Trans and interesterified fat and palm oil during the pregnancy and lactation period inhibit the central anorexigenic action of insulin in adult male rat offspring

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Abstract  Palm oil and interesterified fat have been used to replace partially hydrogenated fats, rich in trans isomers, in processed foods. This study investigated whether the maternal consumption of normolipidic diets containing these lipids affects the insulin receptor and Akt/protein kinase B (PKB) contents in the hypothalamus and the hypophagic effect of centrally administered insulin in 3-month-old male offspring. At 90 days, the intracerebroventricular injection of insulin decreased 24-h feeding in control rats but not in the palm, interesterified or trans groups. The palm group exhibited increases in the insulin receptor content of 64 and 69 % compared to the control and trans groups, respectively. However, the quantifications of PKB did not differ significantly across groups. We conclude that the intake of trans fatty acid substitutes during the early perinatal period affects food intake regulation in response to centrally administered insulin in the young adult offspring; however, the underlying mechanisms remain unclear.

Keywords  Interesterified fat · Palm oil · Insulin receptor · Metabolic programming · Hypothalamus

Introduction

Data about trans-fatty acids (TFAs) implicate this lipid subclass as particularly deleterious to human health [1, 2], and experimental evidence in animals suggests that the intake of TFAs during the prenatal and early stages of the postnatal life perturbs development, which, in turn, permanently alters the structure, function and metabolism of the tissues and organs of neonates and results in an increased susceptibility to diet-related diseases in adult life [3–5].

In view of these lines of evidence, most public health agencies have implemented labelling or ingredient restrictions on trans fats, which have led food industries to take steps to develop TFA-reduced or TFA-free processed food products [6]. One strategy is the interesterification of highly hydrogenated fats with liquid oils via chemical or enzymatically driven procedures. Unlike hydrogenation, interesterification neither affects the degree of saturation nor causes isomerisation of the double bonds. Instead, interesterification rearranges the fatty acids in the glycerol molecule. Random interesterification changes to the crystal forms of oils or blends are used to produce the desired solid fat content curves or to produce blends with high levels of polyunsaturated fatty acids and TFA-free blends [7]. However, nearly no data about the health effects of interesterified fat intake are available. Impaired insulin secretion, high LDL/HDL ratios and high blood pressure have been described [8]. Additionally, changes in plasma triacylglycerol in obese individuals but not lean individuals following interesterified fat intake have also been shown [9, 10].

Another technological procedure is the replacement of partially hydrogenated soybean oil with palm oil. Unlike soybean oil, palm oil can be used without hydrogenation to achieve a certain product hardness because of its semisolid texture at room temperature; therefore, palm oil exhibits...
the appropriate physical properties for use in the food industry [11, 12]. Palm oil consists of 50 % saturated and 50 % unsaturated fatty acids and has a content of 44 % palmitic acid and 10.6 % linoleic acid. Although many studies related to the effects of palm oil consumption have been performed, the literature has not reached a consensus. Positive effects on plasma lipid profiles have been demonstrated [13, 14]. However, increased risks of developing cardiovascular disease and obesity because of palm oil intake have also been suggested by some studies [15–17].

Energy homeostasis is stringently regulated by neuronal populations in the arcuate nucleus (ARC) of the hypothalamus that senses and integrates peripheral signals mediated by nutrients, cytokines and hormones such as insulin [18]. The hypothalamic insulin receptor (IR) is a tyrosine kinase that undergoes autophosphorylation upon binding to insulin, which results in the phosphorylation of the insulin receptor substrate [19]. The action of insulin on its hypothalamic receptors is known to reduce food intake [18, 20]. Both acute and prolonged intracerebroventricular administrations of insulin doses dependently reduce food intake and body weight [21, 22].

Central effects of TFA intake have previously been demonstrated by our group. Albuquerque et al. [23] observed that intrauterine/perinatal exposure to TFA-rich hydrogenated fat adversely affects insulin-induced hypophagia and hypothalamic levels of IR and IRS-1 as assessed in adulthood, which indicates that the presence of TFA in the brain during early development affects these central mechanisms later in life. Nevertheless, given that the food industry in many countries has been gradually replacing partially hydrogenated fat by alternative lipid sources [14], it is of interest to investigate whether the early exposure to these trans fat substitutes differentially impacts the central control of energy homeostasis in adulthood. To the best of our knowledge, no studies have examined the effects of dietary palm and interesterified fat on central insulin-induced hypophagia, particularly during fetal and neonatal life, period the complex process of developmental plasticity.

Thus, the purpose of the present study was to investigate the effects of normolipidic diets containing TFA-rich hydrogenated fat or its industrial substitute lipid sources (i.e., interesterified fat or palm oil) during gestation and lactation on hypothalamic insulin sensitivity in adult male rat offspring.

Materials and methods

Animals, diets and experimental design

The experimental protocol was approved by the Animal Research Ethics Committee of the Health and Science Center of the Universidade Federal do Rio de Janeiro (Rio de Janeiro, Brazil). Wistar rats obtained from the animal breeding unit of the Institute of Nutrition of the University were maintained under controlled light (12 h light:12 h dark cycle) and temperature (24 ± 1 °C) conditions. Three-month-old virgin female rats were mated, and the first day of pregnancy was determined by the presence of sperm in the vaginal smears. From day 0 of pregnancy, the dams were isolated in individual cages and randomly divided into four groups according to the experimental normolipidic diets, assigned to be a control group (SG), palm group (PG), interesterified group (IG) or partially hydrogenated fat group (PHG). The diets were maintained throughout pregnancy and lactation. On the day of delivery (day 1 of lactation), the litters were adjusted to eight male pups per dam. After weaning (day 22 of life), the pups received the same diet as the control group until the 90th day of life.

The diets were prepared according to the recommendations of the American Institute of Nutrition (AIN-93 G, Growth and M, Maintenance) [24] and were isoenergetic (all diets provided 4.1 kcal/g of dry diet) and normolipidic, but differed in their fatty acid (FA) profiles (Table 1). The control group (SG) received a diet that contained 9 % soy oil (rich in n-6 fatty acids); the palm group (PG) received a diet that contained 7 % palm oil (rich in saturated and monounsaturated FA) and 2 % soy oil; the interesterified group (IG) received a diet that contained 7 % interesterified fat (rich in saturated FA) and 2 % soy oil; the partially hydrogenated fatty acid group (PHG) received a diet that contained 8 % partially hydrogenated fat (rich in TFA) and 1 % soy oil. Soy oil was added to the diets to ensure the minimum requirement for essential fatty acids. The FA compositions of the diets are summarised in Table 2. Intesterified fat was prepared using different types of lipids including palm kernel oil (2.5 %), palm stearin (45 %), soybean oil (45 %) and fully hydrogenated fat (7.5 %). The interesterified fat was generously donated by Triângulo Alimentos, São Paulo, Brazil. The animals received food and water ad libitum throughout the experimental period. The food consumptions of the offspring were measured daily based on daily weaning and body weights from birth until 90 days of life.

To evaluate the adiposity index of the offspring at the 90th day of life, epididymal, mesenteric and lumbar adipose tissues were collected and weighed immediately after euthanasia by guillotine.

Analyses of the fatty acid compositions of the diets

Tridecanoic acid (13:0) (Sigma Chemical Co.) was added as an internal standard to fresh aliquots of each diet, which were used for lipid extraction, purification and transesterification based on the alkaline direct methylation method.
described by AOCS [25]. Fatty acid methyl esters were separated and quantified with a gas chromatograph (Agilent Technologies 7890 A and EZ Chrom Elite, USA) equipped with a flame ionization detector and a 100 meter Supelco SP-2560 (Supelco Inc., PA, USA) fused silica capillary column (100 m, 0.25 mm and 0.2 μm film thickness). Hydrogen was used as the carrier gas, and the fatty acid methyl esters were compared to purified

### Table 1 Diet composition (g/kg)

| Constituents (g/kg of diet) | Control diet (soy oil) | Partially hydrogenated fat diet (trans) | Palm oil diet | Interesterified fat diet |
|----------------------------|------------------------|----------------------------------------|--------------|--------------------------|
| Casein (vitamin free)      | 200.0 (140.0)          | 200.0                                  | 200.0        | 200.0                    |
| Cornstarch                 | 397.4 (465.7)          | 397.4                                  | 397.4        | 397.4                    |
| Dextrinized cornstarch     | 132.0 (155)            | 132.0                                  | 132.0        | 132.0                    |
| Sucrose                    | 100.0                  | 100.0                                  | 100.0        | 100.0                    |
| Cellulose                  | 50.0                   | 50.0                                   | 50.0         | 50.0                     |
| Salt mix G (M)             | 10.0                   | 10.0                                   | 10.0         | 10.0                     |
| Vitamin mix                | 35.0                   | 35.0                                   | 35.0         | 35.0                     |
| β-Choline                  | 2.5                    | 2.5                                    | 2.5          | 2.5                      |
| Butylhydroquinone-BHT      | 0.014                  | 0.01                                   | 0.01         | 0.01                     |
| Soy oil                    | 70.0 (40.0)            | 10.0                                   | 20.0         | 20.0                     |
| Partially hydrogenated fat | –                      | 60.0                                   | –            | –                        |
| Palm oil                   | –                      | 50.0                                   | –            | –                        |
| Interesterified fat        | –                      | –                                      | –            | 50.0                     |
| Energy value (kcal/kg)     | 3,950                  | 3,950                                  | 3,950        | 3,950                    |

Amounts during maintenance periods (from 60 days of age onwards) are presented within parentheses (Reeves)

### Table 2 Fatty acid profile (mg/g of diet) of total lipids of experimental diets consumed by mothers during pregnancy and lactation

| Fatty acid | SG Mean ± SEM | IG Mean ± SEM | PHG Mean ± SEM | PG Mean ± SEM |
|------------|---------------|---------------|----------------|---------------|
| 16:0       | 12.06 ± 0.14  | 14.54 ± 0.13  | 16.80 ± 0.06   | 33.02 ± 2.93  |
| 18:0       | 3.93 ± 0.21   | 23.81 ± 1.02  | 20.81 ± 0.74   | 5.04 ± 0.20   |
| Σ SFA       | 17.57 ± 0.30  | 48.83 ± 0.76  | 41.43 ± 0.68   | 40.33 ± 2.90  |
| 18:1 (n-9)  | 24.08 ± 0.38  | 19.76 ± 0.04  | 16.95 ± 0.00   | 36.40 ± 3.59  |
| Σ MUFA       | 26.21 ± 0.18  | 21.68 ± 0.28  | 23.12 ± 0.14   | 37.82 ± 3.48  |
| 18:2 (n-6)  | 50.38 ± 0.18  | 25.95 ± 0.17  | 10.46 ± 0.02   | 20.00 ± 0.33  |
| 18:3 (n-3)  | 5.13 ± 0.18   | 2.13 ± 0.05   | 0.95 ± 0.02    | 1.42 ± 0.22   |
| Σ PUFA       | 55.71 ± 0.21  | 28.20 ± 0.25  | 11.41 ± 0.01   | 21.46 ± 0.52  |
| Σ n-6        | 50.58 ± 0.39  | 26.07 ± 0.30  | 10.46 ± 0.02   | 20.04 ± 0.30  |
| Σ n-3        | 5.13 ± 0.18   | 2.13 ± 0.05   | 0.95 ± 0.02    | 1.42 ± 0.22   |
| Σ TFA        | 0.50 ± 0.10   | 1.28 ± 0.73   | 24.04 ± 0.83   | 0.39 ± 0.07   |
| LA=6/ALA-3   | 9.84 ± 0.40   | 12.20 ± 0.40  | 11.00 ± 0.20   | 14.40 ± 2.00  |

Data are expressed as mean ± SEM (n = 6 per group)

Different letters at the same row mean statistical difference between experimental groups (p < 0.05)

SG control group, IG interesterified group, PHG partially hydrogenated fatty acid group, PG palm oil group, Σ SFA sum of saturated fatty acids, Σ MUFA sum of monounsaturated fatty acids, Σ PUFA sum of polyunsaturated fatty acids, Σ TFA sum of trans fatty acids, LA linoleic acid, ALA α-linolenic acid
standards (Nu-Chek Prep, Inc., mix 463). Fatty acid quantification was performed by comparing the corresponding peak areas to those of the internal standard. One gram of the diets was used to analyse the fatty acid compositions. The values are expressed as mg FA/g of sample.

Intracerebroventricular (ICV) insulin administration and measurement of food intake

On day 90 of life, the animals were anesthetised with a ketamine/xylazine mixture (66/13 mg/kg) and stereotaxically implanted with a 23-gauge guide cannula aimed at the left lateral ventricle (A 0.9 mm, L +1.5 mm and V 3.0 mm from the bregma). The cannulas were fixed to the skull using two screws and dental cement. Subsequently, the animals were individually caged with ad libitum access to food and water. After 5 days, the animals received ICV injections containing 2.0 µl angiotensin II (1.0 ng/ml) to ensure that the cannulas were correctly positioned [26]. The animals that did not immediately begin drinking water were excluded from this study. On another day, the animals were fasted for 6 h and received ICV injections of 2.0 µl regular insulin (Humulin, Eli Lilly) (10 mU/µl) or 2.0 µl of vehicle (0.9 % NaCl). The injections were performed 15 min before lights out, and pre-weighed food was introduced to the cage. Food intakes were recorded at 12 and 24 h. The animals were killed by guillotine after ICV infusion, and the hypothalami were collected and stored at −80 °C for further analysis with Western blotting.

Western blotting for the determination of the hypothalamic IR and Akt/protein kinase B (PKB) proteins

The hypothalami were homogenised in 1.0 ml cold solubilisation buffer (5 mM Tris-HCl pH 7.4, 10 mM EDTA, 1 mM sodium orthovanadate, 5 mM NaF, 1 mM fenilarsin oxide, 1 µM okadaic acid, 10 % protease inhibitor cocktail (P8340 SIGMA), 1 mM PMSF and 10 % Triton X-100). The samples were sonicated for 5 min and centrifuged; 10 µl of the samples was used for the protein analyses (Pierce BCA Protein Assay Kit). Next, 100 µg of protein from all samples was loaded in SDS electrophoresis gel (10 %), electrophoretically separated and transferred to nitrocellulose membranes. The membranes were incubated with primary antibody against IR (Cell Signaling 3025) or Akt/protein kinase B (PKB) (Cell Signaling 9272). After incubation with the primary antibodies, the membranes were incubated with secondary antibody (anti-rabbit, Cell Signaling 7074), and detections were performed with a chemiluminescent reagent (ECL, Thermo Scientific, USA). The quantitative analyses were performed with ImageJ software. Next, the membranes were stripped and rebotted with α-tubulin antibody (Cell Signaling 2144) [27]. The results are expressed as percent changes relative to the control group in arbitrary units.

Statistical analyses

The data are expressed as the means ± SEM. The statistical analyses were performed with GraphPad Prism version 5.0 (GraphPad Software Inc., La Jolla, CA). The distributions of the studied variables were identified as normal via examinations using the Shapiro-Wilk test, and parametric analyses were subsequently applied. The data were compared with one-way analyses of variance followed by Newman-Keuls simultaneous tests. Unpaired Student’s t tests were applied to compare the animals that received insulin and saline ICV injections. Statistical significance was set at p < 0.05.

Results

The body weights and food intakes were similar across all of the dam groups during pregnancy and lactation (data not shown). Additionally, no significant differences across groups were found in the offspring body weights from birth until the 90th day of life (Fig. 1).

At weaning (day 21), the pups from the dams that received the interesterified fat and palm oil diets exhibited lower food intake (21.31 ± 0.96 and 20.82 ± 0.47 g, respectively) than the control group (23.99 ± 0.73 g). Throughout the remainder of the period studied, the daily food intakes exhibited small but significant and specific variations (data not shown); however at day 90, none of these differences remained.

![Body weight gain of pups from experimental groups from the 1st week until the 14th week after weaning. Values are mean ± SEM of 12–16 rats. SG control group, IG interesterified group, PHG partially hydrogenated fatty acid group, PG palm group](image-url)
At the 90th day of life, the studied groups exhibited no significant differences in the adiposity index (SG 7.24 ± 0.47 g; IG 6.95 ± 0.19 g; PHG 7.01 ± 0.26 g; PG 6.60 ± 0.38 g).

We measured the 12- and 24-h food intakes of the SG, IG, PHG and PG rats that had been treated with ICV injections of vehicle or insulin. Insulin significantly decreased the 12- and 24-h food intakes (by 28 and 33 %, respectively) exclusively in the SG animals compared to the vehicle animals (Fig. 2).

The amount of IR protein in the hypothalamus was 64 % higher in the group in which the dams were fed the palm oil diet compared to the control group. The IR protein levels were 69 % lower in the PHG than in the PG group (Fig. 3). No differences in Akt/PKB protein content were detected across all studied groups (Fig. 4).

**Discussion**

In recent years, research investigating the effects of excess maternal dietary lipid intake on the in utero programming of adult metabolic disease has provided much evidence that perinatal lipid dietary manipulations result in pronounced metabolic dysfunctions later in life [28, 29]. However, currently available data on the relatively new field of the developmental origins of health and disease and the relations of specific exposures to isocaloric and normolipidic diets with distinct fatty acid qualities during early life are scarce.

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In the present study, the anorexigenic effects of an ICV dose of insulin were evaluated in the adult male progeny of rats that had ingested a control diet or diets containing TFA-rich hydrogenated fat or its industrial substitutive
lipid sources, interesterified fat or palm oil, throughout pregnancy and lactation.

Exogenous insulin activates the central insulin pathway and involves IR and PKB phosphorylation, which stimulates anorexigenic neurons in the hypothalamus and leads to reduced food intake [30]. In our study, the control group exhibited reduced consumption 12 and 24 h after acute ICV insulin injections compared to the group that received saline vehicle ICV injections. However, the PHG, IG and PG rats failed to decrease their food intake. Thus, the intakes of lipid sources that are rich in trans fatty acids or the industrial alternatives to trans fatty acids during pregnancy and the lactation period impaired the central insulin-induced effects in later life.

This central insulin signalling effect is similar to that previously reported by our group in an experimental model of foetal programming with different trans fatty acid dietary interventions [23]. In our previous study, Wistar dams were fed isocaloric/normolipidic diets containing soybean oil (control) or soybean oil-derived hydrogenated fat (trans diet) as lipid source throughout pregnancy and lactation, and, after weaning, the offspring continued to receive the same experimental diet (control group and trans group) or switched to the control diet (trans-control group). Compared with the control and trans groups, the trans-control offspring, which were exposed to TFA during the critical developmental phase and received the control diet after weaning, expressed a more disrupted phenotype. In trans-control animals, the insulin receptor was 26 % lower and IRS-1 was 50 % lower than in control rats (p < 0.05). ICV infused insulin decreased 24-h feeding in control (27 %) and trans (38 %) rats, but failed to do so in the trans-control ones [23]. Altogether, these findings suggest that intrauterine and early postnatal exposure to hydrogenated fat, interesterified fat or palm oil promotes adaptations in the hypothalamic mechanisms of food intake control, which might be deleterious later in life after environmental changes, such as the main dietary lipid source.

Notably, despite the observed hypothalamic resistance to insulin, the PHG, IG and PG adult animals exhibited normal daily food intakes and no fat mass alterations. It seems that compensatory adaptations occurred that succeeded in overcoming the compromised ability of insulin to inhibit feeding. This finding is not surprising given the numerous hypothalamic systems that regulate energy homeostasis [31–33]. Evidence gathered from expression and injection studies suggests that food intake is stimulated by different orexigenic peptides, such as neuropeptide Y, galanin, orexin and melanin-concentrating hormone, acting within the hypothalamus or other cerebral structures. Besides being sensitive to insulin levels, these neurochemical peptide systems also respond to changes in circulating levels of leptin, which interacts with the former hormone on hypothalamic neurons [33, 34]. Clear understanding of the relationship among these various determinants of eating behaviour will allow pointing out the effective factor that might have influenced our results.

To ascertain whether functional resistance to insulin might be due to altered receptor densities, we measured the amounts of IR protein in the hypothalamus. The group of animals in which the dams were fed the palm oil diet exhibited an increased IR level of 64 % compared to the SG animals. In contrast, no differences were found in the PHG or IG animals. Other authors have reported similar hypothalamic IR levels in 2-month-old rats fed a hypercaloric diet rich in n-6 fatty acids over 8 weeks; these animals exhibited impaired anorexigenic effects following ICV insulin [35]. The female progeny of dams subjected to food restriction during the first 2 weeks of pregnancy exhibited higher hypothalamic IR protein levels than did controls, although the study that reported this finding failed to show decreased food intake after ICV injections of insulin [36]. Our own data and these previously reported data are consistent with the suggestion that adaptations occur that are not able to counterbalance the hypothalamic resistance to insulin.

It is well established that, even at the hypothalamic level, the continuity of insulin signalling depends on the phosphatidylinositol 3-kinase (PI3-K) pathway following the binding of insulin to the IR. The activation of PI3-K results in the phosphorylation of PKB, which is a serine/threonine
kinase primarily involved in mediating the metabolic effects of insulin [37–39]. In the present investigation, no differences in hypothalamic Akt/PKB levels were found between the studied groups, which suggests that either an impaired interaction of insulin with its hypothalamic receptor or a defective stimulation of the transducing pathways following receptor binding could be involved in the altered ability of the hormone to reduce food intake. Experiments that are specifically designed to explore these aspects will help to ascertain the extent to which each of these putative abnormalities contributes to the alterations in insulin action that were observed in the PHG, IG and PG rats.

Several other different mechanisms might blunt the hypophagic response to insulin in the hypothalamus [40, 41]. Saturated fatty acids are known to be one of the activators of Toll-like receptors (TLR), particularly TLR4, which is involved in mediating augmentations of the inflammatory response. In the case of prolonged exposure to these fatty acids, this inflammation can activate a proapoptotic pathway that leads to the death of the anorexigenic neurons of the aqueous nucleus [42, 43].

We demonstrated an impairment of insulin-induced hypophagia in the hypothalami of animals whose dams consumed diets that were manipulated with lipid sources that were rich in saturated fatty acids, i.e., palm oil and interesterified fat. Thus, we speculate that the organisation of the hypothalamic feeding control circuits might be affected by exposure to saturated fatty acids during their critical periods [40] to promote the release of proinflammatory signals. Therefore, the inflammation of the immature hypothalamus during early life might lead to a reduced number of neurons, which might derange the central control of feeding despite the maintenance of hypothalamic IR and Akt/PKB levels.

Besides providing saturated fatty acids, palm oil contains high amounts of phenolic compounds, which may play a dual role in the central nervous system. Palm oil phenolics could have beneficial neuroprotective and anti-inflammatory properties in the brain [44]. However, its antioxidant activity could impair reactive oxygen species signalling in the hypothalamus, which is required for insulin-induced food intake inhibition [45]. Therefore, other experiments designed to explore these aspects of the different trans fat substitutes are needed.

### Conclusion

In conclusion, our results indicate that exposure to either partially hydrogenated fat or its substitute lipid sources (i.e., palm oil and interesterified fat) during the critical periods of development lead to a compromised ability of insulin to inhibit feeding in adult life. The excess of saturated fatty acids in the normolipidic diets offered to the dams might have played an important role in promoting these outcomes in the progeny. Given that the effects of metabolic programming are ostensibly established later in life [46–48], it is possible that these animals were still sufficiently young to manifest changes in body weight at older ages. These results imply that the quality of dietary fat during sensitive periods of development might “programme” the long-term or lifetime structure or function of the organism.

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### Conflict of interest

The authors declare that there are no conflicts of interest.

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