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Region-specific differences in bioenergetic proteins and protein response to acute high fat diet in brains of low and high capacity runner rats

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Abstract

Aerobic capacity is a strong predictor of mortality. Low capacity runner (LCR) rats exhibit reduced mitochondrial function in peripheral organs. A high fat diet (HFD) can worsen metabolic phenotype in LCR rats. Little is known about metabolic changes in the brains of these rats, however. This study examined protein markers of mitochondrial function and metabolism as a function of aerobic running capacity and an acute HFD in four brain regions: the striatum, hippocampus, hypothalamus, and substantia nigra. After 3 days HFD or chow diets, we measured peroxisome proliferator-activated receptor- γ coactivator 1 α (PGC1- α), nuclear respiratory factors 1 (Nrf-1), mitochondrial transcription factor A (TFAM), and phosphorylated (activated) AMP-activated protein kinase (p-AMPK) protein levels in the four brain regions. LCR rats exhibited lower levels of mitochondrial proteins (PGC1- α , Nrf-1, TFAM), and greater p-AMPK, in striatum, but not in the other brain regions. Mitochondrial protein levels were greater in HFD LCR striatum,

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while p-AMPK was lower in this group. Markers of lower mitochondrial biogenesis and increased metabolic demand were limited to the LCR striatum, which nevertheless maintained the capacity to respond to an acute HFD challenge.

Keywords

intrinsic aerobic running capacity; acute high fat diet; mitochondrial proteins

Introduction

Low intrinsic aerobic capacity is linked to obesity, diabetes, and cardiovascular disease [1, 2]. To explore mechanisms that underlie this link, a novel rat model was developed through two-way artificial selection for either low (LCR) or high (HCR) capacity running performance [1, 3]. LCR rats exhibit metabolic syndrome, heart dysfunction, hepatic steatosis, decreased skeletal muscle oxidation, and decreased longevity [4, 5]. They also exhibit greater vulnerability to the adverse effects of a high fat diet (HFD), which is a metabolic stressor [6, 7]. Little is known, however, about the link between intrinsic aerobic capacity and mitochondrial function and energy metabolism in the brain. LCR rats exhibit markers of mitochondrial dysfunction and reduced energy metabolism in skeletal muscle, heart, and liver [4, 5, 8]. We wanted to determine the extent that these markers differ between LCR and HCR rats in the brain. Peripheral organs like the liver and skeletal muscle are responsive to the metabolic challenge of an acute HFD within 3 days [7, 9]. Therefore, we also wanted to determine whether an acute HFD affects these markers in the brains of LCR vs HCR rats as it does in these metabolically-sensitive peripheral organs. Metabolic syndrome and HFD have been linked to neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) [10, 11, 12]. We selected the substantia nigra and striatum due to the role of the nigrostriatal pathway in PD, the hippocampus due to its role in AD, and the hypothalamus due to its role in homeostasis. A long-term HFD has been reported to affect mitochondrial function in each of these brain regions [13, 14, 15, 16].

Material and Methods

1. Animals

Male rats (6–7 months) used in the current study were the same rats used in a recently-published study focused on peripheral measures [9]. Studies were approved by the Institutional Animal Care and Use Committees at the University of Kansas Medical Center, University of Michigan, the University of Missouri, and the Subcommittee for Animal Safety at the Harry S. Truman Memorial VA Hospital. The development of LCR and HCR rats has been described [3], and the rats in the current study were from generation 25. Animals were housed individually in a temperature controlled facility with 12:12 h light:dark cycles and provided standard chow diets (D12450B, 10% kcal from fat; Research Diets, New Brunswick, NJ) and water ad libitum upon arrival until the experimental diet was started. An attempt was made to balance LCR and HCR rats for body weights before assigning them to diet groups. The HFD group were then fed HFD (D12451, 45% kcal from fat; Research Diets) for 3 days (N=6 for each group except for HCR HFD, which had 5).

Body weights (g) before the 3-day diet were: HCR Chow (364.3 ± 11.2), HCR HFD (358.3 ± 10.0), LCR Chow (464.9 ± 14.5), LCR HFD (455.6 ± 12.7). As reported [9], food intake (g/day), energy intake (kcal/day), and weight gain (g/day) were greater for the HFD group within each strain, and were greatest in the LCR HFD group. When normalized to body weight, however, energy intake/day was greater in the HFD groups but did not differ between LCR and HCR rats.

2. Tissue harvest

After the acute diet phase, rats were anesthetized with sodium pentobarbital (50 mg/kg) and brains were removed and placed on an ice-cold brain block. Samples of striatum, hippocampus, hypothalamus and substantia nigra (SN) were carefully dissected, weighed, frozen on dry ice, and stored into -80°C for Western blotting analysis.

3. Western immunoblotting

For protein extraction, frozen brain tissue samples were diluted 15 times in cell extraction buffer (Invitrogen) with protease inhibitor cocktail (500 ul, Invitrogen), sodium fluoride (200mM), sodium orthovanadate (200mM), and phenylmethanesulfonylfluoride (200mM) added. Samples were placed on ice for 1 hour and vortexed every 15 min, then centrifuged at 3000g at 4°C for 20 min before supernatants were collected. Bradford assay determined protein concentration. Samples were diluted with HES buffer (20 mM HEPES, 1mM EDTA, 250 M sucrose, pH 7.4), and reducing sample buffer (0.3 MTris-HCL, 5% SDS, 50% glycerol, 100mM dithiothreitol, Thermo Scientific).

Individual samples from each rat were run on 10% SDS-PAGE gels and transferred to nitrocellulose membranes at 200 mA for 90 min. Nonspecific membrane binding sites were blocked using 5% milk for 1 hour. Membranes were incubated overnight with primary antibody at 4°C . Membranes were washed with TBST then incubated with horseradish peroxidase-conjugated secondary antibody for 1 hour at room temperature. Films were scanned at high resolution, and densitometry measurements were analyzed using Image J software. Protein content was normalized to β -actin. Antibodies from Cell Signaling (Beverly, MA) included: β -actin; phospho-AMP-activated protein kinase (AMPK) (T172), total AMPK; Nuclear factor E2-related factor 1 (Nrf1); (Mitochondrial transcription factor A), and TFAM. Antibody for peroxisome proliferator-activated receptor- γ coactivator 1 α (PGC-1 α) was obtained from Calbiochem (San Diego, CA).

6. Statistical analyses

All data are presented as means $\pm$ SEM and were analyzed using SPSS. Results were analyzed using a two-way (strain $\times$ diet) ANOVA followed by post hoc test. Significance was set at $p < 0.05$.

Results

In the striatum, PGC1- α was lower in chow-fed LCR than chow-fed HCR rats ($p < 0.01$; Fig. 1A). PGC1- α was greater in the striatum of HFD LCR group than in the chow-fed LCR group ($p < 0.01$). There were no significant differences in PGC1- α levels in the other three

brain regions (Table 1). Striatal Nrf-1 ($p<0.01$; Fig. 1B) and TFAM ($p<0.05$; Fig. 1C) protein levels were lower in the chow-fed LCR rats compared to HCR rats. Like PGC1- α , Nrf-1 ($p<0.05$) and TFAM ($p<0.01$) levels were greater in HFD LCR striatum than in chow-fed LCR striatum. Also like PGC1- α , these mitochondrial proteins did not differ between chow-fed LCR and HCR rats in the other brain regions (Table 1). The activated form of AMPK (p-AMPK) was significantly greater in LCR rat striatum compared to HCR rats in the chow group ($p<0.01$; Fig 1D). Within LCR rats, p-AMPK was lower in the HFD striatum than in the chow-fed striatum ($p<0.05$). p-AMPK did not differ in the other brain regions (Table 1).

Discussion

Here we report that in the striatum, LCR rats exhibit lower levels of mitochondrial proteins and greater levels of p-AMPK than HCR rats. An acute HFD negated these differences by making mitochondrial and p-AMPK protein levels in LCR striatum similar to those in HCR striatum. Striatal mitochondrial protein levels and p-AMPK levels did not differ between chow-fed and HFD-fed HCR rats. None of the proteins measured differed between strain or diet in the hippocampus, hypothalamus, or substantia nigra.

PGC1- α plays important roles in mitochondrial biogenesis, cellular metabolism, and resistance to oxidative stress [17, 18]. Nrf-1 is a transcriptional regulator that acts on the nuclear genes that code for constituent subunits of the oxidative phosphorylation system [19]. TFAM is essential for transcription, replication and maintenance of mtDNA [18]. Nrf-1 and Tfam are both downstream proteins of PGC1- α . Protein levels of PGC1- α , Nrf-1, and TFAM were lower in LCR than HCR striatum, but not in hippocampus, hypothalamus, or substantia nigra. This regional specificity is consistent with studies reporting a greater sensitivity to mitochondrial and metabolic stresses in the striatum than in other brain regions [20, 21]. The fact that PGC1- α and TFAM levels were reported to be lower in aged (23 months) LCR rat hippocampus [22] suggests that in addition to regional differences, some effects of low aerobic capacity might be age-dependent in LCR rats.

Low aerobic endurance capacity has been linked to reduced mitochondrial content and molecular signaling in skeletal muscle [5, 8, 23]. While skeletal muscle function is involved in sustained endurance capacity, the striatum also plays an important role in regulating motor and endurance capacity [24]. While speculative, it is possible that striatal mitochondrial function contributes to differences in intrinsic aerobic capacity between LCR and HCR rats. Further testing in younger LCR and HCR animals is necessary to test this hypothesis.

AMPK plays critical roles in the regulation of cell energy metabolism and in neuroprotection [25, 26]. AMPK is activated when cellular AMP/ATP ratios are elevated [25]. Basal phosphorylation of AMPK was reported to be similar in LCR and HCR rat muscle [26]. Because AMPK can induce phosphorylation and increase gene expression of PGC1- α in skeletal muscle and adipose tissue [26], our results showing greater p-AMPK but lower PGC1- α protein expression in LCR compared to HCR rat striatum were surprising. Conversely, p-AMPK was lower while PGC1- α was greater in HFD LCR striatum. While speculative, it is possible that PGC1- α protein levels provide a feedback signal to regulate

activation of AMPK. In this case, low PGC1- α levels may have activated upstream AMPK. Alternatively, because mitochondria plays an important role in ATP synthesis, low PGC1- α protein levels and accompanying mitochondrial dysfunction may have increased AMP/ATP ratios. This may have led to compensatory AMPK activation.

A previous study reported reduced total AMPK and p-AMPK in rat hippocampus after chronic high fat consumption [28]. We reported lower p-AMPK in rat striatum, but not the hippocampus, after a HFD [29]. The reason for the discrepancy between these studies is unclear, but may be related to greater sucrose content in the study by Wu and colleagues [28]. While most studies have focused on chronic HFD, a human study reported that a short-term HFD reduced AMPK activity in peripheral blood mononuclear cells [30]. We found that p-AMPK was significantly lower in the striatum of LCR rats fed an acute HFD. Our findings therefore extend these findings and provide more evidence that activation of AMPK is inhibited by acute HFD. In addition, acute vs chronic HFD could have also accounted for disparate findings for mitochondrial proteins and AMPK activation between our current and previous studies. Previous findings suggest that over time, mitochondrial proteins would likely have been affected by a HFD in the other brain regions [13, 16, 17, 18, 28]. It would be interesting to determine potential differences between LCR and HCR rats.

LCR rats exhibit decreased metabolic flexibility, impaired metabolic function, obesity, and insulin resistance [1, 8]. The fact that a HFD did not further increase the greater levels of mitochondrial proteins in HCR striatum is likely related to the lower vulnerability to the metabolic stress of a HFD in these rats [6, 7]. It has been hypothesized that insulin resistance is mediated by mitochondrial deficiency in skeletal muscle [31, 32]. Some studies report that feeding rodents and humans a HFD results in lower skeletal muscle PGC1- α mRNA [33, 34, 35, 36]. This hypothesis is controversial, however, as other studies report that a HFD results in elevated mitochondrial biogenesis in skeletal muscle [37, 38, 39]. Our previous study reported that a chronic (31 weeks) HFD resulted in insulin resistance and greater PGC1- α protein levels in rat striatum [40]. Here we provide evidence that despite whole body insulin resistance [9] and lower levels of mitochondrial proteins in the striatum when fed normal chow, LCR rats exhibited greater PGC1- α , Nrf-1 and TFAM protein expression after an acute HFD. These results align with findings that do not support the hypothesis that mitochondrial deficiency underlies insulin resistance. Furthermore, they extend these findings to the striatum, a key brain region that is involved with motor function and that is especially sensitive to metabolic challenges.

Conclusions

In summary, our findings indicate that low aerobic running capacity is associated with lower levels of proteins involved with mitochondrial function in striatum. Despite this, these striatal mitochondrial proteins remain responsive to an acute HFD in LCR rats. Our results also demonstrate brain region-specific differences in the pathways involved in mitochondrial function and energy metabolism, at least as they relate to intrinsic aerobic capacity.

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Highlights

- PGC1- α , Nrf-1, and TFAM were lower in the striatum of LCR rats.
- p-AMPK was greater in the striatum of LCR rats.
- Striatal PGC1- α , Nrf-1, TFAM, and pAMPK were responsive to an acute HFD in LCR rats.
- Markers did not differ in substantia nigra, hippocampus, or hypothalamus.

Fig. 1.

Striatal (A) PGC1- α , (B) Nrf-1, (C) TFAM, and (D) p-AMPK as a function of LCR vs HCR and chow vs HFD groups. PGC1- α , Nrf-1, and TFAM were lower in LCR than in HCR chow-fed rats. Within LCR rats, each of the mitochondrial markers was greater in the acute HFD group than in the chow group. Striatal p-AMPK was greater in LCR than in HCR chow-fed rats. Within LCR rats, p-AMPK was lower in the acute HFD group than in the chow group. Values are expressed as mean $\pm$ S.E. for 6 rats per group. Brackets above the graphs indicate significant HCR VS LCR differences (main effect for strain). * $P<0.05$,

** $P < 0.01$, HCR VS LCR within diets (post hoc); # $P < 0.05$, ## $P < 0.01$, chow diet vs HFD within strains (post hoc).

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PGC1- α , Nrf-1, TFAM and p-AMPK proteins expression did not differ between HCR and LCR rats ($P>0.05$) or between chow diet and acute HFD group in Hippocampus, Hypothalamus and Substantia nigra ($P>0.05$). Values are means $\pm$ S.E.M.

Table 1

		HCR		LCR	
		Chow (n=6)	HFD (n=5)	Chow (n=6)	HFD (n=6)
Hippocampus	PGC1- α	1.06 $\pm$ 0.06	1.08 $\pm$ 0.12	1.05 $\pm$ 0.17	1.26 $\pm$ 0.15
	Nrf-1	0.80 $\pm$ 0.13	0.87 $\pm$ 0.07	0.84 $\pm$ 0.14	0.99 $\pm$ 0.21
	TFAM	0.93 $\pm$ 0.05	1.21 $\pm$ 0.19	1.12 $\pm$ 0.09	1.25 $\pm$ 0.12
	pAMPK	1.02 $\pm$ 0.05	0.93 $\pm$ 0.08	0.98 $\pm$ 0.05	0.97 $\pm$ 0.07
Hypothalamus	PGC1- α	1.66 $\pm$ 0.26	2.33 $\pm$ 0.42	1.83 $\pm$ 0.53	2.24 $\pm$ 0.61
	Nrf-1	0.88 $\pm$ 0.06	0.99 $\pm$ 0.13	0.94 $\pm$ 0.10	1.10 $\pm$ 0.08
	TFAM	0.90 $\pm$ 0.10	1.00 $\pm$ 0.16	1.06 $\pm$ 0.16	0.94 $\pm$ 0.14
	pAMPK	0.90 $\pm$ 0.04	0.89 $\pm$ 0.07	0.96 $\pm$ 0.05	0.90 $\pm$ 0.07
Substantia Nigra	PGC1- α	0.68 $\pm$ 0.11	0.80 $\pm$ 0.13	0.75 $\pm$ 0.10	0.74 $\pm$ 0.10
	Nrf-1	0.84 $\pm$ 0.08	0.95 $\pm$ 0.07	1.07 $\pm$ 0.14	1.03 $\pm$ 0.14
	TFAM	0.96 $\pm$ 0.11	1.19 $\pm$ 0.18	1.07 $\pm$ 0.10	1.15 $\pm$ 0.14
	pAMPK	0.90 $\pm$ 0.04	0.95 $\pm$ 0.06	0.94 $\pm$ 0.06	1.07 $\pm$ 0.09