (i.e., the effect of treatment) was different from that in the control group. Likewise, apo C3 decreased in the FO group, and the change from study entry was different from that seen in the control group, whereas the increase in apo E in the FO group was less than that in the control group. Thus, including marine n–3 PUFAs in a high-carbohydrate, high-fructose diet prevented the hypertriglyceridemic effect of that diet. Plasma insulin concentration and the total insulin AUC during a 60-min intravenous-glucose-tolerance test were not significantly altered in the FO group, indicating that FO prevented the diet-induced decline in insulin sensitivity seen in the control group. Plasma leptin was not significantly increased from study entry in the FO group, although there was a small elevation of ~6.5%. Comparison of data for change in leptin concentration from study entry showed that this was significantly less in the FO group than that in the control group, suggesting that FO reduces the development of adiposity induced by the high-carbohydrate, high-fructose diet. Curiously, FO did not affect the diet-induced decrease in plasma adiponectin.

This study provides sound evidence to support that marine n–3 PUFAs have effects that can prevent the deleterious metabolic consequences of a diet high in carbohydrates, including a substantial amount of fructose. That these effects were observed in nonhuman primates is a significant advance, because much of the existing data of this type come from studies in rodents and rabbits; many of these small animals have significant differences in diet, metabolic rate, and lipid metabolism compared with humans, limiting the ability to translate the findings. Nevertheless, the diet of the rhesus monkeys studied here was rather different from a typical human diet. Dietary protein was higher than in most human diets, whereas fat, at 11% of energy, was lower than in most Western diets. It would be interesting to study the effect of n–3 FAs in this sort of high-carbohydrate,
high-fructose model but against a background of a higher fat intake. This would be more akin to the human setting. Furthermore, most (>90%) of the fat in the basal diet came from n-6 FAs, mainly linoleic acid, whereas a Western diet will typically contain 15% to 35% of FAs as n-6 FAs and will contain much higher proportions of SFAs and MUFAs than used here. This study (3) clearly shows that marine n-3 PUFAs can limit the metabolic disturbances induced by a high-carbohydrate, high-fructose intake against the background of a high contribution of linoleic acid to dietary fat. Again, it will be important to demonstrate the benefit of marine n-3 PUFAs against a background of a more mixed fat supply. This is important in the context of translation to the human situation. However, in this model, n-3 PUFAs are acting to prevent the adverse metabolic effects of a high-carbohydrate, high-fructose diet, and it may be that the type of fat in the diet is of limited importance.

Blood TG concentrations increase because of an altered balance between appearance and clearance; both can be affected by dietary change. It is known that a high-fructose diet promotes hepatic lipogenesis resulting in increased appearance of TGs in the bloodstream. These TGs will be targeted to peripheral tissues expressing lipoprotein lipase (LPL). Adipose tissue expression of LPL will promote clearance and subsequent uptake of TG-derived FAs that will be stored as reformed TGs in adipose tissue, therefore contributing to adiposity. LPL activity is inhibited by apo C3 (4). Interestingly, Bremer et al. (3) demonstrate that high-carbohydrate, high-fructose–fed animals show an elevation in plasma apo C3 concentration. This would suggest that these animals have an impaired ability to clear TGs, which would contribute to the elevated TG concentrations seen. However, the overriding effect of the high-carbohydrate, high-fructose diet is likely to be enhanced hepatic lipogenesis. Bremer et al. (3) demonstrate in rhesus monkeys that marine n-3 PUFAs prevent diet-induced elevations in blood TG concentrations, as shown previously in several animal models (5). Human studies also show that marine n-3 PUFAs can lower preexisting elevated TG concentrations (6,7). This effect seems to involve both lower hepatic output and increased peripheral clearance of TGs (8). Part of this latter effect is due to enhanced activity of LPL. The observation by Bremer et al. (3) that FO decreased the plasma concentration of the LPL inhibitor apo C3 may provide 1 mechanism for improved clearance of TGs leading to the lower concentration seen in that group. Of course, this would act to promote TG storage in adipose tissue, a pro-obesity effect, which was not seen by Bremer et al. (3). This is likely because marine n-3 PUFAs are also acting on the liver to reduce TG formation and release. Therefore, as far as the effects on TGs are concerned, it is likely that both fructose and n-3 PUFAs are acting mainly at the hepatic level.

The limited decline in insulin sensitivity seen in the FO group may be due to a peroxisome proliferator-activated receptor-γ-related effect (9,10). Activation of peroxisome proliferator-activated receptor-γ is associated with decreased leptin concentrations, as seen by Bremer et al. (3) in the FO group, and with increased adiponectin concentration, which was not seen by Bremer et al. (3). The reason for this latter discrepancy is not clear but probably reflects the multiple metabolic effects of both a high-carbohydrate, high-fructose diet and marine n-3 PUFAs.

In summary, this study confirms a model for components of metabolic syndrome in rhesus monkeys involving feeding for a prolonged period a high-carbohydrate, high-fructose diet (2) and demonstrates for the first time in this model that a modest supplemental intake of marine n-3 PUFAs can prevent diet-induced hypertriglyceridemia and insulin resistance. The investigations presented here provide new insights into the action of n-3 PUFAs to improve metabolism in the context of reducing risk of cardiometabolic disease.

Acknowledgments
The sole author had responsibility for all parts of the manuscript.

Literature Cited