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Influence of maternal protein malnutrition on oxidative stress and regulators of mitochondrial biogenesis in female rat hearts over succeeding generations

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ABSTRACT

Aims: We sought to evaluate the effects of maternal protein restriction (LP) on oxidative balance and transcription factors for mitochondrial biogenesis in the hearts of young female rats of both the first (F1) and second (F2) generation.

Main methods: We evaluated oxidative stress biomarkers (lipid peroxidation and protein oxidation), enzymatic antioxidant defense (activity of superoxide dismutase-SOD, catalase, and glutathione-S-transferase-GST), nonenzymatic antioxidant defense (reduced glutathione-GSH and sulfhydryl groups) and gene expression of AMPK, PGC-1α and TFAM.

Key findings: Interestingly, lipid peroxidation was decreased (49%, $p < 0.001$) in the LP-F1 group and 59% ($p < 0.001$) in LP-F2. In enzymatic defense, we observed increases in SOD activity in the LP-F1 group (79%, $p = 0.036$) and in CAT activity (approximately 40%, $p = 0.041$). GSH was increased in F2 in both groups (LP 546%, $p < 0.0001$ and in NP 491.7%, $p < 0.0001$). With respect to mitochondrial biogenesis gene transcription, we observed a decrease in AMPK (60%, $p < 0.0001$) and an increase in PGC-1α (340%, $p < 0.001$) in LP compared to NP in the F1 generation. TFAM was decreased in LP-F2L compared to NP-F2L (42%, $p = 0.0069$) and increased in LP-F2 compared to LP-F1 (160%, $p = 0.0037$).

Significance: Our study contributes to knowledge of inheritance, showing that despite the potential mitochondrial 'inheritance' of cardiovascular damage caused by maternal malnutrition, that damage is not cross-generational and can be eliminated with proper nutrition in the F1 generation.

1. Introduction

Nutritional deficiency during pregnancy and lactation has been shown to predispose the first generation to development of lifelong metabolic and cardiovascular disease [1,2]. According to WHO, by 2030, nearly 23.6 million people will die from cardiovascular disease (CVD) [3], primarily in developing countries that are most affected by poor maternal diet. Experimental studies on protein restriction have been linked to increased incidence of metabolic disease in the offspring of undernourished mothers and to long-lasting impairments in mitochondrial function [4]. These include increased generation of reactive oxygen species (ROS) in central and peripheral tissues, including the brainstem and heart, as we previously demonstrated in the F1 generation of male rats born to malnourished mothers [5,6]. Oxidative stress, in turn, alters the structure and function of both lipids and proteins [7], which contributes directly to cardiac injury [8]. Our research group has also recently shown that females are less susceptible to oxidative stress induced by maternal low-protein (LP) diet than are males [9], suggesting that in reasonable concentrations, estrogen may act as an antioxidant to reduce the risk of cardiac disease [10]. Its protective effect may be related to the removal of free radicals [11] and to its transcriptional regulation of antioxidant enzymes that contribute to

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mitochondrial dynamics [12].

Mitochondria are the primary organelles responsible for cellular energy supply, and both their number and their capacity for ATP generation generally correspond to energy demands. In the heart, mitochondria comprise an especially high percentage (34%) of cardiomyocyte volume to accommodate the high energetic demands of this organ [13,14], which are achieved through the activities of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). This master regulator of mitochondrial biogenesis [15] is highly expressed in cardiac tissue due to the actions of intra- and extracellular factors, including ROS and AMP-activated protein kinase (AMPK) [16].

There is evidence that alterations in mitochondrial biogenesis coactivators, such as PGC-1α contribute to the emergence of a number of metabolic and neurodegenerative diseases due to the impairment in energy regulation [17–19]. According to Kemper et al., estrogen can stimulate mitochondrial biogenesis and favors oxidative balance through ROS regulation [20]. In addition, Barbosa et al. [21] showed that lower estradiol levels decrease PGC-1α and TFAM expression in the muscle of young rats.

Nutritional deficits during pregnancy affect maternal mitochondria, and these changes are expected to extend through the next generation since females are responsible for the passage of mitochondrial DNA to offspring. Therefore, regulatory molecules that affect bioenergetics, including transcription factors, could be damaged by maternal malnutrition and passed to the next generation without undergoing repair [22]. Although such metabolic-related consequences have received considerable attention, there is a scarcity of literature investigating the effects of maternal protein restriction on metabolic impairments in subsequent generations, examining cardiac mitochondrial biogenesis as a possible cross-generational effect. In this study, we sought to evaluate the effects of maternal protein restriction on oxidative balance and transcription factors for mitochondrial biogenesis in the hearts of young female rats of both F1 and F2 generations.

2. Materials and methods

2.1. Animals and diet

The present study was approved by the local Ethics Committee for animal experimentation from the Biosciences Center of the Federal University of Pernambuco (Process number: 0026/2017). Manipulation and animal care of animals followed the recommendations of the *Guide for the Care and Use of Laboratory Animals* from the National Institutes of Health. Eight pregnant *Wistar* rats were divided into two groups according to diet: normoprotein (NP, 17% casein) and low-protein (LP, 8% casein) [23]. Rats were mated 2 females:1 male and received their respective diets during gestation and lactation. At weaning (21 days of age), offspring received commercial chow (Presence) and water ad libitum. Some of the female offspring were sacrificed at 30 days for molecular and biochemical analysis and consisted of two groups of the first generation (F1): NP-F1 (n = 5 per group) and LP-F1 groups (n = 5 per group). The rest of the female offspring were bred at 70 days of age at the same ratio mentioned above to generate the second generation (F2). Pregnant rats though the F1 generation were re-exposed or not to the nutritional insult, composing four new groups: F2 re-exposed to NP and LP diets (NP-F2, n = 6 per group and LP-F2, n = 6 per group) and F2 fed commercial chow (Labina) (NP-F2L n = 6 per group and LP-F2L, n = 6 per group). Only the female offspring of these groups were sacrificed at 30 of age for biochemical and molecular analysis. A schematic representation of the experimental design is shown in Fig. 1.

2.2. Tissue collection and homogenization

At 30 days of age, female rats from both F1 and F2 generations were used for cardiac tissue collection, and the left ventricles were homogenized in cold extraction buffer (100 mM Tris base, pH 7.4; 1 mM EDTA; 10 mM sodium orthovanadate; 2 mM phenylmethylsulfonylfluoride (PMSF); 1% Nonidet). After homogenization, samples were centrifuged at 4 °C at 1180 ×*g* for 10 min, and supernatants were used for protein quantification according to the Bradford method [24].

2.3. Oxidative stress biomarkers

Lipid peroxidation was evaluated by measuring malondialdehyde formation (MDA) according to Buege [25]. Results are expressed as mmol TBARS/mg of protein. Protein oxidation was evaluated by incubation of samples with guanidine hydrochloride according to Levine [26]. Absorbance was measured spectrophotometrically at 380 nm, and data are expressed as mmol carbonyl/mg of protein.

2.4. Enzymatic defense

Superoxide dismutase (SOD) activity was evaluated using autooxidation of epinephrine according Misra [27]. Catalase (CAT) activity was evaluated according to Aebi [28] at 240 nm. Glutathione-S-transferase (GST) was evaluated according to Habig [29]. All results are expressed as U/mg protein.

2.5. Non-enzymatic defense

Reduced glutathione (GSH) content was measured using the method of Hissin and Hilf [30]. Fluorescence intensity was measured using a spectrofluorimeter at 355 nm excitation and 460 nm emission. A standard GSH curve with known concentrations was used for calibration. Results are expressed as μmol/mg protein.

Quantification of sulfhydryl (total thiol) groups was based on the reduction of 5,5′-dithio-bis (2-nitrobenzoic acid) (DTNB). Absorbance at 412 nm was measured and results are expressed as mmol/mg protein [31].

2.6. mRNA evaluation

Total RNA was extracted from heart tissues using TRIzol reagent and the guanidine isothiocyanate method [32] according to the manufacturer's instructions (Invitrogen, Carlsbad, CA, USA). RNA pellets were washed in 75% ethanol and centrifuged at 7500 ×*g* for 5 min at 4 °C, air-dried and dissolved in DEPC-treated ultrapure water. RNA quantification was performed in a NanoDrop 2000 spectrophotometer (Thermo Scientific, US), and purity was assessed using the ratio of 260/280 nm absorbance [33]. Real-time polymerase chain reaction (RT-PCR) experiments for β2-microglobulin (β2M), AMPK, PGC1-α and TFAM genes were performed using the SuperScript® III Platinum® SYBR® Green One-Step qRT-PCR Kit (Invitrogen, USA) [34]. Samples (n = 5 per group) were processed in duplicate, and the cycle threshold (Ct) values of each targeted gene were normalized to the β2M Ct determined in an identical sample. Relative mRNA expression was determined using the $2^{-\Delta\Delta Ct}$ method [35] (Table 1).

2.7. Statistical analysis

All data were analyzed for normality of distribution by the Kolmogorov-Smirnov test followed by two-way ANOVA and Tukey's test to assess differences among groups. Data are expressed as the mean ± SEM and differences were considered significant at $p < 0.05$ for all analyses. Statistical analyses were performed using GraphPad Prism software 6.0 (GraphPad Software Inc., La Jolla, CA, USA).

3. Results

3.1. Oxidative stress biomarkers

MDA (Fig. 2A) was decreased by 49% in the LP-F1 group compared

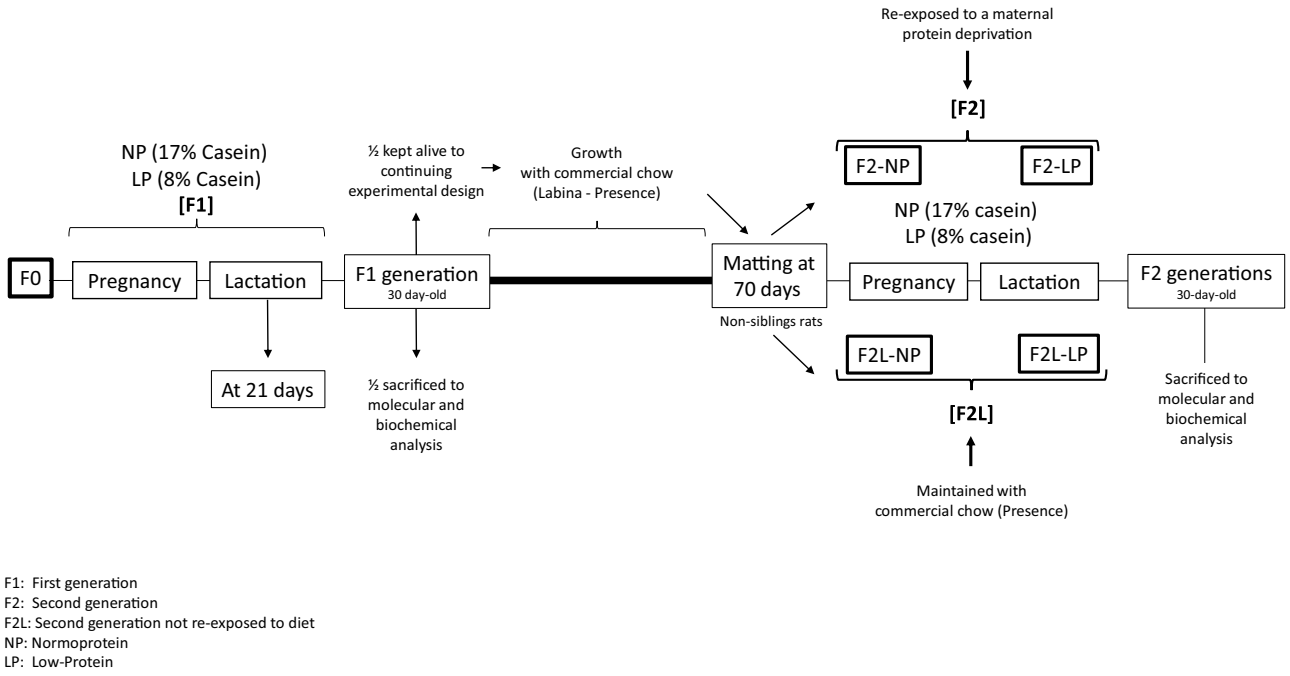

Fig. 1. Schematic representation of the experimental model.

to the NP-F1 group ($p < 0.001$). In the F2 generation, MDA was reduced by 59% in the LP-F2 group compared to the NP-F2 group ($p < 0.001$) (Fig. 2A). In contrast, F2L offspring of either LP or NP group exhibited no differences in MDA levels between NP and LP as in the parent generation. MDA levels in the NP-F2L group, however, were reduced by 64% ($p > 0.0001$) and 53% ($p = 0.0067$), respectively, compared to NP-F1 and NP-F2 groups.

There were no significant differences in protein oxidation induced by diet when comparing LP vs NP animals in their respective generations. However, there were significant differences in protein oxidation in both F2 generations compared to F1 animals. Strikingly, carbonyl content in the F2 groups was significantly lower than in F1 and F2L groups when comparing NP and LP animals to their respective counterparts in the other generations, and in the F2L groups, carbonyl content was significantly higher than in their counterparts in the F1 generation (Fig. 2B).

3.2. Enzymatic antioxidant defense

There was a 79% increase in SOD activity in the LP-F1 group compared to the NP-F1 group ($p = 0.036$) (Fig. 3A). However, this difference did not persist into the F2 generation, regardless of diet. With respect to differences between generations, NP-F2 and LP-F2 groups showed significantly increased SOD activity compared to their respective F1 groups (Fig. 3A). Similar to SOD, CAT activity was significantly increased by approximately 40% in the LP-F1 group compared to the NP-F1 group ($p = 0.023$). Additionally, similar to SOD results, differences in CAT between offspring born to LP-F1 and NP-F1 mothers, respectively, were eliminated in the F2 generation. Furthermore, in both F2-L groups (LP-F2L and NP-F2L), CAT levels were significantly lower than in their respective F2 counterparts (LP-F2 and NPF2) (Fig. 3B). GST activity was no difference between LP and NP animals in either the F1 or F2 generations. However, GST in the NP-F2L group was increased 6-fold compared to NP-F1 ($p < 0.0001$). GST was also decreased by a similar amount in LP-F2 compared to LP-F2L ($p < 0.0001$) (Fig. 3C).

3.3. Nonenzymatic antioxidant defense

GSH content was increased in LP-F2 by 546% compared to LP-F1 ($p < 0.0001$) and increased in NP-F2 by 491% compared to NP-F1 ($p < 0.0001$) (Fig. 4A). Moreover, there was a small but significant increase in GSH in LP-F2 animals compared to NP-F2 animals (11%, $p = 0.019$). The F2L group showed no difference compared to the F1 group (Fig. 4A). Total thiol groups did not differ between diets in the F1 generation (Fig. 4B) but were significantly increased in LP compared to NP in F2 animals (73%, $p = 0.028$). In addition, both F2 groups exhibited significantly reduced thiol content compared to their respective F2L groups (42%, $p = 0.021$).

3.4. Regulation of factors involved in mitochondrial biogenesis

AMPK was significantly reduced (60%, $p < 0.0001$) by LP compared to NP in the F1 generation but not in animals from F2 generations. However, both F2 and F2L animals possessed significantly reduced AMPK content compared to their respective LP counterparts in the F1 generation (Fig. 5A). Concerning regulation of PGC-1α expression by maternal protein deprivation (Fig. 5B), our results revealed that LP-F1 and LP-F2L had significantly higher levels of this transcription factor than NP-F1 (340%, $p < 0.0001$) and NP-F2L (89%, $p = 0.0009$)

Table 1
Primers used to PCRs analyze.

Gene	Forward sequence (5′ to 3′)	Reverse sequence (5′ to 3′)	Temp (°C)
β2M	TGACCGTGATCTTTCTGGTG	ACTTGAATTTGGGGAGTTTTCTG	48.0
AMPK	ACCATTTAACTCGGCCTCAC	TTGCTCTACACACTTCTGCC	48.0
PGC-1α	AACAGCAAAAGCCACAAAGA	AAGTTGTTGGTTTGGCTTGA	48.0
TFAM	TCTCATGATGAAAAGCAGGCA	GAGATCACTTCGCCCAACTT	48.0

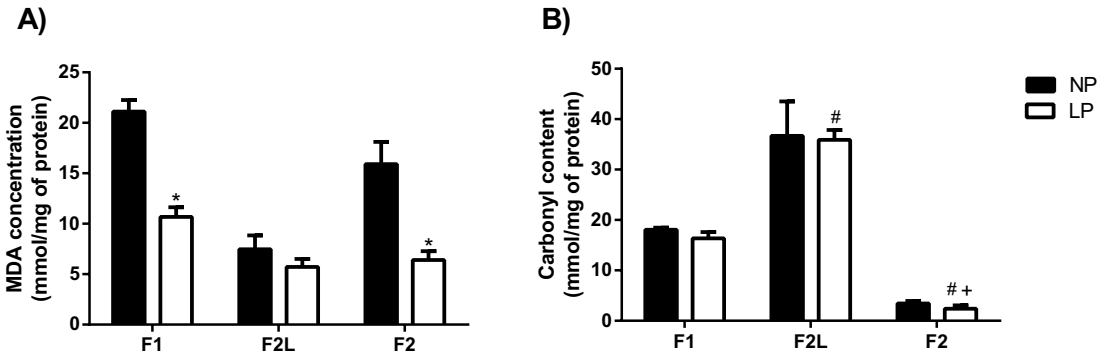

Fig. 2. Levels of lipid peroxidation (A) and protein oxidation (B) in hearts of 30-day-old female rats of F1, F2L and F2 groups. Values are presented as the mean ± SEM compared using two-way ANOVA. *p < 0.05 vs NP of the respective group; #p < 0.05 vs LP-F1; +p < 0.05 vs LP-F2L. LP = low protein group; NP = normoprotein group; F1 = first generation; F2L = second generation without protein deprivation re-exposure; F2 = second generation with protein deprivation re-exposure.

animals. Contrary to the results in F1 animals, LP-F2 animals exhibited decreased PGC-1α (21%, p = 0.0258), but levels were still increased compared to LP-F1 animals (83%, p > 0.0001). TFAM expression was decreased in LP-F2L animals compared to NP-F2L animals (42%, p = 0.0069) and was increased in LP-F2 compared to LP-F1 (160%, p = 0.0037) (Fig. 5C).

4. Discussion

4.1. Effect on oxidative stress

In marked contrast to our earlier findings with male rats born to and nursed by dams on either an LP or NP diet [6], we observed decreased lipid peroxidation (approximately 50%) in LP offspring from F1 and F2 generations compared to NP offspring from the same generation. Remarkably, the same LP regimen significantly elevated oxidized lipid levels by approximately 50% compared to respective NP controls in *male* offspring [6]. Another study from our group [9] seemed to indicate distinct estrogen levels between males and females as an explanation for this difference. In that study, we observed that newly weaned female rats from the LP group showed a 2-fold increase in MDA levels [9]. However, at maturity, female offspring of the LP group exhibited decreased MDA levels (50%) compared to the NP group. Our present results suggest that they reflect the effect of a maternal LP diet on MDA in fully mature rats with elevated estradiol levels, rather than the effect in weanlings with much lower levels of estrogen.

Continuation of the LP diet into the F2 generation, in turn, maintained the reduction in lipid peroxidation. In contrast, F2L animals from either LP or NP mothers did not present lipid peroxidation when compared to each other. These results suggest that the effects of

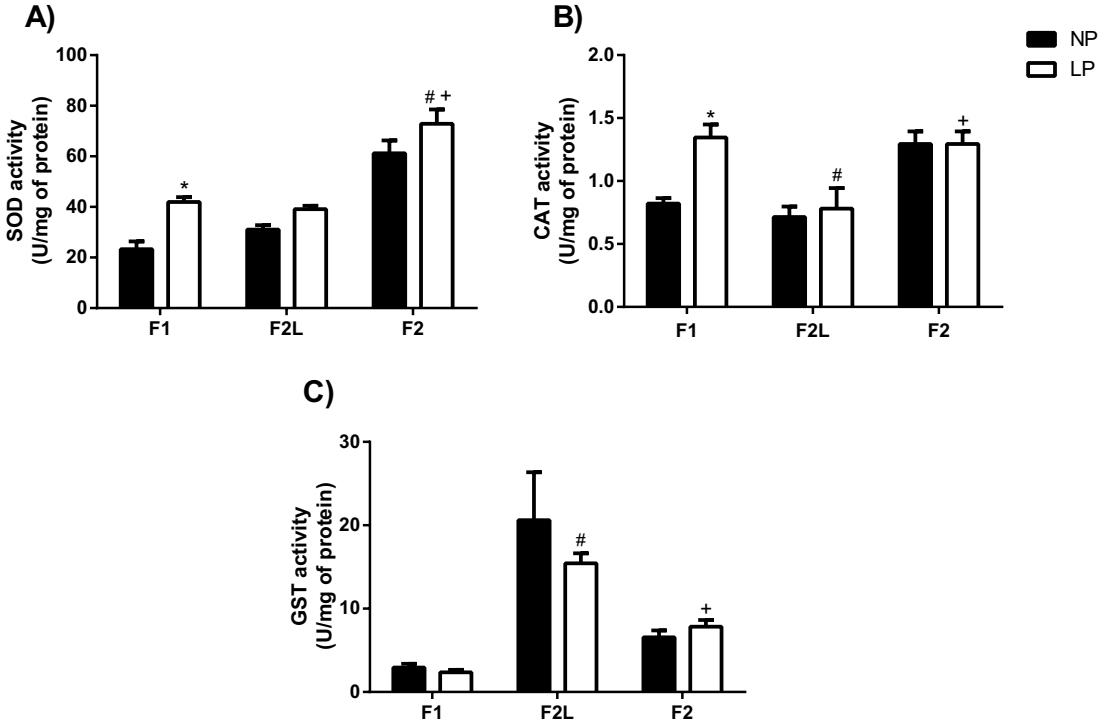

Fig. 3. Enzymatic antioxidant activity. Superoxide dismutase (SOD) activity (A), catalase (CAT) activity (B) and glutathione - S – Transferase (GST) activity (C) in the hearts of 30-day-old female rats from F1, F2L and F2 groups. Values are presented as the mean ± SEM compared using two-way ANOVA. *p < 0.05 vs NP of the respective group; #p < 0.05 vs LP-F1; +p < 0.05 vs LP-F2L. LP = low protein group; NP = normoprotein group; F1 = first generation; F2L = second generation without protein deprivation re-exposure; F2 = second generation with protein deprivation re-exposure.

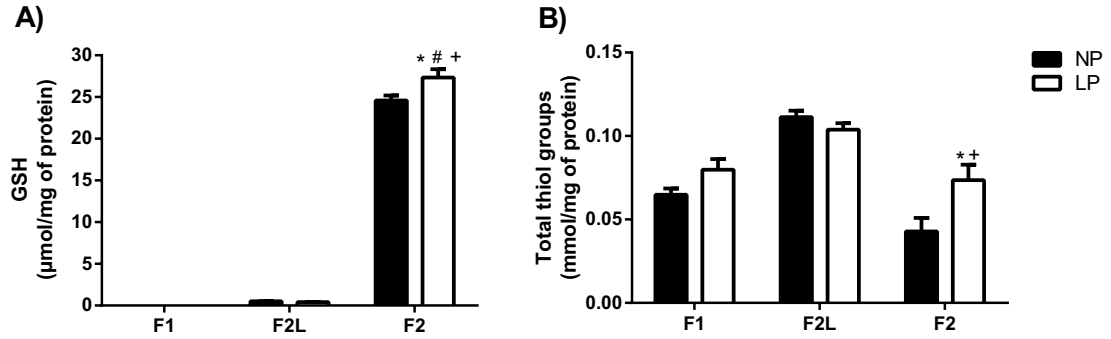

Fig. 4. Nonenzymatic antioxidant defense. Levels of reduced glutathione (GSH) (A) and total thiol groups (B) in the heart of 30-day-old female rats of F1, F2L and F2 groups. Values are presented as the mean ± SEM compared using two-way ANOVA. *$p < 0.05$ vs NP of respective group; $^{\#}p < 0.05$ vs LP-F1; $^{+}p < 0.05$ vs LP-F2L. LP = low protein group; NP = normoprotein group; F1 = first generation; F2L = second generation without protein deprivation re-exposure; F2 = second generation with protein deprivation re-exposure.

maternal LP on lipid peroxidation evident in first generation offspring are not continued into the next generation (F2) unless the low protein diet is maintained in F1 individuals. In fact, our results fail to support an intergenerational effect of maternal LP on most of the oxidative parameters that we examined, as significant differences in those parameters observed in the F1 generation were eliminated in the F2L generation. Specifically, significant differences in MDA, SOD and catalase activity between F1 animals from LP or NP mothers were eliminated in the F2 generation when their F1 mothers were returned to standard chow diet. This would suggest that despite the matrilineal inheritance of most mitochondria, damage to the health of individuals born from malnourished mothers was not continued into the next generation when their inadequate diet was corrected.

Protein oxidation as measured by carbonyl levels did not differ with respect to diet in either the F1 or F2 groups. These results disagree with those of Banos-Gomez, who showed that protein carbonylation was significantly increased by in utero malnutrition in rat hearts. One possible reason for this discrepancy is that Banos-Gomez used mixed male/female groups in their studies, whereas our experimental and control groups were entirely composed of females and therefore, were presumably exposed to the protective effects of estrogen [9,36]. Supporting this idea, we previously demonstrated that carbonyl content was increased by about two-fold in weanling female rats from LP mothers and were unchanged in female offspring born to LP mothers when measured in adulthood after high estrogen levels had been achieved [9].

In addition, nonenzymatic antioxidant defenses as measured by GSH level and thiol groups in the F1 offspring did not differ between LP and NP offspring. Remarkably, however, nonenzymatic defenses were significantly increased in F2 rats raised in an LP maternal background compared to those raised in an NP background, possibly because of exposition to an LP environment for two generations. GSH content was increased only slightly in LP-F2 compared to NP-F2, but thiol content was increased by >50%. These data suggest that even with possible damage from the LP diet over two generations in a row, the LP environment may have induced a compensatory increase in nonenzymatic defenses that helped ameliorate further oxidative damage.

4.2. Effects on mitochondrial biogenesis

AMPK is a cellular energy manager that controls energetic homeostasis and signaling in the heart [39]. AMPK was significantly reduced in F1-LP compared to F1-NP, suggesting that offspring of the malnourished females lost the positive effect induced by AMPK activation [40], but this reduction in AMPK may be compensated for or modulated by increased PGC1α expression.

Maintenance of mitochondrial function in response to fluctuating energy demands depends on adequate mitochondrial biogenesis or production of new mitochondria, which can be coactivated by peroxisome proliferator-activated receptor coactivator alpha (PGC-1α) [37]. PGC-1α is highly expressed in organs with high energy demand, elevated oxidative metabolism and high β-oxidation of fatty acids, such as the heart [38]. PCG-1α was up regulated in LP-F2L and LP-F2 groups compared to LP-F1L. Increased mitochondrial biosynthesis in response to PGC-1α elevation could help compensate for LP-induced damage in both F1 and F2 offspring who were returned to a normal diet (F2L) after being born to malnourished mothers. Given that re-exposure of F2 animals to the LP environment had distinct effects when compared between generations or nutritional insult, TFAM expression was assessed to better understand our data.

We showed that LP-F2L animals exhibited reduced TFAM expression compared to NP-F2L and LP-F2 animals with increased TFAM

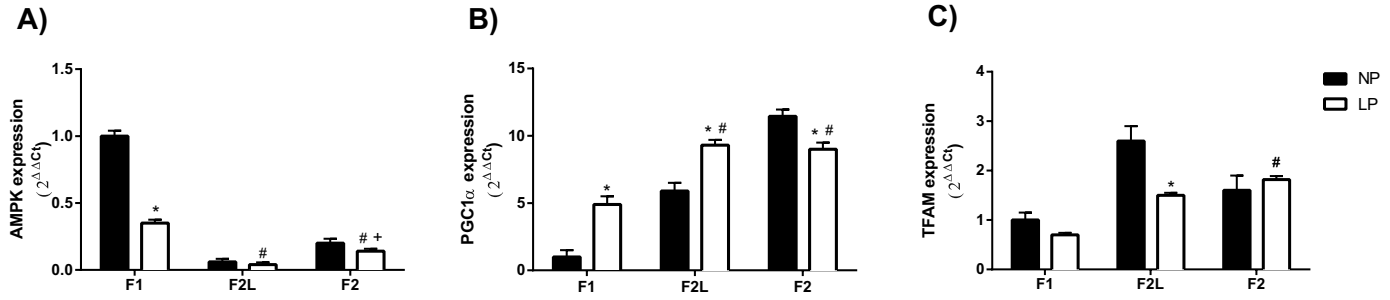

Fig. 5. Gene expression of AMPK (A), PGC-1α (B) and TFAM (C) in the hearts of 30-day-old female rats of F1, F2L and F2 groups. Values are presented as the mean ± SEM compared using two-way ANOVA. *$p < 0.05$ vs NP of the respective group; $^{\#}p < 0.05$ vs LP-F1; $^{+}p < 0.05$ vs LP-F2L. LP = low protein group; NP = normoprotein group; F1 = first generation; F2L = second generation without protein deprivation re-exposure; F2 = second generation with protein deprivation re-exposure.

expression compared to LP-F1. Taken together, our data suggest that PGC-1α may have temporal effects in inducing mitochondrial biogenesis promoter responses. By the time of mRNA evaluation, TFAM expression may no longer be necessary for mitochondrial biogenesis stimulation in LP-F2L animals, suggesting positive adaptation to nutritional re-establishment. In addition, even with the decrease of PGC-1α levels in LP-F2 animals, TFAM remained at the same level as the control group, suggesting that mitochondrial biogenesis may play a crucial role in the defense of cardiac tissue.

5. Conclusions

The present results suggest that nutritional insult during the critical early period of development encompassing gestation and nursing does not induce oxidative stress in the heart of female rats, possibly due to the protective effect of estrogen. In addition, low maternal protein levels sustained across two generations resulted in significant upregulation of antioxidant defenses that were not activated in the earlier generation. Taken together, our study suggests that despite the potential mitochondrial 'inheritance' of cardiovascular damage caused by maternal malnutrition, damage is not cross generational and can be eliminated with proper nutrition in the F1 generation.

Declaration of Competing Interest

None.

Acknowledgments

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