HHS Public Access

Author manuscript

Neuroreport. Author manuscript; available in PMC 2016 May 27.

Published in final edited form as:

Neuroreport. 2015 May 27; 26(8): 467–472. doi:10.1097/WNR.0000000000000371.

Lifelong Parental Voluntary Wheel Running Increases Offspring Hippocampal *Pgc-1α* mRNA Expression But Not Mitochondrial Content or *Bdnf* Expression

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Abstract

When exercise is initiated during pregnancy, offspring of physically active mothers have higher hippocampal expression of brain derived neurotrophic factor (*Bdnf*) and other plasticity and mitochondrial-associated genes, resulting in hippocampal structural and functional adaptations. In the present study, we examined the effects of lifelong parental voluntary wheel running (before, during, and after pregnancy) on offspring hippocampal mRNA expression of genes implicated in the exercise-induced improvement of cognitive function. C57BL/6 mice were individually housed at 8 weeks of age with (EX; n=20) or without (SED; n=20) access to a computer-monitored voluntary running wheel (VRW) for 12 weeks prior to breeding. EX breeders maintained access to the VRW throughout breeding, pregnancy, and lactation. Male offspring were housed in sedentary cages, regardless of parental group, and were sacrificed at 8 (n=18) or 28 weeks (n=19). PCR was used to assess mRNA expression of several genes and mitochondrial content (ratio of mitochondrial to nuclear DNA) in hippocampal homogenates. We found significantly higher peroxisome proliferator-activated receptor γ coactivator 1 alpha (*Pgc-1α)* mRNA expression in EX offspring compared to SED offspring at 8 wks (p=0.04), though the effect was no longer present at 28 wks. There was no difference in mitochondrial content or expression of *Bdnf* or any other mRNA targets between offspring at 8 or 28 wks. In contrast to exercise initiated during pregnancy, parental voluntary physical activity initiated early in life and maintained throughout pregnancy has little effect on offspring mRNA expression of genes implicated in exercise-induced hippocampal plasticity.

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Competing interest

None declared

Authors' contributions.

ACV, LMG, EES, and SMR designed the study; ACV and LMG collected the data; data analysis, preparation of figures, and drafting the manuscript was done by ACV; ACV, LMG, EES, and SMR edited and revised this manuscript; and all authors approved the final version.

Keywords

Brain derived neurotrophic factor; BDNF; PGC-1; Exercise; Pregnancy; Offspring; Hippocampus

Introduction

Physical exercise during pregnancy improves health-related outcomes in both mother and offspring [1–3]. In the pregnant mother, exercise can reduce the risk of gestational diabetes, preeclampsia, and excessive gestational weight gain, conditions associated with negative health outcomes in the offspring [2]. Remarkably, exercise during pregnancy also impacts offspring brain health both in early postnatal development and adulthood [4–11]. In humans, *in utero* exercise exposure is associated with greater cognitive performance in early postnatal development [10] and higher intelligence scores at 5 years of age [9] relative to children of mothers that did not exercise during pregnancy. Numerous studies in rodents show that *in utero* exercise exposure increases hippocampal expression of brain derived neurotrophic factor (Bdnf) [4; 5; 7; 12]; cell proliferation and neuron differentiation [5; 6]; increased mitochondrial content and expression of genes associated with mitochondrial biogenesis [13]; and improved performance on spatial [4; 8] and non-spatial memory tasks [5; 7; 14]. In addition to the influence of maternal exercise, long-term paternal forced exercise enhances male offspring neurotrophin expression and spatial learning and memory performance [15], suggesting transgenerational inheritance of exercise effects beyond direct *in utero* exposure. There is remarkable consistency between the effects of *in utero* and adult exercise exposure on the hippocampus. For example, adult exercise exposure increases Bdnf protein and mRNA expression, enhances neurogenesis and cell survival, increases mitochondrial content, and improves learning and memory [reviewed in 16; 17]. Further, exercise lowers the risk of Alzheimer's disease (AD) in humans and reduces pathology after disease onset in transgenic animals [18]. Similar results are observed following *in utero* exercise exposure in AD transgenic mice [19].

To examine the impact of parental exercise on offspring hippocampal phenotype, researchers have primarily initiated maternal exercise during pregnancy, rather than prior to gestation. Exercise during pregnancy is useful for highlighting the specific effect of *in utero* exercise exposure; however, though beginning exercise during pregnancy is recommended [2], only a low percentage of women report being more active during pregnancy than before [20]. As the physical changes that occur during pregnancy favor a sedentary lifestyle, it is more likely that women who exercise regularly will continue to exercise during pregnancy, while women who are sedentary prior to pregnancy will remain sedentary. Thus, examining the impact of exercise prior to and during pregnancy on offspring phenotypes is important to understand the effectiveness of *in utero* exercise exposure for enhancing brain health. For this reason we investigated the influence of lifelong parental exercise on offspring hippocampal gene expression and mitochondrial copy number at two different offspring ages. Our gene targets were specifically selected based on previous literature reporting sensitivity to adult exercise training and/or *in utero* exercise exposure and we hypothesized that mRNA for *Bdnf* (and related processing and signaling markers), growth factors, the mitochondrial biogenesis regulator peroxisome proliferator-activated receptor γ coactivator

1 α (*Pgc-1α*), and synaptic markers would be elevated in offspring of lifelong physically active parents.

Methods

Animals and Experimental Design

All animal procedures were performed in accordance with the National Institutes of Health guidelines and were approved by the Institutional Animal Care and Use Committee at the University of Maryland. This investigation was part of a larger investigation designed to examine whole body and tissue (skeletal muscle, white adipose, liver) metabolic phenotypes in multiple generations of offspring of exercised vs. sedentary parents. The availability of these mice offered a unique opportunity to test an equally important yet unrelated hypothesis that lifelong parental physical activity increases plasticity associated mRNA expression in offspring hippocampus.

Twenty male and twenty virgin female eight-week-old C57BL/6J mice (Jackson Laboratories, Bar Harbor, ME, USA) were randomly separated into individual cages with (F_0 EX) or without (F_0 SED) access to a computer monitored running wheel (Lafayette Instruments, Lafayette IN). Though individual housing may influence behavior and hippocampal plasticity it does not influence rodent running behavior [21] and is consistent with previous investigations of maternal exercise [4–8]. After 12 weeks of voluntary wheel running, males were randomly housed with females from like groups (1 male and 1 female per cage; EX with EX and SED with SED). During the breeding period, both males and females in the EX mating group maintained running wheel access; however, running activity could not be monitored during this period. Males were removed after pregnancy was visually confirmed by vaginal plug or after 2 weeks of pairing. EX females maintained running wheel access during pregnancy and lactation. Two F_0 EX breeding pairs did not produce viable F_1 offspring. The resulting offspring made up the F_1 generation. Average litter size for F_1 offspring was 6.1 ± 0.6 EX and 6.4 ± 0.5 SED offspring/litter; there was no significant difference in litter size between groups. Litters with 8 or fewer offspring were included for analysis. Only male offspring are presented due to fewer female mice available from exercised parents compared to sedentary parents. F_1 males were weaned at 21 days of age, group-housed in standard cages without running wheel access and were sacrificed at 8 (n=18) or 28 weeks (n=19). The animals sacrificed at 28 weeks were bred at 8 weeks of age and individually housed thereafter until sacrifice. No more than 3 offspring per litter were studied per age group. A standard diet (Purina Mills LLC, St. Louis, MO, USA; RMH 3000; 60% carbohydrate, 14% fat, and 26% protein) and water were provided *ad libitum* to animals of all experimental groups.

Tissue Collection & Processing

Twenty-four hours prior to sacrifice, all F_1 mice were exposed to intraperitoneal glucose tolerance testing. This procedure was performed to address the overall hypothesis of the investigation, though the data will not be discussed in this report. Euthanasia by exsanguination by cardiac puncture followed by removal of the heart was performed under isoflurane anesthesia. The hippocampus was isolated, halved, and immediately frozen in

liquid nitrogen. Prior to nucleic acid isolation, hippocampi were homogenized using a glass Dounce homogenizer. Total RNA was isolated with TRIzol reagent (Life Technologies, Grand Island, NY, USA) following manufacturers instructions and quantified via spectrophotometry. Reverse transcription was performed with 1 μg of total RNA with the High-Capacity cDNA RT kit (Life Technologies). Following RNA isolation DNA was isolated from TRIzol reagent and quantified via spectrophotometry.

Gene Expression

Real-time quantitative PCR was used to assess mRNA expression of total brain derived neurotrophic factor (*Bdnf*; exon IX), *Bdnf* exon IV (*Bdnf IV*), *Pgc-1α,* tissue plasminogen activator (*tPa*), and glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*; expression control). Primer and probe sequences were purchased pre-made *(Pgc-1α, tPa, Gapdh)* or designed (*Bdnf IX, Bdnf IV*) for the mRNA sequence of each gene using Integrated DNA Technologies' PrimeTime qPCR Assay designer. Primer sequences are listed in Supplemental Table 1. *Bdnf IV, Pgc-1α, tPa,* and *Gapdh* primer pairs spanned exons to prevent amplification of genomic DNA. Because *Bdnf* total is represented by amplification of exon IX, the protein coding exon that is present in each transcript, this primer pair could not span exons. Efficiency for each primer:probe assay was determined prior to use. RT-PCR was used to measure the expression of insulin like growth factor 1 (*Igf1*), vascular endothelial growth factor (*Vegf*), neurotrophic tyrosine kinase receptor type 2 (*TrkB*), calpactin (*p11*), synapsin 1 (*Syn1*), synaptobrevin (*Vamp2*), synaptotagmin 1 (*Syt1*), and synaptophysin (*Syp*). *Gapdh* was used as an expression control for RT-PCR. All RT-PCR primers were designed to span exons.

Mitochondrial Copy Number

DNA was subjected to real-time quantitative PCR and comparison of *β-actin* and *cytochrome b* amplification was used to determine the relative amounts of nuclear and mtDNA, respectively. These primer:probe assays were purchased pre-made from Integrated DNA Technologies and efficiency tested prior to use. Primer sequences are listed in Supplemental Table 1.

Statistical Analysis

Unpaired t-tests were used to compare gene expression between EX and SED groups within age using SAS version 4.2. One-tailed t-tests were used to examine *Bdnf* mRNA expression, *Pgc-1α* mRNA expression, and mitochondrial copy number. Two-tailed t-tests were used to examine all other mRNA targets. Significance was achieved at $p<0.05$.

Results

F_0 Wheel Activity

Running data for the F_0 breeders are shown in Figure 1. Peak running was achieved during week 4 (6689 meters/24hrs) for males and week 2 for females (7209 meters/24hrs). In males there was a steady decline in running activity until the final week, when the lowest running distances were recorded (1505 meters/24hrs). In females, lowest activity was recorded

during pregnancy (347 meters/24hrs). Running activity increased to pre-pregnancy levels following pregnancy.

F_1 Eight-Week Offspring Outcomes

Hippocampal gene expression data for F_1 8-week offspring are shown in Figure 2. Eight-week old offspring of EX parents had significantly higher *Pgc-1α* mRNA expression compared to offspring of SED parents (p=0.04, Fig. 2a). We observed no significant differences between offspring of EX and SED parents in any other targets measured (Fig. 2b). There was no effect of parental exercise on offspring *Gapdh* expression (confirmed with both qPCR and gel-based RT-PCR). We also observed no differences between offspring of EX and SED parents in mitochondrial copy number (Figure 3).

F_1 Twenty-Eight Week Offspring Outcomes

Hippocampal gene expression data for F_1 28 week are shown in Figure 4. The difference in *Pgc-1α* mRNA expression observed in 8-week old animals was no longer present in the 28-week old offspring. We observed no differences any mRNA target between 28-week old offspring of EX and SED parents. There was no effect of parental exercise on offspring *Gapdh* expression (confirmed with both qPCR and gel-based RT-PCR). We observed no differences in mitochondrial copy number between 28-week-old offspring of EX and SED parents (Fig. 3).

Discussion

We report here that parental exercise training prior to, during, and after (lactation) gestation results in greater hippocampal *Pgc-1α* gene expression at 8 weeks of age in male EX offspring that returns to baseline by 28 weeks of age. This change in *Pgc-1α* expression was not accompanied by higher mitochondrial copy number, as might be expected based on the known role of *Pgc-1α* in mitochondrial biogenesis [22; 23]. In contrast to previous studies initiating exercise during pregnancy, we observed no significant difference in *Bdnf* mRNA expression between offspring of EX and SED parents at 8 or 28 weeks of age.

Maternal exercise beginning during pregnancy has numerous health benefits to offspring. In the offspring hippocampus, maternal exercise (whether swimming, treadmill running, or voluntary wheel running) beginning during pregnancy leads to changes in Bdnf mRNA and protein expression [4; 5; 7; 12], enhanced learning and memory performance [4; 5; 7; 8; 14], neurogenesis [5; 6], mitochondrial biogenesis, and mRNA expression of genes associated with mitochondrial biogenesis and oxidative metabolism [13]. We observed that maternal and paternal exercise beginning early in life and continuing through mating, gestation, and lactation resulted in no difference in male offspring hippocampal mRNA expression of any of our targets with the exception of *Pgc-1α*. *Pgc-1α* was elevated at 8 weeks in offspring of EX parents, though returned to baseline by 28 weeks. *Pgc-1α* is a co-transcription factor that is considered a regulator of mitochondrial biogenesis. When co-expressed with other tissue- and temporal-specific transcription factors, *Pgc-1α* stimulates the transcription of genes necessary for mitochondrial biogenesis [24]. *Pgc-1α* expression is induced in many tissues, including the brain, in response to physical exertion [17; 23]. Using three different exercise

durations, Park et al. [13] showed that offspring of treadmill-exercised mothers had more hippocampal mitochondria, determined by measuring mitochondrial DNA relative to nuclear DNA, and greater levels of Pgc-1α protein expression. This effect was observed in offspring of mothers who exercised the longest of three exercise durations. Even though we observed a significant effect of parental exercise on offspring *Pgc-1α* expression at 8 weeks, we did not observe an accompanying increase in mitochondrial content at 8 or 28 weeks. Potentially, we missed the window of observation for a change in mitochondrial content that took place between 8 and 28 weeks before returning to baseline.

Based on previous literature, we hypothesized that parental physical activity prior to, during, and after gestation would result in an increase in neurotrophin and growth factor mRNA expression, however this hypothesis was not supported. A number of studies have reported an effect of maternal and paternal exercise on offspring hippocampal *Bdnf* expression, though how long this effect persists still remains to be determined. Parnpiansil et al. [4] showed that treadmill exercise in pregnant rats resulted in greater offspring hippocampal *Bdnf* mRNA expression at post-natal (PN) day 0 (PN0), no difference at PN14, and significantly lower *Bdnf* expression at PN28. In contrast, Kim et al. [7] and Lee et al. [5] showed that *Bdnf* mRNA expression was elevated in offspring of treadmill- and swim-trained mothers, respectively, at 29 days after birth. Even though these studies reported significantly greater *Bdnf* expression in offspring of exercise mothers compared to offspring of sedentary mothers one month after birth, our youngest time point was two months of age which may explain why even in our youngest group of offspring, we observed no differences in neurotrophin (*Bdnf*) or growth factor (*Igf1* and *Vegf*) mRNA expression. Yin et al. [15] reported enhanced *Bdnf* expression (mRNA and protein) and spatial memory performance in ~one-month old male offspring of treadmill exercised male C57BL/6J mice. Again, this is much younger than our youngest group, suggesting the influence of parental exercise is relatively short-lived. It is important to note that the offspring in these studies, and in our study, were all sedentary and it is possible that offspring of physically active parents would maintain the benefits of parental physical activity if they themselves are provided access to exercise.

Though we did not observe differences in synaptic (*Syn1*, *Vamp2*, *Syt1*, *Syp*), neurotrophin (*Bdnf, Bdnf IV)*, neurotrophin receptor (*TrkB)*, posttranslational processor (*tPa, p11*), or growth factor (*Vegf, Igf1*) mRNA expression, structural adaptations may have occurred that were not represented by differences in mRNA expression. Bick-Sander et al [6] reported differences between offspring of exercise (beginning during pregnancy) and sedentary mothers in neuron survival and total granule cell numbers at PN36, despite no significant differences in mRNA expression of *Vegf, Fgf-2, or Igf1*. These data suggest lasting structural changes that are not mirrored by lasting differences in mRNA expression. Future studies are needed to determine if lifelong parental physical activity influences hippocampal structure and function in offspring in the absence of differences in mRNA expression.

In addition to the age at which the offspring were examined, another difference between our study and previous studies is the timing and mode of exercise exposure. We provided mice with a running wheel for 12 weeks prior to mating and pregnancy. Previous studies have used forced exercise modes such as swimming or treadmill running, which add additional

stress, but also have the benefit of controlled exercise duration (swimming and treadmill) and intensity (treadmill). Studies that have used voluntary wheel running have initiated exercise during pregnancy. In addition to the influence of novelty/enrichment, mice are very active in the first few weeks of wheel exposure, with declining activity thereafter (Fig 1). Compared to Bick-Sander et al. [6], who used the same strain of mice as our study, our pregnant mice ran much less. Between days 5 and 10 of pregnancy, mice in the Bick-Sander study ran between 2500 and 3000 meters/day, while in our study, pregnant mice ran less than 700 meters/day (see Fig 1). The dependence of the exercise volume is also supported by investigations using forced exercise. Park et al. [13] reported that offspring of the most active pregnant mice were significantly different than controls when hippocampal mitochondrial content, mitochondrial enzyme activity, and Pgc-1α protein expression were assessed.

A limitation of this investigation was the exposure of offspring to glucose tolerance testing, which may have added additional stress to the animals and influenced hippocampal gene expression. Weekly handling of our mice to prepare them for the stress of the GTT likely reduced the stress response, though we cannot rule out an influence of the procedure on gene expression. Another limitation of our study is that we did not observe and record maternal care, which can strongly influence hippocampal development and plasticity [25]. Though not a limitation of our study, it is possible that providing offspring access to a voluntary running wheel may expose an exercise-induced adaptation to parental exercise, which provides these mice with a plasticity advantage above offspring of sedentary parents. This is a question that should be addressed in future investigations.

We believe that our data, in the light of previously reported findings, suggest a high volume and/or intensity of physical activity during pregnancy must be maintained to observe the beneficial effects of maternal physical activity on hippocampal plasticity-associated gene expression and mitochondrial copy number. The steady decrease in voluntary wheel running observed over the 12 weeks prior to mating, in both parents, and during pregnancy in mothers, may have prevented the strong effect observed in other investigations. Treadmill exercise may be more effective at maintaining intensity and volume prior to and during pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

This work was supported by NIH grant HD062868, The College of Health and Human Performance Public Health Research Seed Money Program award (S.M.R. and E.E.S.), and NIH T32 AG000268 (A.C.V and L.M.G.).

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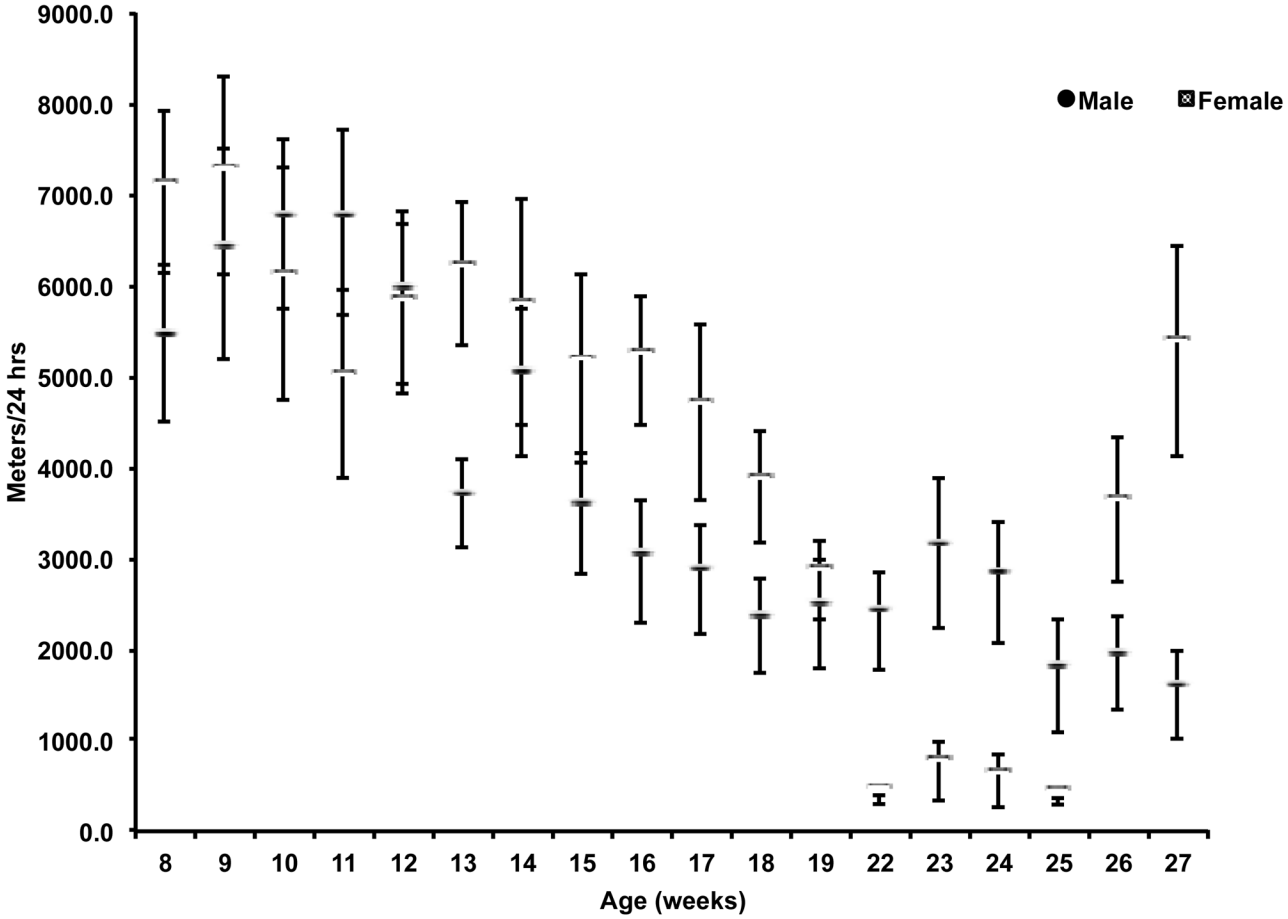

Figure 1.

Average running activity of mice. Data are shown as average distance run over 24 hours per week. Running data were not collected during mating due to the presence of two mice in the cage and the inability to determine which mouse was using the running wheel. The litters were delivered between 23 and 24 weeks on the timeline. There was a six-day span between first and last litter, thus pre-weaned mice had access to the wheel. We cannot rule out the possibility that pre-weaned mice are contributing to recorded wheel revolutions during week 27.

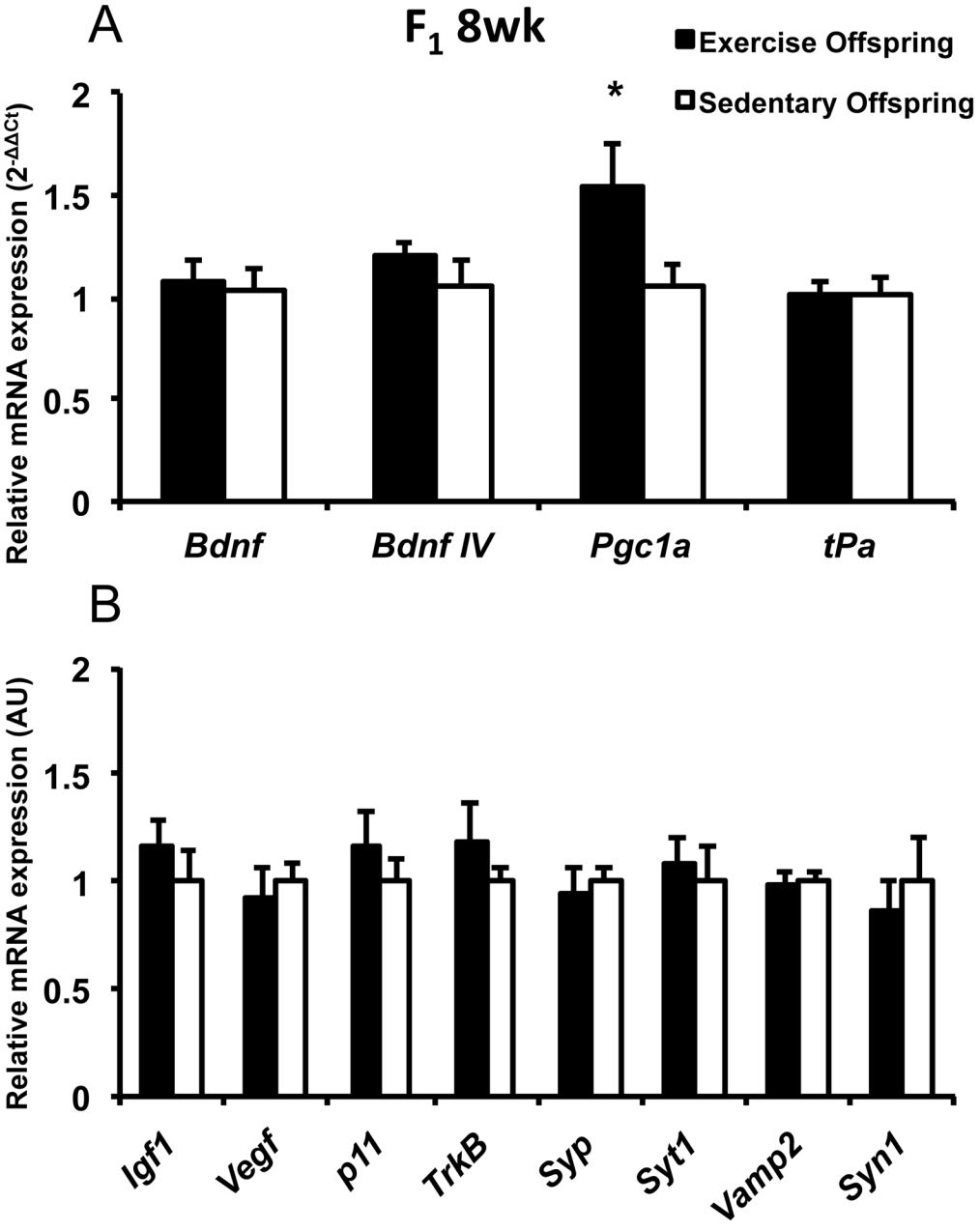

Figure 2.

(A–B). Whole hippocampal homogenate mRNA levels in F_1 8 week old male offspring of exercise (n=10) and sedentary (n=8) parents. Bars represent mean (±SEM) mRNA expression relative to *Gapdh* mRNA expression. * denotes significance at $p<0.05$.

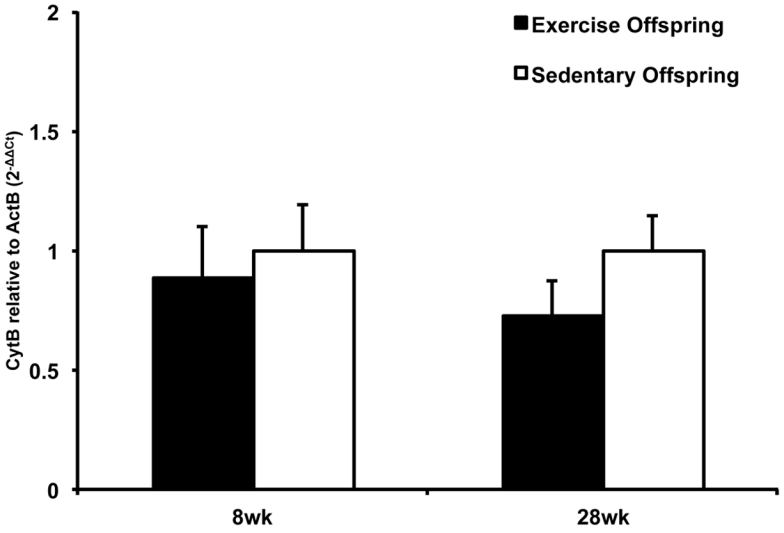

Figure 3.

Mitochondrial DNA content in F_1 8 wk and 28wk old male offspring of exercise and sedentary parents. There were no significant differences in *CytB* mitochondrial DNA content relative to *ActB* DNA content between offspring of exercise and sedentary parents at 8 weeks or 28 weeks of age. Results are means ±SEM.

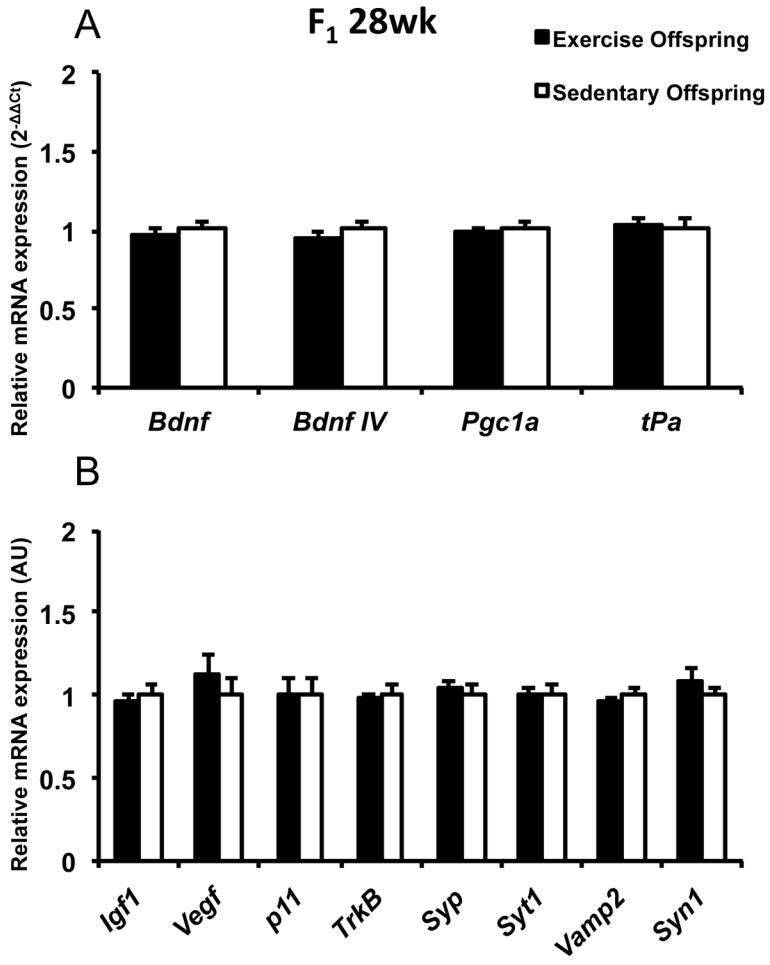

Figure 4.

(A–B). Whole hippocampal homogenate mRNA levels in F_1 28 week old male offspring of exercise (n=9) and sedentary (n=10) parents. Bars represent mean (±SEM) mRNA expression relative to *Gapdh* mRNA expression. * denotes significance at $p<0.05$.