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Protective effects by co-administration of eicosapentaenoic acid, capsaicin, and dextrin against obesity-related metabolic dysregulation in ob/ob mice

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ABSTRACT

Background: Obesity and its related metabolic syndrome are closely associated with major risk factors for chronic diseases, including dyslipidemia and insulin resistance. This study aimed to investigate whether a combination of eicosapentaenoic acid (EPA), capsaicin (Cap), and indigestible dextrin (Dx) could protect mice against obesity and its related metabolic disorders.

Methods: We fed male C57BL/6J and genetically obese ob/ob mice various diets for 10 weeks. The normal group was standard chow (SC; 5.3% fat content)-fed C57BL/6J mice. The control group was SC-fed ob/ob mice. The experimental groups were SC-fed ob/ob mice whose diets were supplemented with either 4% (w/w) EPA (EPA group), a combination of 4% (w/w) EPA and 0.01% (w/w) Cap (EPA+Cap group), or 4% (w/w) EPA, 0.01% (w/w) Cap, and Dx (EPA+Cap+Dx group).

Results: We discovered that the weight of body and fat tissue, levels of serum glucose, insulin, total cholesterol, high-density lipoprotein cholesterol, aspartate aminotransferase and alanine aminotransferase, and the homeostasis model assessment of insulin resistance (HOMA-IR) index were significantly higher in the control group than in the normal group ($P < 0.05$ for all parameters). However, the weight of body and fat tissue, the serum glucose, total cholesterol, alanine aminotransferase levels, and the HOMA-IR index were lower in the EPA+Cap+Dx group than in the EPA and EPA+Cap groups.

Conclusions: Our findings suggest that the co-administration of EPA, Cap, and Dx may suppress the progression of obesity-related metabolic dysregulation and subsequent complications.

Keywords: eicosapentaenoic acid, capsaicin, dextrin, mice, obesity

BACKGROUND

The prevalence of obesity is a serious health issue. Obesity is one of the most important underlying risk factors for chronic diseases like diabetes, heart disease, and certain cancers [1]. Furthermore, obesity and its related metabolic syndrome are closely associated with major risk factors for chronic diseases, factors like dyslipidemia and insulin resistance. High-fat diet (HFD)-induced metabolic syndrome is responsible for the development of non-alcoholic fatty liver disease (NAFLD) [2]. Marchesini et al reported that 90% of NAFLD patients have insulin resistance or features of metabolic syndrome [3].

Dietary interventions targeting adipose tissue inflammation for metabolic syndrome has been explored. Some studies have demonstrated n-3 polyunsaturated fatty acid (n-3 PUFA) treatment can alleviate hepatic steatosis [4, 5]. Furthermore, dietary intake of n-3 PUFAs sensitizes the liver and adipose tissue to insulin and improves insulin tolerance in obese mice. Long-chain n-3 PUFAs like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been reported to have anti-inflammatory properties [6]. Similarly, EPA exhibits cardioprotective properties and exerts lipid-lowering effects [7, 8]. EPA can also prevent and reverse obesity [9-11]. We reported previously how EPA supplementation has a beneficial effect on NAFLD progression [12].

Capsaicin (Cap) has anti-obesity effects [13, 14]. Dietary Cap can reduce obesity-induced inflammation and ameliorate metabolic disorders such as insulin resistance and hepatic steatosis in HFD-fed obese mice [13]. These findings on Cap treatment for obesity confirm our previous findings that the combination of EPA and Cap may be beneficial for delaying the progression of obesity-related metabolic dysregulation and subsequent complications [15].

Dietary fiber is another instrumental anti-obesity supplement that plays a role in gut health.

Higher fiber intake has been linked to lower body weight [16]. Indigestible dextrin (Dx), a soluble dietary fiber, can improve hyperlipidemia and glucose tolerance [17]. Dietary fiber may also have therapeutic efficacy in disease states, including obesity, insulin resistance, and diabetes.

Therefore, the purpose of this study was to evaluate whether the administration of a combination of EPA, Cap, and dietary fiber could prevent obesity-related metabolic syndromes, including high body weight, hyperlipidemia, insulin resistance, and NAFLD. Previous studies demonstrated that mice or rats feeding on an HFD supplemented with Cap presented less obesity-induced metabolic dysregulation than those on an HFD alone [13, 14]. Accordingly, we focused on the enhanced benefits of EPA, Cap, and fiber compared to those of EPA alone or EPA+Cap [9-11, 15].

METHODS

Materials: We purchased highly purified EPA ethyl ester (purity: 98%) from Mochida Pharmaceutical (Tokyo, Japan), Cap from Sigma–Aldrich (St. Louis, MO, USA), and Dx (dextrin hydrate) from Wako Pure Chemical Industries (Osaka, Japan).

Animals: Six-week-old, male C57BL/6J and ob/ob mice (Charles River Japan, Yokohama, Japan) were housed in a room maintained at 22 ± 2°C on a 12-h light/dark cycle (lights off at 8:00 $_{PM}$), with free access to chow and water. We fed the mice a standard powder diet (MF® diet; Oriental Yeast, Tokyo, Japan) during a 1-week adjustment period. All mouse experimental protocols were approved and carried out in accordance with the Osaka Ohtani University Guidelines for the Care and Use of Laboratory Animals (approval No. 1007 (4)).

Animal experiments and sample preparation: The C57BL/6J mice were fed a standard chow diet (SCD) for 10 weeks (360 kcal/100 g fresh weight of food) composed of 7.7g water, 23.6g protein (26.2%; energy ratio), 5.3g fat (13.3%), 2.9g fiber, and 54.4g nitrogen-free extracts (60.5%) (normal group) measured by dry weight. We indicated the fatty acid composition (%) of standard diet (Table1). The ob/ob mice, which were fed an SCD for 10 weeks, were randomly divided into 4 subgroups (n = 6 in each group): a group that was fed SCD alone (control group); a group that was fed SCD supplemented with 4% (w/w) EPA (EPA group); a group that was fed SCD supplemented with 4% (w/w) EPA and 0.01% (w/w) Cap (EPA+Cap group); and a group that was fed SCD supplemented with 4% (w/w) EPA, 0.01% (w/w) Cap, and 10% (w/w) Dx (EPA+Cap+Dx group). The mice had ad libitum access to chow and tap water. We measured the mice's body weight and food intake per cage on a weekly basis. After 10 weeks, the mice fasted for 12 h and anesthetized under diethyl ether. We collected blood samples from the

inferior vena cava. We also separated serum by centrifugation (3,000 × g for 15 min), which we stored at −80 °C. We sacrificed the mice by deep anesthesia with diethyl ether. We excised their livers and epididymal adipose tissues, which we rinsed with cold saline, weighed, and stored at -80 °C.

Table 1. Fatty acid composition (%) of standard diet

Fatty acid	standard diet
14:0 (Myristic acid)	0.4
16:0 (Palmitic)	14.6
16:1n-7 (Palmitoleic)	0.7
17:0 (Heptadecanoic)	0.2
18:0 (Stearic)	2.6
18:1n-9 (Oleic)	24.6
18:1n-7 (Vaccenic)	1.3
18:2n-6 (Linoleic)	46.6
18:3n-3 (Linolenic)	3.8
20:0 (Arachic)	0.4
20:1n-9 (Eicosenoic)	0.6
20:5n-3 (Eicosapentaenoic)	1.3
22:0 (Behenic)	0.3
22:1n-11 (Setoleic)	0.6
22:5n-3 (Docosapentaenoic)	0.4
22:6n-3 (Docosahexaenoic)	1.3
24:0 (Lignoceric)	ND
24:1n-9 (Tetracosenic)	ND
Unidentified	0.3

Analytical methods: We determined aspartate aminotransferase (AST), alanine aminotransferase (ALT), and glucose levels using the Transaminase CII-Test Wako (for AST and ALT) and Glucose CII-Test Wako kits (Wako Pure Chemical Industries). We measured serum insulin levels using an enzyme-linked immunosorbent assay kit (Morinaga, Yokohama, Japan). We determined serum triglyceride, high-density lipoprotein (HDL) cholesterol, and total cholesterol levels using the Triglyceride E-Test Wako, HDL-Cholesterol E-Test Wako, and Cholesterol E-Test Wako kits respectively (Wako Pure Chemical Industries). We

determined serum adiponectin levels using the Mouse/Rat Adiponectin ELISA kit (Otsuka Pharmaceutical, Tokushima, Japan).

Statistical analysis: The data are expressed as the mean ± standard deviation and % of 0 week values. We performed statistical analyses of the differences between the mean values via Tukey's multiple comparison test using SPSS Statistics software (version 18.0, IBM Corporation, Armonk, NY, USA). Differences where the *P*-values were <0.05 were considered statistically significant.

RESULTS

The mice's body weight in the EPA+Cap+Dx group were lower during the period of supplementation (Fig. 1A). The mean body weight of the EPA+Cap+Dx group was significantly lower than those of the EPA and EPA+Cap groups in the 10th week (Fig. 1B; $P < 0.01$) and did not significantly differ from that of the normal group after 10 weeks of treatment (Fig. 1B). We also observed that dietary Cap didn't alter the amount of food ingested, except during the 2nd week. One possibility is that body weight was temporarily decreased by the irritation of Cap. Afterwards, mice that were fed Cap adapted to the stimulating taste. The average food intake per day of the control, EPA, EPA+Cap, and EPA+Cap+Dx groups tended to be lower than that of the mice in the normal group. The average food intake of the EPA+Cap group was slightly higher than that of the control, EPA, and EPA+Cap+Dx groups (data not shown). Additionally, as anticipated these supplements did not affect the appetite of each group mice based on the average amount of food intake of each group mice. However, we did not observe a relationship between food intake and average body weight in the 4 ob/ob groups during treatment.

The mean liver wet weight/body weight ratios (%) were significantly higher in the EPA, EPA+Cap, and EPA+Cap+Dx groups than in the normal group (Table 2; $P < 0.01$ for all versus normal). The mean epididymal fat tissue weight/body weight ratios (%) were significantly higher in the control, EPA, and EPA+Cap groups than in the normal group ($P < 0.001$ for all versus normal). However, this ratio was significantly lower in the EPA+Cap+Dx group than in the control, EPA, and EPA+Cap groups (Table 2; $P < 0.001$ versus the control and EPA groups, $P < 0.01$ versus the EPA+Cap group).

The mean serum glucose level of the control group was significantly higher than that of the normal group, and the mean serum glucose level of the EPA+Cap+Dx group was significantly lower than that of the control group (Table 2; $P < 0.01$ for both parameters versus control). The insulin levels and the homeostasis model assessment of insulin resistance (HOMA-IR) indices

of the control, EPA, EPA+Cap, and EPA+Cap+Dx groups were significantly higher than those of the normal group (Table 2; $P < 0.01$ for all versus normal). Significantly, the mean HOMA-IR index of the EPA+Cap+Dx group was noticeably lower than those of the control, EPA, and EPA+Cap groups (Table 2; $P < 0.05$ for all comparisons).

The serum total cholesterol levels of the control, EPA, and EPA+Cap groups were significantly higher than that of the normal group ($P < 0.001$ versus control, $P < 0.05$ versus EPA, $P < 0.01$ versus EPA+Cap). However, the serum total cholesterol level of the EPA+Cap+Dx group did not significantly differ from that of the normal group (Table 2). The mean serum triglyceride and HDL cholesterol levels of the control group were significantly higher than those of the normal group (Table 2; $P < 0.05$). The mean serum AST and ALT levels were higher in the control group than in the normal group ($P < 0.001$ for both parameters versus normal). However, the AST levels were significantly lower in the EPA, EPA+Cap, and EPA+Cap+Dx groups ($P < 0.01$) than in the control group, in addition to the ALT level in the EPA+Cap+Dx group ($P < 0.001$). Furthermore, the mean serum ALT level of the EPA+Cap+Dx group was significantly lower than those of the EPA and EPA+Cap groups (Table 2; $P < 0.001$ versus EPA, $P < 0.01$ versus EPA+Cap). The mean serum adiponectin level of the control group was significantly lower than that of the normal group ($P < 0.05$), and those of the EPA, EPA+Cap, and EPA+Cap+Dx groups tended to be higher than that of the control group (Table 2).

Table 2. Effects of EPA, Cap, and Dx on tissue weight and biochemical analysis of serum in ob/ob mice.

	Normal	Control	EPA	EPA+Cap	EPA+Cap+Dx
Liver wt ratio (%)	100±6	127±28	143±11 **	145±12 **	142±19 **
Fat wt ratio (%)	100±18	343±96 ***	277±26 ***	262±21 $^{***,\#}$	159±19 $^{\#\#\#,\dagger\dagger\dagger,\S\S}$
Serum					
glucose (%)	100±20	200±63 **	159±27	159±31	117±11 $^{\#\#}$
insulin (%)	100±8	549±172 **	547±143 **	620±228 ***	599±165 **
HOMA-IR (%)	100±18	1092±539 **	843±251 ***	1025±433 **	449±120 $^{***,\#,\dagger,\S}$
Total cholesterol (%)	100 ±11	188±33 ***	131±30 $^{*,\#\#}$	126±15 $^{**,\#\#}$	115±23 $^{\#\#\#}$
Triglycerides (%)	100±15	69±19 *	75±24	99±55	91±40
HDL-cholesterol (%)	100±16	141±40 *	99±27	123±32	134±16
AST (%)	100±22	464±110 ***	230±86 $^{*,\#\#}$	229±86 $^{*,\#\#}$	262±37 $^{*,\#\#}$
ALT (%)	100±23	1610±659 ***	926±225 ***	812±420 **	141±13 $^{**,\#\#,\dagger\dagger\dagger,\S\S}$
Adiponectin (%)	100±9	94±3 *	126±33	137±37	121±18

$^{*}P < 0.05$, $^{**}P<0.01$, $^{***}P<0.001$ compared Normal group, $^{\#}P < 0.05$, $^{\#\#}P <0.01$ $^{\#\#\#}P <0.001$ compared with Control group. $^{\dagger\dagger\dagger}P < 0.001$ compared with EPA group. $^{\S\S}P < 0.01$ compared with EPA+Cap group. AST, aspartate-aminotransferase; ALT, alanine aminotransferase. Data are expressed as mean±SD.

※ HOMA-IR = insulin (μU/mL) × glucose (mg/dL)/405 (insulin; 1 μg/L x 26= μU/mL)

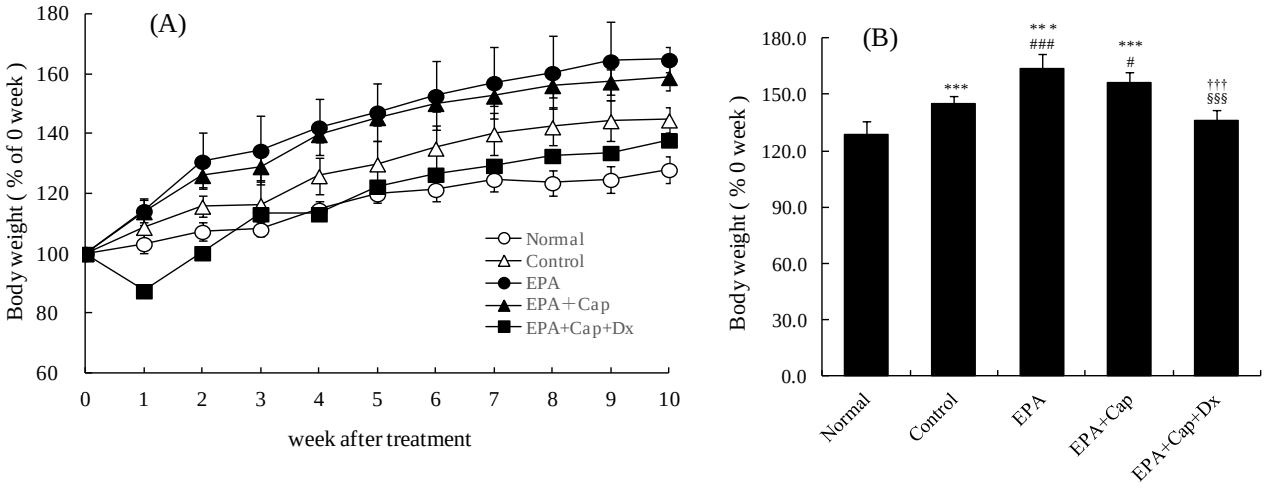

Figure 1. Effects of EPA, Cap and Dx on body weight gain of ob/ob mice.
A: body weight development. B: body weight gain (10th week). $^{***}P$<0.001 compared Normal group, $^{\#}P < 0.05$, $^{\#\#\#}P$ <0.001 compared with Control group. $^{\dagger\dagger\dagger}P < 0.001$ compared with EPA group. $^{\S\S\S}P < 0.001$ compared with EPA+Cap group. Data are expressed as mean ±SD.

DISCUSSION

The chronic inflammation resulting from obesity leads to the development of metabolic diseases like insulin resistance, type 2 diabetes, hepatic steatosis, and cardiovascular disease [18, 19]. We sought to investigate a novel treatment regimen to manage obesity and prevent these associated health problems.

Rats fed an HFD supplemented with n-3 PUFAs were protected against severe NAFLD development [2]. Furthermore, we demonstrated that EPA supplementation for 12 weeks diminished body weight, hepatic lipid peroxidation, and the levels of serum total cholesterol, hepatic triglyceride, total cholesterol, AST, and ALT in obese mice, thereby preventing NAFLD progression and improving hepatic function [12]. Specifically, we observed that hepatic superoxide dismutase activity and glutathione levels, which were lower in obese mice than in mice with a healthy body weight, increased in mice treated with EPA, which suggests EPA may prevent the early stages of NAFLD and that EPA may promote lipid metabolism [12]. Nonetheless, our previous studies did not demonstrate the attenuating effects of EPA alone on insulin resistance and epididymal fat tissue weight in HFD-fed mice. The dosage of EPA in the long-term treatment of this study is based on the report that 5% EPA (wt/wt) is capable of reducing the adipose tissue weights after 4-week administration [20].

Conversely, Cap may be useful for improving obesity-related dysregulation like insulin resistance, which is often triggered by obesity-induced inflammation [13]. Dietary Cap may reduce obesity-induced glucose intolerance not only by suppressing inflammatory responses but also enhancing fatty acid oxidation in adipose tissue and/or liver [13]. We previously

reported the effects of co-administering of EPA and Cap on HFD-induced obesity-related complications in mice. Dietary Cap supplementation (0.014%) in combination with EPA for 10 days lowers the adipose tissue weight, body weight, and levels of serum triglycerides in obese rats [14]. We set the dose of Cap in our study to 0.01%, which is suitable for long-term administration to protect mucosa in the gut. Our results indicated that the combined administration of EPA and Cap decreased the weight of body and fat tissue in obese mice. This result suggests that the combination of EPA and Cap mediates anti-obesity effects and improvement in insulin resistance induced by both supplements was mainly due to the reduced serum glucose levels, which may be attributed to the decrease in adipose tissue weight [15]. Therefore, combined Cap and EPA treatment may reduce body weight and visceral adipose fat in HFD-induced obese mice more effectively than EPA by itself. However, additional supplementation is required to more extensively ameliorate obesity-induced inflammation and subsequent complications.

Resistant Dx supplementation can modulate inflammation and improve insulin resistance in women with type 2 diabetes; it is a safe intervention for the management of type 2 diabetes and its complications [21]. Before our study, the effects of Dx in combination with EPA and Cap on adiposity, weight, and liver function were previously unknown in animal and clinical studies. Dietary fiber reduces the risk of diabetes, obesity, and gastrointestinal disorders [16, 17]. Dx not only improves obesity but also attenuates associated fatty liver [22]. In this study, the dosage of Dx set 10% content that improved the obesity, lipid profiles, and glycemic control in C57BL/6J mice fed a high-fat diet [23].

We discovered that obese mice treated with a combination of EPA, Cap, and Dx had lower body weights than the control obese mice and significantly decreased fat tissue weight compared with the control, EPA, and EPA+Cap group mice. These results suggest that the combination has anti-obesity effects and ameliorates metabolic disorder. However, the body weight of the EPA group and EPA+Cap group mice increased compared with the control group. The mechanisms of these results remain to be elucidated. The mechanisms of these results remain to be elucidated. The ameliorating effect for abnormal serum glucose (HOMA-R) may be responsible primarily in activation of TRPV1-mediated GLP-1 secretion in the intestinal cells by Cap [24]. Furthermore, obese mice treated with a combination of EPA, Cap, and Dx had better hepatic function than untreated obese mice, as indicated by their serum ALT levels. The effect for serum ALT may be responsible primarily in the suppression of inflammation in the liver and enhancing fatty acid oxidation in adipose tissue by Cap [13]. In future studies, these changes should be confirmed histologically or via the determination of hepatic total cholesterol and triglyceride levels after EPA, Cap, and Dx administration.

Given that obese mice on the triple supplement regimen had lower serum total cholesterol

and improved insulin resistance compared to the untreated obese mice, we conclude that the combination of Dx with EPA and Cap more effectively counters the effects of an HFD in obese mice than EPA alone and the combination of EPA and Cap. Our current study suggests that the combination of EPA, Cap, and Dx may have potential application in the prevention of obesity and subsequent complications such as insulin resistance and NAFLD at a lower cost.

CONCLUSIONS

Further human and animal studies are needed to confirm the beneficial effects of EPA, Cap, and Dx, in addition to elucidating the mechanism by which the combination protects against NAFLD progression. The sustained supplementation of EPA, Cap, and Dx may delay the progression of HFD-induced obesity and subsequent inflammation, thereby protecting against metabolic dysregulation from the early stage of obesity.

List of Abbreviations: HFD, high-fat diet; NAFLD, non-alcoholic fatty liver disease; n-3 PUFA, n-3 polyunsaturated fatty acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; Cap, Capsaicin; Dx, dextrin; SCD, a standard chow diet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; HOMA-IR, the homeostasis model assessment of insulin resistance.

Competing Interests: The authors have no financial interests or conflicts of interest.

Authors' Contributions: All authors contributed to the study.

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