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Research Report

Effects of discontinuing a high-fat diet on mitochondrial proteins and 6-hydroxydopamine-induced dopamine depletion in rats

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ABSTRACT

Diet-induced obesity can increase the risk for developing age-related neurodegenerative diseases including Parkinson's disease (PD). Increasing evidence suggests that mitochondrial and proteasomal mechanisms are involved in both insulin resistance and PD. The goal of this study was to determine whether diet intervention could influence mitochondrial or proteasomal protein expression and vulnerability to 6-Hydroxydopamine (6-OHDA)-induced nigrostriatal dopamine (DA) depletion in rats' nigrostriatal system. After a 3 month high-fat diet regimen, we switched one group of rats to a low-fat diet for 3 months (HF–LF group), while the other half continued with the high-fat diet (HF group). A chow group was included as a control. Three weeks after unilateral 6-OHDA lesions, HF rats had higher fasting insulin levels and higher Homeostasis model assessment of insulin resistance (HOMA-IR), indicating insulin resistance. HOMA-IR was significantly lower in HF–LF rats than HF rats, indicating that insulin resistance was reversed by switching to a low-fat diet. Compared to the Chow group, the HF group exhibited significantly greater DA depletion in the substantia nigra but not in the striatum. DA depletion did not differ between the HF–LF and HF group. Proteins related to mitochondrial function (such as AMPK, PGC-1α), and to proteasomal function (such as TCF11/Nrf1) were influenced by diet intervention, or by 6-OHDA lesion. Our findings suggest that switching to a low-fat diet

Abbreviations: PD, Parkinson's disease; DA, dopamine; 6-OHDA, 6-hydroxydopamine; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1α; AMPK, AMP-activated protein kinase; pAMPK, phospho-AMP-activated protein kinase; TCF11/Nrf1, transcription factor 11/Nuclear factor E2-related factor 1; HF, high-fat; LF, low-fat; IPGTT, intraperitoneal glucose tolerance test; HOMA-IR, homeostasis model assessment of insulin resistance; HPLC–EC, high pressure liquid chromatography–electrochemical detection; DOPAC, 3,4-dihydroxyphenylacetic acid; DHBA, 3,4-dihydroxybenzylamine

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reverses the effects of a high-fat diet on systemic insulin resistance, and mitochondrial and proteasomal function in the striatum. Conversely, they suggest that the effects of the high-fat diet on nigrostriatal vulnerability to 6-OHDA-induced DA depletion persist.

1. Introduction

Numerous studies indicate links between obesity, type 2 diabetes, and age-related neurodegenerative diseases such as Parkinson's disease (PD) (Hu et al., 2007; Aviles-Olmos et al., 2013). Recent studies from our lab and others demonstrate that a high-fat diet increases dopamine (DA) depletion in the 6-hydroxydopamine (6-OHDA) rat and in the MPTP mouse models of PD (Choi et al., 2005; Morris et al., 2010). These effects resemble the effect of aging of the nigrostriatal pathway, which is the leading contributor to PD. They also suggest that switching to a low-fat diet should decrease neuronal vulnerability. Despite this prediction, little is known about the long-term effects of diet-induced obesity on neuronal vulnerability to PD. Recent findings indicate that a high-fat diet can produce permanent effects on the brain (Thaler et al., 2012; Naef et al., 2013). It is possible that the effects of a high-fat diet on nigrostriatal vulnerability persist even after a switch to a healthier, low-fat diet. The answer to this question is important because it has implications for interventions to prevent Parkinsonism in this population.

Converging evidence suggests that mitochondrial mechanisms are involved in both insulin resistance and neurodegeneration (Aviles-Olmos et al., 2013). Peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), an important regulator of enzymes related to mitochondrial respiration, is associated with type 2 diabetes (Bhat et al., 2007), and has been implicated as playing a critical role in the pathogenesis of PD (Aviles-Olmos et al., 2013). Conversely, abrogation of the ubiquitin–proteasome system is also considered to play a role in the progression of both diseases (Santiago and Potashkin, 2013). It is likely that disruption of multiple pathways puts type 2 diabetic patients at higher risk of PD.

The purpose of this study was to test whether switching to a low-fat diet could reduce the 6-OHDA-induced nigrostriatal DA depletion in rats fed a high-fat diet for 3 months. In addition, we wanted to measure proteins related to mitochondrial (such as AMP-activated protein kinase (AMPK), PGC-1α) and proteasomal (such as Transcription factor 11/Nuclear factor E2-related factor 1(TCF11/Nrf1)) function in striatal tissue in order to determine the extent to which these pathways are affected by diet intervention.

2. Results

2.1. *Effects of feeding on body weight and glucose metabolism*

Three-month-old Fischer 344 rats were randomly divided into a high-fat (HF) group, a high-fat to low-fat (HF–LF) group, and a Chow group. Rats in the HF group ($n=10$) received a high fat diet comprised of 60% calories from fat. Rats in the HF–LF group ($n=10$) received high fat diet (60% calories from fat) for 13 weeks, and then were switched to a low-fat (10% calories from fat) chow. Rats in the Chow group ($n=8$) received standard chow (14% calories from fat) throughout the study. Four weeks before the end of the study, a unilateral 6-OHDA lesion was performed in the medial forebrain bundle of all animals (Fig. 1). After 6 months' feeding of high-fat diet, the HF group had significantly higher body weight than the Chow group ($P<0.001$). Body weight gain in the HF–LF group slowed after switching to LF diet. After 3 months feeding on the LF diet, body weights for the HF–LF group were significant lower than the HF group ($P<0.005$), and did not differ significantly from the Chow group (Fig. 2A).

An intraperitoneal glucose tolerance test (IPGTT) was performed on all rats 1 week before tissue harvest. Comparison of glucose levels between HF and Chow group revealed a significant main effect of time ($P<0.001$), and a significant interaction effect between group and time ($P<0.01$). Glucose comparison between HF–LF and Chow groups also revealed a

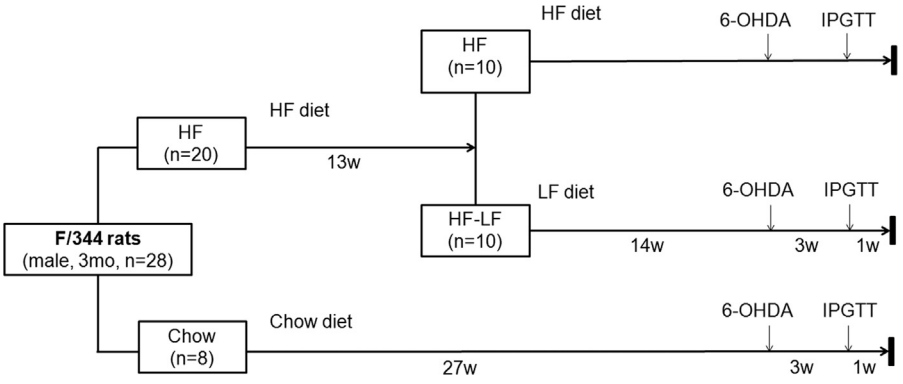

Fig. 1 – Study design.