Reduced cortical BACE1 content with one bout of exercise is accompanied by declines in AMPK, Akt, and MAPK signaling in obese, glucose-intolerant mice

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MacPherson RE, Baumeister P, Peppler WT, Wright DC, Little JP. Reduced cortical BACE1 content with one bout of exercise is accompanied by declines in AMPK, Akt, and MAPK signaling in obese, glucose-intolerant mice. J Appl Physiol 119: 1097–1104, 2015. First published September 24, 2015; doi:10.1152/japplphysiol.00299.2015.—Obesity and type 2 diabetes are significant risk factors in the development of neurodegenerative diseases, such as Alzheimer’s disease. A variety of cellular mechanisms, such as altered Akt and AMPK and increased inflammatory signaling, contribute to neurodegeneration. Exercise training can improve markers of neurodegeneration, but the underlying mechanisms remain unknown. The purpose of this study was to determine the effects of a single bout of exercise on markers of neurodegeneration and inflammation in brains from mice fed a high-fat diet. Male C57BL/6 mice were fed a low (LFD; 10% kcal from lard)- or a high-fat diet (HFD; 60% kcal from lard) for 7 wk. HFD mice underwent an acute bout of exercise (treadmill running: 15 m/min, 5% incline, 120 min) followed by a recovery period of 2 h. The HFD increased body mass and glucose intolerance (both P < 0.05). This was accompanied by an approximately twofold increase in the phosphorylation of Akt, ERK, and GSK in the cortex (P < 0.05). Following exercise, there was a decrease in beta-site amyloid precursor protein cleaving enzyme 1 (BACE1; P < 0.05) and activity (P < 0.001). This was accompanied by a reduction in AMPK phosphorylation, indicative of a decline in cellular stress (P < 0.05). Akt and ERK phosphorylation were decreased following exercise in HFD mice to a level similar to that of the LFD mice (P < 0.05). This study demonstrates that a single bout of exercise can reduce BACE1 content and activity independent of changes in adiposity. This effect is associated with reductions in Akt, ERK, and AMPK signaling in the cortex. Acute exercise; cortex; obesity; beta amyloid

Obesity and insulin resistance are significant risk factors in the development of Alzheimer’s disease (AD) (4, 44). Several studies indicate that high-fat diet (HFD)-induced obesity and insulin resistance are directly implicated in the neuropathological hallmarks of AD (5, 21, 31-33, 56). AD is characterized by neuroinflammation and perturbations in brain energy metabolism. Exercise training is known to improve markers of neurodegeneration (11, 32, 33, 37); however, the exact cellular and molecular mechanisms underlying the beneficial effects of exercise on neurodegenerative disease remain elusive.

Two key features of AD are the accumulation of amyloid-beta plaques and neurofibrillary tangles (19, 43). Amyloid-beta plaques are extracellular masses of aggregated amyloid beta (3, 39). These plaques are detrimental to neuronal networks (15) and play a central role in the molecular mechanisms of early disease progression (13, 52). Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), also known as beta secretase, is one of the key enzymes in amyloid precursor protein (APP) processing and is considered a biomarker for early detection, prediction, and progression of AD (17, 18). Tangles consist of abnormally phosphorylated tau protein, leading to microtubule and cytoskeletal destabilization (2, 19, 24, 25). The exact mechanisms leading to these alterations are multifaceted; however, increased cellular stress and impairments in energy metabolism represent early abnormalities that precede or accompany the initial stages of cognitive impairment (54, 56). Specifically, AD brains display overactive 5'-AMP-activated protein kinase (AMPK) (29, 59), abnormal Akt activity (16, 41), as well as increased mitogen-activated protein kinase (MAPK) signaling (20, 35, 42, 50, 53, 57).

Activation of AMPK may provide a mechanistic link among obesity, insulin resistance, and AD pathology. Considered the cells’ “fuel gauge,” AMPK is an important regulator of metabolism as it is a monitor of cellular energy status (63). AMPK is activated in response to stresses that deplete cellular ATP supplies, such as low glucose, in response to an increase in the AMP-to-ATP ratio (26). AMPK is abnormally activated in AD (29, 59) and is thought to be a marker of perturbed brain energy metabolism (6). AMPK activity has also been shown to increase BACE1 protein content and activity in mouse PO primary cortical cultures treated with metformin (9). Furthermore, AMPK can directly phosphorylate tau in tangle and pretangle bearing neurons (49, 58, 59). Together these studies suggest that AMPK activation precedes plaque formation and tau accumulation. In addition to overactivation of AMPK, the cellular stress observed in AD brains is also associated with increased MAPK signaling (20, 42, 53). MAPK pathways have also been implicated in amyloid-beta accumulation and tau hyperphosphorylation (45, 50). Exercise is a known stimulus activating AMPK in several tissues; however, the effects of an acute bout of exercise on brain AMPK activity have yet to be investigated.

Animal models of obesity and type 2 diabetes provide direct evidence that diets rich in fat accelerate AD-like pathophysiological changes in the brain. Several studies have demonstrated that high-fat feeding of wild-type mice as well as mouse models of AD (APP transgenic mice) is directly associated with increased amyloid-beta plaques, tau phosphorylation, and altered brain metabolic signaling (5, 21, 31, 33). Exercise has beneficial effects on whole body energy metabolism and may represent an attractive therapy to reduce or reverse the HFD-
induced metabolic disturbances associated with neurodegeneration. Furthermore, exercise is known to enhance brain function (11, 27), and previous work has demonstrated that voluntary exercise training ameliorates HFD-induced memory deficit and beta-amyloid deposition in APP transgenic mice (23, 32, 33). However, as exercise training is typically paired with reductions in adiposity and body mass as well as improvements in glucose homeostasis, it is difficult to discern if these improvements in brain health are due to direct effects of the exercise.

The purpose of this study was two pronged; first, we aimed to determine the effects of an acute bout of exercise on early markers of beta-amyloid plaque formation and impairments in energy metabolism in a model of HFD-induced obesity and glucose intolerance. Second, we aimed to elucidate the cellular mechanisms through which a single bout of exercise may improve these markers. To address this question, we fed C57BL/6 mice a HFD for 7 wk and then examined the effects of an acute bout of exercise on markers of BACE1 protein content and activity and the AMPK, Akt, and MAPK signaling pathways.

METHODS

Materials. Molecular weight marker, reagents, and nitrocellulose membranes for SDS-PAGE were purchased from Bio-Rad (Mississauga, ON). SignalFirePlus ECL reagent (cat. no. 12630), protease/phosphatase inhibitor cocktail (cat. no. 5872), and SDS loading buffer/dithiothreitol (cat. no. 7722) were from Cell Signaling Technologies (Danvers, MA). Horseradish peroxidase-conjugated donkey anti-rabbit and goat anti-mouse IgG secondary antibodies were from Jackson ImmunoResearch Laboratories (West Grove, PA). Antibodies against BACE1 (cat. no. 5606), glial fibrillary acidic protein (GFAP; cat. no. 3670), tau (cat. no. 4019), ptau Ser202 (cat. no. 11834), ptau Th181 (cat. no. 12885), AMPK (cat. no. 2794), phospho-Thr172 AMPK (cat. no. 2531), Akt (cat. no. 9611), phosphothreonine 308 Akt (cat. no. 9275), ERK (cat. no. 4695), phospho-ERK (threonine 202/tyrosine 204; cat. no. 9101), p38 (cat. no. 9212), phospho-p38 (threonine 180/tyrosine 182; cat. no. 9211), JNK (cat. no. 9252), phospho-JNK (threonine 183/tyrosine 185; cat. no. 4671), GSK-3αβ (cat. no. 5676), and phospho-GSK-3αβ (serine 9; cat. no. 9316) were purchased from Cell Signaling (Danvers, MA). Ionized calcium binding adaptor molecule 1 (Iba1) antibody was from Wako Chemicals (Richmond, VA; cat. no. 016–20001). Free glycerol and nonesterified fatty acid (NEFA) assay kits (cat. no. FG0100) were purchased from Sigma Aldrich (Oakville, ON, Canada). Beta-secretase activity assay was purchased from Abcam (ab65357). Random primers, SuperScript II Reverse Transcriptase, and dNTP were from Invitrogen (Burlington, ON, Canada). Taqman gene expression assays for BACE1 (Mm00478664_40) was purchased from Life Technologies, and GAPDH (4352932E) was from Applied Biosystems (Foster City, CA).

Animals and diet. Eight-week-old male C57BL6/J mice (Charles River) were fed a low (LFD; 10% kcal from lard; Research Diets D12450; n = 9)- or a high-fat diet (HFD; 60% kcal from lard; Research Diets D12492; n = 18) ad libitum for 7 wk. We have previously demonstrated that this duration and composition of HFD results in obesity and glucose intolerance (30). Animals were housed individually and had free access to water and were maintained a 12/12-h light cycle. All protocols met the guidelines of the University of Guelph Animal Care Committee and the Canadian Council on Animal Care (6a).

Glucose tolerance. Intraperitoneal glucose tolerance tests were performed on fasted (6 h), nonanesthetized mice during the last week of feeding (week 7). Glucose measures were obtained from tail vein blood using an automated glucometer at baseline and at 15, 30, 45, 60, 90, and 120 min following an intraperitoneal injection of glucose (2 g/kg body mass).

Acute exercise protocol. To minimize differences between groups and in stress, both LFD and HFD mice were accustomed to motorized treadmill running during a 3-day period consisting of 15 min of running/day at 15 m/min, 5% grade. This acclimatization period took place during the last week of feeding. The HFD mice were then assigned into one of two groups, sedentary HFD (HFD; n = 9) and exercised HFD (HFD + ex; n = 9). Seventy-two hours following the last day of acclimation mice ran for 120 min at 15 m/min, with an incline of 5%. The acute bout of exercise started at ~10:00 AM, which is the beginning of the light cycle. In previous work from our laboratory (30, 61), we have found that this duration and intensity of exercise is well tolerated. All mice in the exercise treatment group completed the 2 h of treadmill running without issue. Following the exercise bout, mice were placed back in their cages to recover for 2 h without food. Sedentary low- and high-fat-fed mice had their food removed at the same time as the high-fat-fed mice that exercised (38).

Tissue collection. Two hours postexercise, mice were anesthetized with isoflurane and a weight-adjusted bolus injection of sodium pentobarbital (5 mg/100 g body wt). Blood glucose was measured from the tail vein with a glucometer. Thoracic blood was collected for the determination of plasma glyceral and NEFA. The brains were quickly dissected and frontal cortex tissue as well as hippocampus from each hemisphere was collected, snap frozen in liquid nitrogen, and stored at −80 until further analysis (33).

Plasma glyceral, fatty acids, and glucose. Analysis of metabolite concentrations was determined using commercially available kits, following the manufacturer’s instructions. Samples were run in duplicate and the average coefficient of variation was <10%. All samples from one experiment were run on the same plate.

Western blotting. Samples were homogenized on ice with a Polytron (speed 11, 5 × 3 s pulses) in RIPA buffer (ratio ~1:40), supplemented with protease and phosphatase inhibitors. Homogenized samples were centrifuged at 4°C (15 min at 10,000 g), the supernatant was collected, snap frozen in liquid nitrogen, and stored at −80 until further analysis (33).

Real-time PCR. Cortex total RNA was extracted and reversed transcribed into cDNA. Changes in mRNA expression were determined using real-time quantitative PCR as described in detail previously by our laboratory (8). Briefly, RNA was isolated from cortex tissue following homogenization in Trizol reagent using an RNeasy kit according to the manufacturer’s instructions (RNeasy Kit 74104; Qiagen). Quantity and purity were assessed using a NanoDrop Spectrophotometer (NanoDrop 2000, Spectrophotometer; ThermoScientific). Complementary DNA (cDNA) was synthesized from total RNA (1 μg) using SuperScript II Reverse Transcriptase, dNTP, and random primers (Invitrogen). Real-time PCR was carried out using a 7500 Fast Real-Time PCR system (Applied Biosystems). Samples were loaded in duplicate using a 96-well plate layout. Each well contained a total volume of 20 μl comprised of 1 μl gene expression assay, 1 μl cDNA template, 10 μl Taqman Fast Universal PCR Master Mix, and 8 μl RNase-free water. GAPDH was used as a housekeeping gene,
and relative differences in gene expression between groups were determined using the 2−ΔΔCt method (28). The PCR efficiency was similar between GAPDH and genes of interest. Similarly, our experimental manipulations did not alter the expression of the housekeeping gene (GAPDH).

Beta-secretase activity. Beta-secretase activity in cortex samples was determined using a commercially available beta-secretase activity assay kit (Abcam). Briefly, protein was extracted using ice-cold extraction buffer, incubated on ice 15 min and centrifuged at 10,000 g for 5 min at 4°C. The supernatant was collected. A total of 50 μl of sample (total protein 150 μg) was added to each well. This was followed by 50 μl of 2× reaction buffer and 2 μl of beta-secretase substrate and then incubation in the dark at 37°C for 1 h. Each sample was run in duplicate. Fluorescence was read at excitation and emission wavelengths of 355 and 510 nm, respectively.

Statistics. Comparisons between LFD and HFD groups were made using unpaired, two-tailed t-tests. Differences in protein content, fatty acids, and glucose over time were determined using a one-way ANOVA followed by Tukey’s post hoc analysis. In cases where data were not normally distributed, data were logaritically transformed. Data are expressed as means ± SE with significance set at P < 0.05.

RESULTS

High-fat feeding induced glucose intolerance and increased body and adipose tissue mass. To induce a state of obesity and glucose intolerance mice were fed a HFD for 7 wk. The HFD resulted in an increased fat (inguinal subcutaneous and epididymal mass) as well as body mass compared with the LFD mice (Fig. 1A; P < 0.05). Following an intraperitoneal glucose injection, the HFD mice cleared glucose less effectively and had a higher glucose area under the curve compared with LFD mice (Fig. 1B, P < 0.05). These results demonstrate that 7 wk of a HFD resulted in obese, glucose-intolerant mice.

Acute exercise decreases cortical BACE1 protein content and activity in obese mice. To examine the effects of an acute bout of exercise on markers of beta-amyloid plaque formation, gliosis, and tau, we examined cortical BACE1, Iba1, GFAP, and tau S202 and T181 phosphorylation. BACE1 content was measured as an early marker of amyloid-beta plaque formation (17). Iba1 and GFAP were measured as evidence of inflammation and gliosis. Our results demonstrate that 2 h following an acute bout of exercise cortex BACE1 protein content was lower than both the HFD group and the LFD group (Fig. 2B; P < 0.05). There were no apparent effects of HFD or exercise on gliosis, assessed as the total protein content of GFAP or Iba1 in the cortex. No change in tau Th181 phosphorylation was observed in the cortex in any group; however, tau S202 phosphorylation was lower in the HFD. There were no changes in BACE1, GFAP, Iba1, or phosphorylated tau in the hippocampus in response to the HFD or acute exercise (Fig. 2A). There were no changes in total tau in either the cortex or hippocampus of our mice fed the HFD or following exercise (data not shown).

To further assess the effects of exercise on BACE1 in the cortex from mice fed a HFD, we measured BACE1 mRNA and activity. As shown in Fig. 3A, there were no differences among groups in BACE1 mRNA expression. However, BACE1 activity was increased in the cortex from mice fed the HFD and this was reduced in HFD mice 2 h postexercise (Fig. 3B; P < 0.0001).

Acute exercise decreases AMPK and MAPK phosphorylation in parallel with declines in BACE1 content. Since both AMPK and MAPK signaling are implicated in the upregulation of BACE1 content (9, 50), we measured the phosphorylation status of these proteins. As BACE1 did not change in the hippocampus, these measures were completed in the cortex. High-fat feeding resulted in an approximately twofold increase in ERK phosphorylation in the cerebral cortex (P < 0.05). No significant changes were observed in the cortex for p38 Thr180/Tyr182 (ANOVA, P = 0.1368) with the HFD. Following acute exercise, cortex ERK Thr202/Tyr204 phosphorylation...
was decreased to a level similar to that of the LFD mice \((P < 0.05)\). There was no effect of diet on AMPK Thr172 or acetyl CoA carboxylase (ACC) phosphorylation. Following acute exercise, AMPK Thr172 phosphorylation was reduced \((P < 0.05)\), as was phosphorylation of its direct downstream target ACC (Fig. 4; \(P = 0.07\)).

**HFD-induced increase in Akt phosphorylation is decreased with acute exercise.** Abnormal activation of Akt is commonly observed in AD (16, 41), and our results demonstrate that high-fat feeding resulted in an approximately twofold increase in the phosphorylation of Akt Thr308 in the cerebral cortex \((P < 0.05)\). Following exercise, Akt phosphorylation was decreased to a level similar to that of the LFD mice \((P < 0.05; \text{Fig. 5})\).
observed in brain protein content or phosphorylation would not be secondary to changes in circulating glucose, NEFAs, or glycerol.

**DISCUSSION**

Obesity and glucose intolerance induced by a HFD are associated with AD-like pathological changes in the brain. In this study we demonstrate the novel effects of one bout of exercise on reducing BACE1 content and activity and reversing HFD-induced markers of energetic stress in mouse cortex. Specifically, findings from this study demonstrate for the first time that an acute bout of exercise results in a decline in AMPK, MAPK, and Akt phosphorylation in brains from obese glucose intolerant mice. These results highlight the therapeutic

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**Fig. 4.** Acute exercise decreases cortical AMPK and MAPK phosphorylation. HFD had no effect on AMPK or acetyl CoA carboxylase (ACC) phosphorylation. A: acute exercise reduced AMPK phosphorylation. B: HFD resulted in increased ERK phosphorylation and this was reduced with an acute bout of exercise. Representative blots are shown beside the quantified data (LFD, n = 9; HFD, n = 9; HFD + ex 2 h after exercise, n = 9). Data are presented as means ± SE. *P < 0.05, as determined using a one-way ANOVA followed by Tukey’s post hoc analysis.

**Fig. 5.** HFD-induced increase in Akt phosphorylation is decreased with acute exercise. HFD resulted in an increased Akt and GSK phosphorylation. This was reduced with an acute bout of exercise. Representative blots are shown beside the quantified data (LFD, n = 9; HFD, n = 9; HFD + ex 2 h after exercise, n = 9). Data are presented as means ± SE. *P < 0.05, as determined using a one-way ANOVA followed by Tukey’s post hoc analysis.
potential of exercise, independent of alterations in body mass or adiposity, as a tool to ameliorate early changes in early AD-associated pathology.

Combined evidence from genetic, neurobiological, molecular, and behavioral studies suggest that increased accumulation of amyloid beta, derived from beta0 and gamma-secretase-induced cleavage of APP, is the primary initiating trigger for synaptic defects and cognitive declines in AD (17, 22, 51). Maesako et al. (32) have demonstrated that HFD-induced obesity and glucose abnormalities in APP transgenic mice are associated with upregulating BACE1 enzyme activity and the production of amyloid-beta and that chronic voluntary exercise downregulates BACE1, inhibiting the HFD-induced amyloid-beta accumulation and memory deficit. However, these changes were accompanied by a significant reduction in body mass as well as improved glucose homeostasis, making it difficult to tease out the direct effects of exercise on the brain. Previous work has determined that increased AMPK activity can lead to increased BACE1 protein content (9). Here, we show that with one bout of acute exercise BACE1 protein content and activity are decreased and that these were accompanied by a decline in AMPK phosphorylation as well as Akt and MAPK phosphorylation. Our results demonstrate an effect of exercise on reducing BACE1 content and activity, an early sign of neurodegeneration, independent of alterations in adiposity and circulating metabolites in high-fat-fed mice. Further investigation is necessary to determine if there is a direct relationship to the changes in AMPK, Akt, and MAPK phosphorylation and BACE1 content or activity.

AMPK is highly expressed in brains and acts as a sensor of cellular stress (48). Exercise is a known stimulus activating AMPK in several tissues (7, 40), however, before this investigation the effects of an acute bout of exercise on brain AMPK activity had yet to be investigated. Previous work has demonstrated that AMPK phosphorylation (Thr172) is abnormally activated not only in tangle-containing neurons in AD but also in pretangle neurons (59), indicating that overactivity can be an early sign in AD pathology. A recent study directly examined the impact of inhibiting AMPK on AD-associated synaptic dysfunction. They found that AMPK prevents disruptions in synaptic plasticity caused by either exogenous amyloid-beta exposure or in APP/PS1 transgenic mice, consistent with the observation that AMPK signaling is hyperactive in AD brains (29). Our results show that while high-fat feeding did not result in a significant increase in phosphorylated AMPK, 2 h of acute aerobic exercise resulted in a reduction in phospho-AMPK beyond that of the LFD sedentary group. This result demonstrates the effectiveness of exercise to reduce brain energetic stress. The exact mechanisms in which AMPK may have an effect on neurodegeneration are likely multifaceted and will require further examination.

Increased Akt activation has been described in both hippocampal and cortical neurons in the AD brain (16, 41, 46). Our results show that a HFD results in excessive phosphorylation of Akt. This is similar to results from mice fed a HFD for 5 mo (36) as well as temporal cortex from postmortem AD patients (16, 41). It is possible that this increase in Akt activity is due to an increase in circulating glucose levels. In line with this, Clodfelder-Miller et al. (10) demonstrated that physiological variations in serum glucose levels affected brain Akt phosphorylation status in the hippocampus. Moreover, streptozotocin-induced hyperglycemia caused persistent Akt hyperphosphorylation (10). Following the acute bout of exercise, these increases in Akt and GSK phosphorylation were absent. Exercise is well known for improving whole body energy metabolism and restoring glucose homeostasis. It is known that the brain increases glucose utilization as an energy source

### Table 1. Plasma glucose, nonesterified fatty acids, and glycerol levels in mice fed a LFD or HFD at rest and following an acute bout of exercise

<table>
<thead>
<tr>
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<th>Glucose, mmol/l</th>
<th>NEFA, mmol/l</th>
<th>Glycerol, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFD</td>
<td>10.7 ± 0.8</td>
<td>0.6 ± 0.07</td>
<td>0.4 ± 0.03</td>
</tr>
<tr>
<td>HFD</td>
<td>12.9 ± 0.7</td>
<td>0.7 ± 0.11</td>
<td>0.5 ± 0.09</td>
</tr>
<tr>
<td>2 h LFD</td>
<td>10.9 ± 1.2</td>
<td>0.6 ± 0.13</td>
<td>0.5 ± 0.08</td>
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NEFA, nonesterified fatty acids; LFD, low-fat diet; HFD, high-fat diet.

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Fig. 6. Acute exercise has no effect on BACE1, AMPK, ERK, or Akt phosphorylation in LFD control mice. Representative blots are shown beside the quantified data (LFD, n = 7; HFD, n = 7; HFD + ex 2 h after exercise, n = 7). Data are presented as means ± SE.
during exercise (60); therefore, it is possible that the exercise-induced decline in Akt activity seen here is due to improved glucose metabolism; however, this was not reflected in the plasma glucose concentrations in our study. This is the first evidence of a role for an acute bout of exercise in normalizing alterations in Akt/insulin-signaling in the brain.

Akt interacts with several other kinases including the MAPK family (34). Our results show that following high-fat feeding there is an increase in ERK phosphorylation as well as a trend for increased p38 phosphorylation. Together with the HFD induced increase in AMPK phosphorylation our results indicate cellular stress (1, 14). Tissue from postmortem AD patients as well as animal models of AD also demonstrate increased activation of ERK, p38, and JNK (35, 42, 50, 57), as well as AMPK activity (29, 59). Our findings demonstrate that an acute bout of exercise rescues HFD induced overactivation of ERK, p38, and AMPK. These kinases have all been implicated in amyloid-beta accumulation and tau hyperphosphorylation (45, 50, 59); therefore, the reduction in activation of one or all of these kinases following exercise may have neuroprotective properties.

Neurofibrillary tangles, resulting from hyperphosphorylation of the microtubule-interacting protein tau, leads to microtubule destabilization and neurodegeneration and is also considered a hallmark of AD pathology (2). In this study we observed a lower tau S202 phosphorylation in the cortex from mice fed a HFD. It is difficult to discern the importance and the underlying mechanisms of this reduced S202 phosphorylation with the HFD given the large number of tau phosphorylation sites (potentially 80 serine/threonine and 5 tyrosine phosphorylation sites) and multiple upstream kinases that may be involved (62).

This study demonstrates, for the first time, that an acute bout of exercise can decrease BACE1 content and activity in the cortex of obese, glucose-intolerant mice, independent of changes in adiposity and circulating metabolites. The decline in BACE1 was accompanied by reductions in the phosphorylation of AMPK, Akt, and MAPK in mouse cortex. Future work should strive to understand the roles of these pathways in AD-related pathology and their potential as targets for the prevention and treatment of AD.

GRANTS
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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

REFERENCES
12. Cundy T, Davie J, Karpe F, Jolley D, Pearson P, Thayabalan K, Pilling M. Possible implications of an age-related increase in fasting plasma glucose concentrations in our study. This is the first evidence of a role for an acute bout of exercise in normalizing alterations in Akt/insulin-signaling in the brain.

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