Neurodegeneration in an animal model of Parkinson’s disease is exacerbated by a high-fat diet

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Morris JK, Bomhoff GL, Stanford JA, Geiger PC. Neurodegeneration in an animal model of Parkinson’s disease is exacerbated by a high-fat diet. Am J Physiol Regul Integr Comp Physiol 299: R1082–R1090, 2010. First published August 11, 2010; doi:10.1152/ajpregu.00449.2010.—Despite numerous clinical studies supporting a link between type 2 diabetes (T2D) and Parkinson’s disease (PD), the clinical literature remains equivocal. We, therefore, sought to address the relationship between insulin resistance and nigrostriatal dopamine (DA) in a preclinical animal model. High-fat feeding in rodents is an established model of insulin resistance, characterized by increased adiposity, systemic oxidative stress, and hyperglycemia. We subjected rats to a normal chow or high-fat diet for 5 wk before infusing 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle. Our goal was to determine whether a high-fat diet and the resulting peripheral insulin resistance would exacerbate 6-OHDA-induced nigrostriatal DA depletion. Prior to 6-OHDA infusion, animals on the high-fat diet exhibited greater body weight, increased adiposity, and impaired glucose tolerance. Two weeks after 6-OHDA, locomotor activity was tested, and brain and muscle tissue was harvested. Locomotor activity did not differ between the groups nor did cholesterol levels or measures of muscle atrophy. High-fat-fed animals exhibited higher homeostatic model assessment of insulin resistance (HOMA-IR) values and attenuated insulin-stimulated glucose uptake in fast-twitch muscle, indicating decreased insulin sensitivity. Animals in the high-fat group also exhibited greater DA depletion in the substantia nigra and the striatum, which correlated with HOMA-IR and adiposity. Decreased phosphorylation of HSP27 and degradation of 14kDa in the substantia nigra indicate increased tissue oxidative stress. These findings support the hypothesis that a diet high in fat and the resulting insulin resistance may lower the threshold for developing PD, at least following DA-specific toxin exposure.

CLINICAL STUDIES SUGGEST A LINK between type 2 diabetes (T2D) and Parkinson’s disease (PD) (30, 46), and between fat intake or adiposity and PD (1, 31, 34). Moreover, it was reported over 40 years ago that greater than 50% of PD patients exhibit abnormal glucose tolerance (4, 10) or diabetes (36). Despite this information, very little is known regarding the relationship of these diseases and the impact of comorbidity on their pathogenesis. By 2025, T2D is estimated to impact 300 million individuals (47), with the elderly at greatest risk (54), the population also at greatest risk for neurodegenerative diseases like PD. For these reasons, understanding the potential for T2D, obesity, high dietary fat intake, and insulin resistance to contribute to PD is critical. Although the exact cause of PD is unknown, various environmental factors such as aging, diet, and environmental toxin exposure have been implicated in contributing to its development (29, 34, 51). The idea that “multiple hits” play a role in PD degeneration is supported by the fact that 80% of dopamine (DA)-producing neurons must be lost for symptoms to appear (50). While diabetes and PD do not invariably coincide, several studies suggest that obesity may potentiate neuronal dysfunction or even neurodegeneration (reviewed in Ref. 11). High-fat diet-induced insulin resistance could make DA neurons in the substantia nigra (SN), the origin of DA-producing neurons that degenerate in PD, more susceptible to environmental insults.

While it is possible that a diet high in fat may contribute to the development of PD, much about this relationship remains unknown. In animal models, most studies have focused on the effect of obesity or high-fat (HF) feeding on the mesolimbic DA pathway (17, 22, 23), which modulates response to reward and is likely affected in obese individuals. However, few studies have addressed this issue in the nigrostriatal DA pathway, which is involved in the production of movement and affected in PD. Although best known for its role in movement disorders, the nigrostriatal pathway has also been shown to play an important role in feeding behavior (41) and may also be affected by obesity or HF feeding. Although it is possible that HF feeding may make DA neurons more vulnerable to environmental insults, such as neurotoxins, only one preclinical study has investigated the effect of a HF diet on DA neurodegeneration (15). These authors found that treatment with the neurotoxin methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (used to model PD) produced greater striatal DA depletion in HF-fed mice than in chow-fed controls. We wanted to further characterize the effect of a high-fat diet on toxin-induced nigrostriatal DA depletion using the 6-hydroxydopamine (6-OHDA) rat model of PD. Unlike MPTP, 6-OHDA may play a role as an endogenous neurotoxin (reviewed in Ref. 7). Iron is abundant in the SN and can react in a Fenton-type reaction with DA and hydrogen peroxide (produced extensively by monoamine oxidase during DA turnover) to produce 6-OHDA (43), which, in turn, can increase iron release from ferritin (35). This suggests that 6-OHDA may play an important role in perpetuating this damaging endogenous cycle. In addition, 6-OHDA is increased in the urine of patients treated with l-DOPA (3, 32), the most common and effective treatment of PD, and l-DOPA treatment in rodents increases 6-OHDA production in the striatum (9). To determine whether HF-fed animals were indeed more sensitive to 6-OHDA mediated DA depletion, we administered equal amounts of 6-OHDA to HF-fed, insulin-resistant rats and chow-fed controls. We observed that the HF diet group exhibited significantly greater levels of DA depletion in the SN, the origin nucleus of DA neurons in the nigrostriatal pathway, and the striatum, the termination point of this pathway. These
results support an exacerbating role for dietary fat, and consequent insulin resistance, in vulnerability to toxin-induced nigrostriatal DA depletion.

**MATERIALS AND METHODS**

**Animals and diet.** Sixteen-month-old Fischer 344 rats were obtained from National Institutes on Aging colonies (Harlan). Rats were individually housed, maintained on a 12:12-h light-dark cycle, and provided food and water ad libitum. Rats in the chow group (n = 10) received normal chow (Harlan Teklad rodent diet 8604), while animals in the HF diet group (n = 8) received a diet with 60% calories from fat. The composition of the HF diet has been described previously (26). During the 7 wk of the experiment, food intake was measured every 2–3 days. Body weight was measured weekly. Protocols for animal use were approved by the University of Kansas Medical Center Institutional Animal Care and Use Committee and adhered to the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996).

**Materials.** Chemicals used in HPLC [norepinephrine, DA, 3,4-dihydroxyphenylacetic acid (DOPAC), and 3,4-dihydroxybenzylamine] and D(+)-glucose were obtained from Sigma-Aldrich (St. Louis, MO). [14C]mammitol and 2-deoxy[1,2-3H]glucose were purchased from American Radiolabeled Chemicals (St. Louis, MO). Rat insulin ELISA kits were obtained from Alpco Diagnostics (Salem, NH). Cholesterol E and LDL-C kits were purchased from Wako Diagnostics (Richmond, VA). Antibodies against actin were obtained from Abcam (Cambridge, MA). Anti-phospho-heat shock protein 27 and anti-Hsp 25 (the rodent homologue of Hsp27) were from Abcam (Cambridge, MA). Anti-phospho-heat shock protein 27 and anti-Hsp 25 (the rodent homologue of Hsp27) were from Abcam (Cambridge, MA).

**Insulin values.** This method has been validated in rodents and is consistent with other measures of insulin sensitivity (12, 53).

**Epidydmal fat and gastrocnemius muscle atrophy measures.** To measure fat accumulation, epidydmal fat was dissected and weighed. In addition, to analyze whether any muscle atrophy occurred due to disuse of the contralateral muscle postlesion, gastrocnemius muscles were carefully dissected tip to tip and weighed.

**Muscle incubations.** Soleus and extensor digitorum longus (EDL) muscles both ipsilateral and contralateral to the lesioned hemisphere were quickly dissected from anesthetized animals. Glucose transport was measured as previously described by our laboratory (26, 27) Each muscle was cut in half horizontally to avoid diffusion limitation and allow assessment of both basal and insulin-stimulated glucose transport. Both halves were placed into 2 ml of recovery buffer (8 mM glucose, 32 mM mannitol, and 0.01% BSA in KHB) for 30 min at 35°C. One muscle half (insulin-stimulated) was incubated in 8 mM glucose, 32 mM mannitol, 1 μM insulin, and 0.01% BSA in KHB for 1 h at 35°C, while the other muscle half (basal) was retained in recovery buffer. Each muscle half was then rinsed in 40 mM mannitol and 0.01% BSA in KHB for 10 min at 29°C. Finally, the insulin-stimulated muscle half was placed into 4 mM 2-[1,2-3H]deoxyglucose (2-DG) (1.5 μCi/ml), 36 mM [14C]mannitol (0.2 μCi/ml), and 0.01% BSA in KHB containing 1 μM/ml insulin at 29°C. The other half was placed into the same buffer without insulin. After 20 min, both muscles were immediately removed, trimmed, and clamp-frozen. A gas phase of 95% O2-5% CO2 was maintained during all incubations.

Muscles were processed as previously described (56) and analyzed in a scintillation counter to determine intracellular 2-DG content (H dpm) and extracellular space (4°C dpm).

**HPLC-EC analysis of whole tissue dopamine content.** Following muscle harvest, brains were immediately removed and placed on an ice-cold brain block. Striatum and SN samples were dissected from each hemisphere, weighed, and frozen on dry ice to be processed for HPLC-EC and Western blot analysis. For HPLC-EC analysis, burnt citrate acetate mobile phase was added to samples from each tissue.

**Glucose, insulin, and cholesterol measures.** For total cholesterol levels using a Cholesterol E kit (Wako) and low-density lipoprotein cholesterol (LDL-C) levels using a rat insulin ELISA (Alpco). Serum samples were also analyzed using a scintillation counter to determine intracellular 2-DG content (H dpm) and extracellular space (4°C dpm).
Statistical analyses. Data for body weight and food intake were analyzed using two-way ANOVA with diet as the grouping variable and time as the repeated measure. Glucose transport and DA turnover were analyzed using one-way ANOVA with diet and side (ipsilesional vs. contralesional) as grouping variables. Correlations were assessed using Pearson’s method. All other data were analyzed using one-way ANOVA with diet as the grouping variable. Data were considered statistically significant at $P \leq 0.05$.

RESULTS

Body weight and food intake. Analysis of body weight (Fig. 1A) yielded significant main effects for both group ($F = 7.91, P = 0.01$) and time ($F = 25.5, P < 0.0001$), as well as a significant interaction effect ($F = 16.57, P < 0.0001$). As expected, HF-fed animals gained more weight than chow-fed animals, and both groups lost weight postlesion during the recovery period. Statistical analysis of food intake (Fig. 1B) revealed significant main effects for group ($F = 14.43, P < 0.001$) and time ($F = 10.51, P < 0.001$, Fig. 1B). Initially, animals in the HF diet group consumed far more calories than chow-fed animals, although this difference became less pronounced after several weeks of feeding. Food intake dropped in both groups postlesion but rebounded during the recovery period, and was virtually the same between groups postlesion.

Systemic effects of HF feeding. An intraperitoneal glucose tolerance test (IPGTT) was performed on a subgroup of rats after 5 wk of feeding, prior to the 6-OHDA lesion. Glucose measurements revealed a significant effect of group ($F = 4.84, P = 0.04$) and time ($F = 22.27, P < 0.001$; Fig. 2A). Glucose levels increased in response to the glucose bolus and HF-fed animals exhibited higher glucose values over the course of the test than chow-fed animals. Over the course of the test, serum insulin levels were significantly higher at the fasting (0) time point and 120 min postbolus. Serum insulin levels increased in both groups in response to insulin, but remained high in HF-fed animals well after insulin levels had returned to normal in the chow-fed group at the end of the IPGTT. Analysis of serum for total cholesterol and LDL-C levels revealed no statistical difference between groups (Table 2).

Fig. 1. Food intake and body weight. High-fat (HF) feeding affected body weight (A), and food intake (B). HF-fed animals weighed more than chow-fed rats, although food intake in the HF group was increased only initially and was affected to a greater extent by the lesion. Values are expressed as means ± SE for 8–10 rats per group. *$P < 0.05$ chow vs. HF.

Fig. 2. Intraperitoneal glucose tolerance test (IPGTT). After an overnight (12 h) fast, an intraperitoneal injection of 60% glucose was administered at 2 g glucose/kg body wt. Insulin (A) and glucose (B) were measured in tail blood at six time points: 0, 15, 45, 60, 90, and 120 min after the glucose bolus (injection at $t = 0$). The HF group exhibited significantly higher glucose values 90 and 120 min following the bolus. Serum insulin levels were significantly higher at the fasting (0) time point and 120 min postbolus. *$P < 0.05$. 
When spontaneous locomotor activity was assessed 4 days prior to tissue harvest, total distance traveled did not differ significantly between the two groups (Table 2). This indicates no difference in activity level between groups. Fasting blood glucose and serum insulin were measured on the last day of the experiment prior to tissue harvest and values are given in Table 2. HF diet-fed animals exhibited significantly higher fasting glucose levels compared with chow-fed animals. \( F = 12.0, P = 0.003 \). HF animals also exhibited a nonsignificant \( P = 0.07 \) trend toward greater fasting serum insulin levels compared with the chow-fed group. To determine whether the lesion caused peripheral muscle atrophy, gastrocnemius muscles were dissected bilaterally tip-to-tip and weighed. Gastrocnemius muscle weights did not differ significantly between the ipsilesional and contralesional sides, nor did they differ significantly between the two groups (Table 2).

Glucose uptake. The majority of glucose uptake in the body occurs in skeletal muscle. Thus, to analyze the degree of insulin resistance, we assayed 2-deoxyglucose uptake into two different skeletal muscles: the EDL (fast-twitch glycolytic fiber type) and soleus (slow-twitch oxidative fiber type). Because there was no difference in glucose transport between muscles ipsilateral or contralateral to the lesion, muscles for each rat were pooled for these analyses. In the EDL, insulin exposure affected the diet groups differently: glucose uptake was greatly increased in chow-fed animals in response to insulin (Fig. 3A), but only a slight increase from basal was observed in HF diet-fed animals. This led to a significant effect of insulin \( F = 18.4, P = 0.0001 \) and a significant interaction between group and insulin \( F = 7.25, P = 0.01 \). The decrease in insulin action due to HF feeding is characteristic of insulin resistance. Basal glucose uptake did not differ significantly between groups. In the soleus muscle, insulin significantly increased glucose uptake from basal in both groups \( F = 24.7, P < 0.0001 \). No significant difference was observed for either basal or insulin-stimulated glucose uptake between groups in the soleus (Fig. 3B).

DA depletion. In the SN, DA depletion was \( 48.8 \pm 7.2\% \) in the HF group compared with \( 27.8 \pm 6.1\% \) in the chow-fed group (Fig. 4A), a difference that was statistically significant \( F = 4.96, P = 0.04 \). Likewise, striatal DA depletion was also significantly higher in the HF diet group \( F = 4.986, P = 0.04 \), averaging \( 28.3 \pm 4.6\% \) for chow animals and \( 49.0 \pm 8.3\% \) for HF animals (Fig. 4B). Average analyte values for DA and DOPAC in each region are provided in Table 1.

DA depletion and systemic effects of HF feeding. When HOMA-IR was analyzed to take into account both fasting glucose and fasting insulin values (12, 53), HF animals exhibited values that were significantly greater than chow-fed animals \( F = 4.23, P = 0.05 \), indicating decreased insulin sensitivity (Fig. 5A). Interestingly, we observed a significant positive correlation between this index of insulin resistance and DA depletion levels in both the SN \( P = 0.03 \), Fig. 5B) and striatum \( P = 0.02 \), Fig. 5C). Epidydymal fat mass was measured to determine differences in body fat composition and overall adiposity. As expected, HF rats exhibited far greater fat mass than chow fed rats \( F = 38.56, P < 0.001 \); Fig. 5D). A significant positive correlation also existed between fat mass and DA depletion in the SN \( P = 0.04 \), Fig. 5E) and striatum \( P = 0.01 \), Fig. 5F).

Dopamine turnover. To estimate whether diet-induced differences in depletion levels affected DA metabolism, we analyzed the ratio of DOPAC to DA (a measure of DA turnover). In the SN of HF animals, DA turnover was increased in the lesioned hemisphere compared with the nonlesioned hemisphere, while chow animals exhibited a decrease in the lesioned hemisphere (Fig. 6A). This led to a significant main effect for group \( F = 10.9, P = 0.002 \) and a significant interaction between group and hemisphere \( F = 9.97, P = 0.004 \). In the striatum, there were no significant effects for hemisphere or group with regard to DA turnover (Fig. 6B).

Protein effects in the substantia nigra. We measured activation of Hsp27 and protein levels of (IκBα) to indirectly assess oxidative stress in the SN (Fig. 7). Hsp27 is activated by phosphorylation, and phosphorylated Hsp27 was significantly decreased in the HF diet-fed group compared with chow-fed...
controls ($F = 8.01, P = 0.01$). The stress kinase IKKβ is activated by cellular stress, such as oxidative stress and insulin resistance (24, 57) and degrades the protein inhibitor IκBα (IκBα) when active. Thus, protein levels of IκBα can be used to gauge stress kinase activity (28). We observed a strong trend for decreased IκBα protein levels in HF diet-fed rats compared with chow-fed rats ($F = 4.02, P = 0.056$), indicating increased stress kinase activity.

DISCUSSION

We report novel data here that HF-fed, insulin-resistant rats exhibited enhanced nigrostriatal DA depletion following 6-OHDA. These changes occurred in the absence of altered cholesterol levels, diminished locomotor activity, or muscle atrophy. Our results support an exacerbating role for dietary fat, and consequent insulin resistance, in vulnerability to toxin-induced nigrostriatal DA depletion. If 6-OHDA is produced endogenously even in small amounts, the increased vulnerability of DA neurons in response to HF diet-induced insulin resistance could put the nigrostriatal pathway at greater risk of damage during chronic HF feeding.

HF feeding in rodents has been previously characterized by our laboratory to cause weight gain, impaired insulin signaling, and glucose intolerance (26). In the current study, an IPGTT indicated that HF-fed animals were insulin resistant prior to 6-OHDA administration. Skeletal muscle accounts for the vast majority of glucose uptake in the body (18), and muscle glucose uptake decreases as a result of insulin resistance. Thus, to further analyze the extent of insulin resistance in these animals, glucose uptake was measured in two muscles: the EDL (fast-twitch glycolytic) and soleus (slow-twitch oxidative) muscles. In the EDL, insulin action was impaired with HF feeding: insulin exposure elicited a much greater increase in glucose transport in chow-fed animals compared with HF diet-fed rats. However, in the soleus, insulin-stimulated glucose transport did not differ significantly between the two groups. This may be due to different metabolic adaptations to a HF diet between muscle types (27), or different levels of heat shock proteins, which protect tissues against oxidative stress (25).

The fact that HF-fed animals exhibited significantly greater DA depletion than chow-fed animals in both the SN and the striatum after 6-OHDA treatment supports a relationship between insulin resistance and PD. Neurons in the SN exist under a high oxidative load due to DA metabolism. Both enzymatic and nonenzymatic DA metabolism generates reactive oxygen species (37), and in this manner, DA can cause both intracel-

Table 1. Striatal DA and DOPAC values for experimental groups

<table>
<thead>
<tr>
<th>Region</th>
<th>Metabolite</th>
<th>Chow (Nonlesion)</th>
<th>Chow (Lesion)</th>
<th>High Fat (Nonlesion)</th>
<th>High Fat (Lesion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striatum</td>
<td>DA</td>
<td>8485 ± 2683</td>
<td>6026 ± 1905</td>
<td>11329 ± 3776</td>
<td>5918 ± 1972</td>
</tr>
<tr>
<td></td>
<td>DOPAC</td>
<td>1557 ± 492</td>
<td>1141 ± 360</td>
<td>1952 ± 650</td>
<td>1105 ± 368</td>
</tr>
<tr>
<td>Substantia Nigra</td>
<td>DA</td>
<td>629 ± 198</td>
<td>404 ± 127</td>
<td>647 ± 328</td>
<td>322 ± 113</td>
</tr>
<tr>
<td></td>
<td>DOPAC</td>
<td>198 ± 62</td>
<td>88 ± 28</td>
<td>210 ± 74</td>
<td>163 ± 57</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE. All values are given as nanograms per gram.

Table 2. Characteristics of chow- and HF-fed rats

<table>
<thead>
<tr>
<th></th>
<th>Chow</th>
<th>High Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mg/dl</td>
<td>115 ± 2.4</td>
<td>127 ± 1.8</td>
</tr>
<tr>
<td>Insulin, ng/ml</td>
<td>0.675 ± 0.204</td>
<td>1.26 ± 0.420</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>93.3 ± 4.77</td>
<td>90.0 ± 4.13</td>
</tr>
<tr>
<td>LDL-C, mg/dl</td>
<td>36.8 ± 2.2</td>
<td>30.2 ± 2.3</td>
</tr>
<tr>
<td>Distance traveled, m</td>
<td>44.28 ± 3.6</td>
<td>45.27 ± 4.0</td>
</tr>
<tr>
<td>Ipsilateral gastrocnemius wt, mg</td>
<td>1955 ± 54.2</td>
<td>2005 ± 72.8</td>
</tr>
<tr>
<td>Contralateral gastrocnemius wt, mg</td>
<td>2045 ± 51.9</td>
<td>2017 ± 63.9</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SE.
ular and extracellular damage to local neurons (55). The SN also has a very high iron content (48), which may further exacerbate oxidative damage by reacting with byproducts of DA metabolism to generate highly reactive radicals (16). Although the nature of DA neuron degeneration in PD is unclear, it is likely that reactive oxygen species play a role in early disease progression (reviewed in Ref. 33). It is possible that the HF diet may exacerbate further DA depletion in this region because it is already highly vulnerable to damage. Because neurons in the SN project to the striatum and release DA, it follows that DA depletion would be evident in this tissue as well.

Interestingly, DA depletion in both the SN and striatum correlated significantly with HOMA-IR values. HOMA-IR is a widely used assessment of beta cell function and insulin resistance that accounts for both fasting glucose and fasting insulin levels (53). As expected, HF-fed animals exhibited significantly higher epididymal fat weight compared with the chow-fed group. HF feeding and increased adiposity have been shown to increase levels of free fatty acids (14), which are known to contribute to insulin resistance in skeletal muscle (8). Like HOMA-IR, epididymal fat content also correlated significantly with nigral and striatal DA depletion.

Altered DA turnover (indicated by the ratio of DOPAC to DA in whole tissue) is a measure of DA metabolism (2) and reflects a functional response to nigrostriatal degeneration. In the SN, DA turnover was greater in HF-fed animals compared with the chow-fed animals. Previous studies have shown that DA turnover is dependent on the extent of DA depletion, with greater DA depletion resulting in increased turnover (42, 43). In our study, DA turnover was significantly increased in the lesioned compared with nonlesioned SN in HF rats, the group that exhibited nearly 50% DA depletion. Increased DA turnover could be a compensatory mechanism for maintenance of normal synaptic DA levels following DA neuron loss (59), and in a progressive MPTP model, DA turnover increases with greater DA depletion (6). However, the chow group in our study actually exhibited decreased DA turnover in the lesioned vs. nonlesioned SN. It is possible that, with much lower (~30%) DA depletion, decreased turnover could also be a compensatory effect to keep existing DA in the synapse for an extended time period. It is clear that the low depletion level in chow animals was not sufficient to trigger an increase in DA turnover, as occurred in the HF group. In addition, there was no significant effect of group or hemisphere for this measure in the striatum. This suggests either that alterations occurring “upstream” in the SN occur first, or that the partial DA depletions

![Fig. 5. Systemic effects of HF feeding correlate with DA depletion.](http://ajpregu.physiology.org/)}
in the chow-fed rats did not reach the threshold necessary to produce these compensatory effects in the terminal region.

Although our results support an exacerbating role for insulin resistance on toxin-induced DA depletion, other effects of a HF diet may also contribute. Increased inflammatory signaling, adipokine levels, oxidative or nitrostative stress, mitochondrial dysfunction, and lipid metabolism have all been shown to occur with HF feeding (13, 27, reviewed in Ref. 52). Some of these peripheral effects, such as oxidative stress, also occur in the brain following HF feeding (21, 40, 58), and HF feeding increases cognitive impairment, tau deposition, MPTP vulnerability, and inflammation in the brain (15, 38, 44, 45). Although specific contributions of other HF diet effects cannot be ruled out, our observation of increased markers of insulin resistance in the absence of increased total cholesterol or LDL-C levels and a positive correlation between HOMA-IR and DA depletion support a role for insulin resistance in mediating increased toxin-induced DA depletion.

Perspectives and Significance

Our results suggest that a HF diet can increase 6-OHDA-induced DA depletion in the nigrostriatal pathway. This study supports the findings of a previous study reporting enhanced MPTP toxin-induced nigrostriatal DA depletion in mice following a HF diet (15) and extends these findings to a different model and species. Our novel findings regarding 6-OHDA are particularly of interest in light of the fact that 6-OHDA is likely...
produced endogenously by DA metabolism. These findings, which support a “multiple hit” hypothesis regarding insulin resistance and neurotoxin exposure in vulnerability to PD, warrant further investigation into the mechanisms by which DA depletion is increased by a HF diet and insulin resistance.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

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