# A comparison between the impact of two types of dietary protein on brain glucose concentrations and oxidative stress in high fructose-induced metabolic syndrome rats

ZOHRA MADANI[1], WILLY J. MALAISSE[2] and DALILA AIT-YAHIA[1]

[1]Department of Biology, University of Oran Ahmed Ben Bella, Es Sénia, Oran 31000, Algeria;
[2]Department of Biochemistry, Free University of Brussels, B-1070 Brussels, Belgium

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**Abstract.** The present study explored the potential of fish proteins to counteract high glucose levels and oxidative stress induced by fructose in the brain. A total of 24 male Wistar rats consumed sardine protein or casein with or without high fructose (64%). After 2 months, brain tissue was used for analyses. The fructose rats exhibited an increase in body mass index (BMI), body weight, absolute and relative brain weights and brain glucose; however, there was a decrease in food and water intake. Fructose disrupts membrane homeostasis, as evidenced by an increase in the brain hydroperoxides and a decrease in catalase (CAT) and glutathione peroxidase (GSH-Px) compared to the control. The exposure to the sardine protein reduced BMI, food intake, glucose and hydroperoxides, and increased CAT and GSH-Px in the brain. In conclusion, the metabolic dysfunctions associated with the fructose treatment were ameliorated by the presence of sardine protein in the diet by decreasing BMI, brain glucose and lipid peroxidation, and increasing CAT and GSH-Px activities.

## Introduction

Overconsumption of fructose is increasingly being recognized as a public health concern (1). A high fructose (HF) diet causes a number of pathological changes, including oxidative stress, obesity, metabolic syndrome, glucose intolerance, insulin resistance, type II diabetes, liver disease, hypertension and cardiovascular disease (CVD) (2). Unhealthy dietary habits can result in damage to brain health. Brain stress, which is a primary pathogenic basis of metabolic syndrome, can be fundamental in the development of metabolic syndrome associated CVDs. However, as brain stress in the metabolic syndrome is a relatively recent concept, only few mechanistic studies have been performed that directly demonstrate their causal association or the therapeutic potentials of inhibiting brain stress in CVDs.

Consumption of fish has been reported as a protective factor against several types of disease, and numerous literature has identified the benefits of fish consumption and its association with CVD over the past decades (3,4). This is correlated to the long chained *n*-3 polyunsaturated fatty acids (PUFA) content, in particular eicosapentaenoic acid and docosahexaenoic acid. In addition, fish protein is a rich source of bioactive peptides with nutraceutical and pharmaceutical potentials beyond those of *n*-3 PUFAs (3). Previous studies have shown that fish proteins have triacylglycerides-lowering effects (5), antioxidant capacity (6), antihypertensive (5) and cholesterol-lowering effects (7), and the potential to reduce markers of reactive oxygen species (ROS) (8).

The aim of the present study was to quantify the changes in brain glucose and oxidative stress following the consumption of HF, and therefore, to explore the potential of a sardine protein diet to counteract these abnormalities.

## Materials and methods

*Animals and diets.* A total of 24 male Wistar rats obtained from Iffa-Credo (l'Arbresle, France), and weighing 190-200 g at the beginning of the experiment, were used for the study. The rats were maintained in a laboratory animal house with an alternate exposure to 12-h light:dark cycle from 7:00 a.m. to 7:00 p.m. Throughout the experiment, the temperature of the animal room was maintained at 24˚C and humidity was at 60%. Rats were assigned to 4 equal-weight groups and fed the following diet for 2 months: Group 1 (C-HF) received a diet containing 20% casein and 64% fructose; group 2 (S-HF) received 20% sardine protein and 64% fructose; group 3 (C) received 20% casein, 5% sucrose and 59% corn starch; and group 4 (S) received 20% sardine protein, 5% sucrose and 59% corn starch. The fish protein prepared in the laboratory and used in the experiment was isolated from sardine fillets. The heads, internal organs and bones of the sardines were removed and minced. Subsequently, sardine proteins were purified according to the method of Undeland *et al* (9). The residual lipid content

*Correspondence to:* Professor Dalila Ait-Yahia, Department of Biology, University of Oran Ahmed Ben Bella, BP 1524 El M'Naouer, Es Senia, Oran 31000, Algeria
E-mail: aityahiad@yahoo.fr

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of the fish protein was verified by the Soxhlet method. The crude protein (N x 6.25) content of the protein preparations was assayed by the Kjeldahl method using a Kjell Foss autoanalyzer (Foss Electric, Hillerød, Denmark). The constituents (g/100 g) of the protein obtained by these procedures were 93 g protein, 0.9 g lipids, 2.5 g ashes and 3.6 g moisture. The composition of the basic experimental diet is shown in Table I. Diets were isoenergetic (16.28 MJ/kg) and contained identical amounts of lipids, vitamins, minerals and fiber. Food and water were provided *ad libitum*. The body weights of the animals were recorded every week and food intake was measured daily by measuring the food remaining. The distance from the nose tip to the tail tip was the measure of animal length. The BMI value used to identify obesity in the rats was BMI ≥1.00 g/cm$^2$ (10). The experiment was conducted according to the Guidelines for Care and Use of Laboratory Animals, as outlined by the Council of European Communities (11).

*Tissue collection*. At the end of the experimental period, the rats were sacrificed after overnight starvation and under anesthesia by the intraperitoneal injection of a solution containing sodium pentobarbital (60 mg/kg body weight). Fresh brain tissue was harvested, washed with ice-cold saline, weighed and immediately frozen at -70˚C until use.

*Biochemical analysis*. Brain glucose concentrations were assayed according to the method of Hevor *et al* (12). Protein contents were measured using bovine serum albumin as a standard (13).

*Lipid peroxidation markers in the brain*. Thiobarbituric acid (TBA)-reactive substances (TBARS) in the brain were quantified by the method of Quintanilha *et al* (14). Homogenates were prepared on ice in a ratio of 1 g wet brain tissue to 9 ml 150 mmol/l KCl using an ultraturrax homogenizer and the precipitate was treated with TBA at 95˚C for 1 h. The pink color that developed was read at 535 nm. The concentration is expressed as $\mu$mol/g tissue.

Brain lipid hydroperoxides were assayed using the previous method of Eymand and Genot (15), with ferrous ammonium sulfate and xylenol orange (3,3'-Bis[N,N-bis(carboxymethyl)-aminomethyl]-o-cresolsulfonephthalein). The color that developed was read at 560 nm. The concentration is expressed as $\mu$mol/g tissue.

*Antioxidant enzyme activities in the brain*. The brain homogenates that were prepared on ice in a ratio of 1 g wet tissue to 9 ml 150 mmol/l KCl using a Polytron homogenizer, were used for glutathione peroxidase (GPH-Px, EC 1.11.1.9) and catalase (CAT, EC 1.11.1.6) determinations. CAT activity was determined according to the method of Aebi (16) and the results were expressed in nmol/mg of protein. Tissue GPH-Px activity was measured by an enzymatic method using the Cayman Chemical kit (Cayman Chemical Co., Ann Arbor, MI, USA). The data are expressed in nmol/min/mg of protein.

*Statistical analysis*. Data were collected, analyzed and reported as mean ± standard deviation of 6 rats/group. Statistical analysis of the data was carried out with Statistica 6 (Statsoft, Inc., Tulsa, OK, USA). Data were tested using two-way analysis of variance with the type of protein and fructose as independent variables. When the interaction was significant, Fisher's least significant difference test was performed. P<0.05 was considered to indicate a statistically significant difference.

Table I. Composition of the experimental diets[a].

| Ingredient | C (g/kg diet) | S (g/kg diet) | C-HF (g/kg diet) | S-HF (g/kg diet) |
|---|---|---|---|---|
| C[b] | 200 | - | 200 | - |
| S | - | 200 | - | 200 |
| Fructose[b] | - | - | 640 | 640 |
| Corn starch | 590 | 590 | - | - |
| Sucrose | 50 | 50 | - | - |
| Sunflower oil | 50 | 50 | 50 | 50 |
| Cellulose | 50 | 50 | 50 | 50 |
| Vitamin[c] | 20 | 20 | 20 | 20 |
| Mineral[d] | 40 | 40 | 40 | 40 |

[a]Diets were isoenergetic (16.28 MJ/kg of diet) and administered in powdered form. [b]Prolabo (Paris, France). [c]UAR 200; (Villemoisson, 91360 Epinay/Orge, France). The vitamin mixture provided the following amounts (/kg diet): 12 mg retinol, 0.125 mg cholecalciferol, 40 mg thiamine, 30 mg riboflavin, 140 mg pantothenic acid, 20 mg pyridoxine, 300 mg inositol, 0.1 mg cyanocobalamin, 1.6 mg ascorbic acid, 340 mg dl-α-tocopherol, 80 mg menadione, 200 mg nicotinic acid, 100 mg para-aminobenzoic acid, 10 mg folic acid and 0.6 mg biotin. [d]UAR 205 B (Villemoisson). The salt mixture provided the following amounts (/kg diet): 17,200 mg $CaHPO_4$, 4,000 mg KCl, 400 mg NaCl, 420 mg MgO, 2,000 mg $MgSO_4$, 120 mg $Fe_2O_3$, 200 mg $Fe_2SO_4 \cdot 7H_2O$, 400 mg trace elements, 98 mg $MnSO_4 \cdot H_2O$, 20 mg $CuSO_4 \cdot 5H_2O$, 80 mg $ZnSO_4$, 0.16 mg $CoSO_4 \cdot 7H_2O$ and 0.32 mg Kl. S, sardine protein; C, casein; HF, high fructose.

## Results

*Growth parameters*. The data showed significant changes of growth parameters in the fructose-treated rats in comparison to the controls (Table II). Following fructose treatment, body weights and BMI were significantly increased, while length and metabolic body weights were similar. Food intake was decreased in fructose rats as compared to the control rats. Analysis of the fluid intake data during the 8 weeks showed a significant reduction in fructose-fed rats compared to the control rats. Exposition of fructose rats to the sardine protein diet led to a low BMI and food intake as compared to casein, while length, metabolic body weight, water intake and final body weight were similar.

*Absolute and relative brain weights and glucose and protein concentrations*. The absolute values for brain weight as recorded at sacrifice were significantly increased in fructose rats as compared to the control rats (Table III). The presence of sardine protein in diets with or without fructose did not enhance brain weights in rats when compared to casein. The relative brain weights were similar in the 4 groups of rats. As compared to the control animals, the fructose-fed animals had significantly elevated brain glucose (P<0.05). Rats fed sardine

Table II. Food intake, body weight and metabolic body weight of experimental and control rats.

| | Diets[a] | | | | ANOVA (P-value) | | |
|---|---|---|---|---|---|---|---|
| Variables | C | S | C-HF | S-HF | Prot | Fru | Prot vs. Fru |
| Food intake, g/rat/day | 24.45±2.20 | 20.11±1.26[b] | 18.63±0.63[c] | 17.27±1.15[b,c] | P<0.05 | P<0.05 | P<0.05 |
| Water intake, ml/day | 15.00±1.00 | 15.00±1.22 | 10.80±1.30[c] | 11.60±1.14[c] | NS | P<0.05 | NS |
| Final body weight, g | 354.83±9.92 | 339.8±9.14 | 369.95±11.40[c] | 358.92±10.97[c] | NS | P<0.05 | NS |
| Length, cm | 19.17±0.49 | 18.52±1.32 | 18.77±1.05 | 18.83±1.04 | NS | NS | NS |
| BMI, g/cm$^2$ | 0.96±0.07 | 0.99±0.06 | 1.05±0.03[c] | 1.01±0.09[b] | NS | P<0.05 | P<0.05 |
| Metabolic body weight, BW$^{0.75}$ | 81.73±1.72 | 79.06±0.59 | 82.64±2.28 | 82.45±1.89 | NS | NS | NS |

[a]Values are mean ± standard deviation of 6 rats/group. Statistical analysis of the data was carried out with Statistica 6 (Statsoft, Inc., Tulsa, OK, USA). Data were tested using two-way analysis of variance (ANOVA) with type of protein (Prot) and fructose (Frut) as independent variables. When the interaction was significant, Fisher's least significant difference test was performed. Differences were considered significant at P<0.05. [b]P<0.05, sardine protein (S) vs. casein (C), [c]P<0.05, fructose supplementation vs. no supplementation. BMI, body mass index; HF, high fructose; NS, not significant.

Table III. Brain weight and glucose data of experimental and control rats.

| | Diets[a] | | | | ANOVA (P-value) | | |
|---|---|---|---|---|---|---|---|
| Variables | C | S | C-HF | S-HF | Prot | Fru | Prot vs. Fru |
| Brain weight, g | 1.39±0.18 | 1.38±0.20 | 1.61±0.17[c] | 1.68±0.12[c] | NS | P<0.05 | NS |
| Brain weight/100 g body weight | 0.40±0.04 | 0.36±0.04 | 0.44±0.02[c] | 0.45±0.01[c] | NS | P<0.05 | NS |
| Brain glucose, $\mu$g/g tissue | 0.80±0.12 | 0.49±0.09[b] | 1.00±0.17[c] | 0.83±0.14[b,c] | P<0.05 | P<0.05 | P<0.05 |

[a]Values are mean ± standard deviation of 6 rats/group. Statistical analysis of the data was carried out with Statistica 6 (Statsoft, Inc., Tulsa, OK, USA). Data were tested using two-way analysis of variance (ANOVA) with type of protein (Prot) and fructose (Fru) as independent variables. When the interaction was significant, Fisher's least significant difference test was performed. Differences were considered significant at P<0.05. [b]P<0.05, sardine protein (S) vs. casein (C), [c]P<0.05, fructose supplementation vs. no supplementation. HF, high fructose; NS, not significant.

Table IV. Lipid peroxidation markers and antioxidant enzymes in the brains of experimental and control rats.

| | Diets[a] | | | | ANOVA (P-value) | | |
|---|---|---|---|---|---|---|---|
| Variables | C | S | C-HF | S-HF | Prot | Fru | Prot vs. Fru |
| TBARS, $\mu$mol/g | 0.12±0.04 | 0.14±0.01 | 0.13±0.01 | 0.13±0.008 | NS | NS | NS |
| Hydroperoxides, $\mu$mol/g | 1.01±0.11 | 1.03±0.12 | 1.29±0.10[c] | 1.12±0.04[b,c] | NS | P<0.05 | P<0.05 |
| CAT, nmol/mg protein | 22.5±0.15 | 23.5±0.31 | 12.3±0.31[c] | 19.9±0.13[b,c] | NS | P<0.05 | P<0.05 |
| GSH-Px, nmol/min/mg protein | 2.42±0.69 | 3.03±0.32[b] | 1.46±0.47[c] | 1.57±0.63[b,c] | P<0.05 | P<0.05 | P<0.05 |

[a]Values are mean ± standard deviation of 6 rats/group. Statistical analysis of the data was carried out with Statistica 6 (Statsoft, Inc., Tulsa, OK, USA). Data were tested using two-way analysis of variance (ANOVA) with type of protein (Prot) and fructose (Fru) as independent variables. When the interaction was significant, Fisher's least significant difference test was performed. Differences were considered significant at P<0.05. [b]P<0.05, sardine protein (S) vs. casein (C), [c]P<0.05, fructose supplementation vs. no supplementation. HF, high fructose; NS, not significant; TBARS, thiobarbituric acid-reactive substances; CAT, catalase; GSH-Px, glutathione peroxidase.

protein with or without fructose showed a significant decrease in brain glucose concentrations by ~20 and 39% as compared to C-HF and C, respectively.

*Lipid peroxidation markers in the brain tissue*. The level of hydroperoxides, a marker for lipid peroxidation was increased significantly (P<0.05) with fructose intake as compared to the control diets. With respect to TBARS, there was no visible change (Table IV). Rats consuming the sardine protein diet with or without fructose did not exhibit any significant changes in TBARS, while hydroperoxide concentrations in the brain were significantly reduced in S-HF compared to C-HF.

*Antioxidant enzymes activities in the brain tissue*. Rats assigned to the fructose diet showed a significant decrease in brain CAT and GSH-Px activities as compared to the control rats (Table IV). Exposition of the HF rats to sardine protein increased the brain CAT and GSH-Px activities by ~62 and 8% in comparison to C-HF rats. Additionally, an increase by 25% in GSH-Px activity was observed in the S group compared with the C group.

## Discussion

The present study was designed to investigate the fructose-related changes in the glucose concentration and oxidative stress in the brain, and the ability of dietary fish protein to counteract metabolic disorders. The role of brain oxidative stress in the development of metabolic diseases is a relatively new concept.

In the present study, rats fed a high-fructose diet for 8 weeks had a significantly high final body weight, absolute and relative brain weights and BMI, suggesting that obesity is a major contributor to altered structural changes in the brain. However, there was a significant reduction in food and water intake, indicating that fructose had an effect on food and liquid consumption. Certain previous studies reported that HF diets induced weight gain and a higher consumption of liquid in rodents (17,18). The findings of the present research are not in accordance with those of Rafati *et al* (19), which indicated no difference in body and brain weights, and fluid intake in fructose rats. These discordances may be explained by the different types of fructose administration and different species of experimental animals. In addition, a sardine protein diet in combination with fructose improved BMI values, which is possibly reversed following low food intake.

The present study reported that an abundant consumption of fructose leads to an increase in brain glucose levels. We believe that increased glucose may be attributed to peripheral metabolic events that can alter the brain function after crossing the blood-brain barrier, such as hyperglycemia, hyperinsulinemia and insulin resistance, as observed in our previous results (5). Our findings are consistent with those of Zamami *et al* (20) and Aydin *et al* (21). It is likely that higher concentrations of fructose reached the brain and thus had the potential to directly act to influence brain homeostatic responses, as reported previously (22,23). It is possible that fructose feeding increased brain insulin resistance by decreasing the phosphorylation of the insulin receptor and its signaling molecules, including Akt, in the brain (24) and by increasing the expression of fructose-sensitive glucose transporters 5 (Glut5) (25). Fructose is metabolized in the hippocampal microglia (25) and neurons in the cerebellum (26), and cross the blood brain barrier (27) into the hypothalamus, where it can be metabolized and used as an energy source. The exposure to the sardine protein diet decreased brain glucose concentrations, suggesting a protection in the brain of these animals possibly due to the increase in systemic insulin sensitivity (5), which may improve the efficiency of insulin in blocking glucose formation, contributing to the hypoglycemia and hypoinsulinemia of rats.

Incorporation of fructose in the two protein diets induced brain oxidative stress, as evidenced by an increase in the levels of hydroperoxide, suggesting that the fructose diet causes the brain to be more vulnerable to free radical attack. Fructose promotes changes in the brain reward system, which leads to excessive consumption and promotes ROS formation (28). Enhanced lipid peroxidation in HF-fed rats could be associated with high glucose levels, which increases free radical production from glucose autoxidation. Chronic hyperglycemia and hyperinsulinemia primarily stimulates the formation of the advanced glucose end products, leading to an overproduction of ROS. Additionally, the brain utilizes a significant quantity of oxygen and adenosine triphosphate to support its normal functions, resulting in a high susceptibility to oxidative stress (29). The present results also addressed changes in brain antioxidant enzymes; CAT and GSH-Px activities in the brain of rats fed fructose were 45 and 15% lower compared to the controls. The decreased activity of CAT may be a response to increased production of $H_2O_2$ by the auto-oxidation of excess glucose and non-enzymatic glycation of proteins. These increases in the lipid peroxidation and the attenuation in antioxidant enzymes are compatible with the results of our previous studies in adipose tissues (5). Similarly, the response to the incorporation of sardine protein in the diet in terms of brain content of hydroperoxides coincided with the correction of the fructose-induced changes in the activities of CAT and GSH-Px. This protective effect is in accordance with the results reported by Grimstad *et al* (8). The increased activity of GSH-Px in the brain of rats fed sardine protein may be associated with a high content of cystein in sardine protein (1.2 vs. 0.4 g/100 g for casein), which is a substrate for GSH-Px activity and acts as an antioxidant molecule.

Taken together, these results revealed that a sardine protein diet reversed the abnormalities induced by fructose by lowering BMI and brain glucose, and improved oxidative stress by restoring the altered activities of CAT and GSH-Px and lipid peroxidation. These findings provide support for the role of fish protein as a neuroprotective dietary nutrient and may be advocated as potential candidate for metabolic syndrome prevention.

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