Acute exercise reverses aged-induced impairments in insulin signaling in rodent skeletal muscle

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1. Introduction

Physical activity and obesity, associated with ageing, appears to play a large role in the regulation of insulin sensitivity with ageing. Many of the effects of ageing on insulin sensitivity are likely related to increased fat mass and decreased physical activity (Rimbert et al., 2004; Amati et al., 2009). On the other hand, endurance training has emerged as an effective intervention for prolonging life span and delaying the installation of degenerative diseases (Paffenbarger et al., 1986; Holloszy, 1988; Blair et al., 1989; Holloszy and Schechtman, 1991; Blain et al., 2000). The mechanism involved in the positive effects of physical activity remains unknown, although a beneficial effect on the age-related development of insulin resistance has been suggested to play an important role (Holloszy, 1988; Carvalho et al., 1996; Blain et al., 2000).

During the last twenty years, a number of defects in insulin signaling have been reported in aging animals (Barnard et al., 1992; Carvalho et al., 1996; Rocha et al., 2003). A decrease in insulin-induced insulin receptor (IR) and insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation levels has been described in the muscle of old rats (Carvalho et al., 1996; Lima et al., 2002), although these alterations may not directly indicate insulin resistance. Moreover, studies have found a reduction in the association of the IRS-1 with phosphatidylinositol 3-kinase (PI3-K) and a decrease in IRS-1 protein levels in old rats (Carvalho et al., 1996; Arias et al., 2001). Notably, the PI3-K/Akt pathway in the skeletal muscle of old rats is also a critical signal defect of insulin dysfunction with aging (Carvalho et al., 1996; Lima et al., 2002).

Many mechanisms may contribute to the dysregulation of the insulin-signaling pathway, including serine phosphorylation of IRS proteins by protein kinases, such as IKK-β (IKK-β) and c-Jun N-terminal kinase (JNK) (Hotamisligil et al., 1996; Hirosumi...
et al., 2002; Ropelle et al., 2006). Much evidence has shown that, during aging, activation of inflammatory signaling pathways such as IKK-β (Kim et al., 2000; Chung et al., 2001) and JNK (Williamson et al., 2003) may occur, leading to phosphorylation of serine sites on IRS-1 and an attenuated insulin signaling pathway. Serine-phosphorylated forms of IRS-1 fail to associate with and activate PI3-K, resulting in the decreased activation of glucose transport and other downstream events (Bouzakri et al., 2005; Karlsson and Zierath, 2007). In addition, it is possible that, during aging, increases in the expression of protein tyrosine phosphatase 1B (PTP-1B) may impair insulin signaling in the skeletal muscle.

Conversely, it is well established that exercise training can improve the insulin sensitivity of young (Luciano et al., 2002), as well as, aged rats (Kern et al., 1992; Arias et al., 2001). However, the molecular mechanisms involved in the improvement in insulin signaling during aging are not fully understood. Recently, we and others have demonstrated that acute exercise reverses insulin resistance in obese rats in parallel with an improvement in insulin signaling (Ropelle et al., 2006; Thyfault et al., 2007; Pauli et al., 2008). These data show that acute exercise attenuates proinflammatory pathways such as JNK and NF-κB prevent insulin resistance in the context of obesity. However, these effects of exercise have not yet been investigated in insulin resistance during aging.

In the present study, we investigated whether the improvement in insulin sensitivity and insulin signaling, via acute exercise, could be associated with modulation of IRS-1Ser307, JNK, IKK-β and PTP-1B in the skeletal muscle of old rats.

2. Materials and methods

2.1. Animals

Male Wistar rats from the University of Campinas Central Animal Breeding Center were used in the experiments. All experiments were approved by the Ethics Committee of the State University of Campinas (UNICAMP). Eight rats (n ≥ 8) were used per group (young group: control rats of 3 months of age), old sedentary rats (group OS: 27 months of age), and exercised 27-month-old rats (group OE). The temperature was maintained at 24 ± 1°C. This exercise protocol was adapted from a previously published procedure (Flores et al., 2006). After the last bout of exercise, animals were fed ad libitum and food was withdrawn 6 h before the tissue extraction, with free access to water. The rats were anesthetized with intraperitoneal injection of sodium thiopental (40 mg/kg (body weight)).

2.2. Exercise protocol

Rats were accustomed to swimming for 10 min for 2 days. The animals swam in groups of three in plastic barrels of 45 cm in diameter that were filled to a depth of 34 cm, for two 1.5-h long bouts, separated by a 45-min rest period and the water temperature was maintained at 34°C. For this procedure the animals used were different from the animals used in the insulin tolerance test and serum insulin quantification.

2.3. Insulin tolerance test (ITT) and serum insulin quantification

For this procedure the animals used were different from the animals used in the tissue extraction and protein analysis by immunoblotting. The ITT was realized 16 h after the exercise protocol and after 6 h of fasting, with free access to water. Briefly, 1.5 U/kg of human recombinant insulin (Humulin R(Eli Lilly, Indianapolis, IN, USA) was injected intraperitoneally in anesthetized rats, the blood samples were collected at 0, 5, 10, 15, 20, 25 and 30 min from the tail for serum glucose determination. The rat constant for plasma glucose disappearance (Kitt) was calculated using the formula 0.693/(t/2). The plasma glucose (t/2) was calculated from the slope of last square analysis of the plasma glucose concentration during the linear phase of decline (Bonora et al., 1989). The plasma glucose level was determined by a colorimetric method using a glucoseometer (Advantage, Boehringer Mannheim, USA). Plasma was separated by centrifugation (1100 × g) for 15 min at 4°C and stored at −80°C until assayed. RIA was employed to measure serum insulin, according to a previous description.

2.4. Protein analysis by immunoblotting

As soon as anesthesia was assured by the loss of pedal and corneal reflexes, the abdominal cavity was opened, the portal vein exposed, and 0.2 ml of normal saline with or without insulin (10−8 mol/l) was injected. In preliminary experiments, we determined that this dose of insulin can reach peripheral levels that are 3–4 times higher than the dose that can induce the maximal insulin effect on insulin signaling proteins in muscle. At 90 s after the insulin injection, both portions of gastrocnemius (red and white fibers) were ablated, pooled, minced coarsely and homogenized immediately in extraction buffer (1% Triton-X 100, 100 mM Tris, pH 7.4, containing 100 mM sodium pyrophosphate, 100 mM sodium fluoride, 10 mM EDTA, 10 mM sodium vanadate, 2 mM PMSF and 0.1 mg of aprotinin/ml) at 4°C with a Polytron PTA 205 generator (Brinkmann Instruments model PT 10/35) operated at maximum speed for 30 s. The extracts were centrifuged at 9000 × g for 4°C in a Beckman 70.1 Ti rotor (Palo Alto, CA) for 40 min to remove insoluble material, and the supernatants of these tissues were used for protein quantification, performed by the Bradford method (Bradford, 1976). Proteins were denatured by boiling in Laemmli sample buffer containing 100 mM DTT, run on SDS-PAGE, transferred to nitrocellulose membranes, which were blocked, probed and developed as described previously. The β subunit of the IRβ and IRS-1 and IRS-2 were immunoprecipitated from rat muscle with or without previous insulin infusion. Antibodies used for immunoblotting were anti-phosphotyrosine (pY), anti-IR, anti-IRS-1, anti-Akt, anti-phospho-Ser473 Akt, anti-beta-Actin, anti-c-jun N-terminal kinase (JNK), anti-phospho-JNK, anti-phospho-c-jun, anti-IκBα (Santa Cruz Biotecology Inc., CA, USA) anti-p65/PI3 Kinase (PI3-K, anti-SIRT1 (Cell Signaling Technology, MA, USA), anti-PTP-1B and antiphosphoserine-IRS-1307 (Upstate Biotecology, NY, USA). Blots were exposed to pre-flashed Kodak XAR film with Cronex Lightning Plus intensifying screens at 80°C for 12–48 h. Band intensities were quantitated by optical densitometry (Scan Image software, ScanCorp, Frederick, MD) of the developed autoradiographs.

2.5. Statistical analysis

Where appropriate, the results are expressed as means ± SD. Differences between the control group and the old sedentary rat group and between the old sedentary rats and the group submitted to the exercise protocol were evaluated using one-way analysis of variance (ANOVA). When the ANOVA indicated significance, a Bonferroni post hoc test was performed.

3. Results

3.1. Physiological and metabolic parameters

Table 1, comparative data regarding control (C), old sedentary rats (OS) and old rats submitted to an acute exercise (OE) protocol are presented. Twenty-seven-month-old rats (OS and OE) had a higher body weight and epididymal fat pad weight compared to control rats (C). No significant variations were found in body weight and epididymal fat in OE rats, after a single session of exercise, compared to OS rats. The fasting plasma glucose concentrations were similar between the groups, however serum insulin was higher in old rats (OS and OE), when compared with control rats (P < 0.01).

Table 1

<table>
<thead>
<tr>
<th>Animal characteristics</th>
<th>Control</th>
<th>OS</th>
<th>OE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>324.7 ± 22.1</td>
<td>375.5 ± 33.8</td>
<td>575.1 ± 26.5</td>
</tr>
<tr>
<td>Epididymal fat (g/100g)</td>
<td>1.3 ± 0.07</td>
<td>2.3 ± 0.1</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>Blood glucose (mg/dL)</td>
<td>76.8 ± 5.9</td>
<td>87.2 ± 6.9</td>
<td>85.6 ± 5.6</td>
</tr>
<tr>
<td>Serum insulin (ng/ml)</td>
<td>2.2 ± 0.1</td>
<td>5.6 ± 0.8</td>
<td>5.1 ± 0.2</td>
</tr>
</tbody>
</table>

Data are means ± SEM. Each group was composed of eight animals.

P < 0.01 vs. control group.
increase in the muscle of OS rats; after acute exercise this ratio increased by 8.1-fold in the muscle of OS rats, suggesting that exercise improves insulin-induced IR tyrosine phosphorylation in these rats (Fig. 1B) \( (P < 0.05) \). There was no difference in basal levels of IR tyrosine phosphorylation between the three groups (data not shown).

There was a \(-40\%\) decrease in IRS-1 protein levels in the muscle of old rats that was reversed by acute exercise (Fig. 1C). The increase in insulin-induced IRS-1 tyrosine phosphorylation was less marked in old rats, and exercise partially reversed this alteration. The phosphate/protein ratio for IRS-1 increased by 9.0-fold in control animals, compared with a 2.8-fold increase in the muscle of OS rats; after acute exercise this ratio increased by 8.3-fold in the muscle of OE rats, suggesting that exercise improves insulin-induced IRS-1 tyrosine phosphorylation in these rats (Fig. 1C) \( (P < 0.05) \). There was no difference in basal levels of IRS-1 tyrosine phosphorylation between the three groups (data not shown).

The insulin-induced IRS-1/PI3-K association increased by 8.2-fold in control animals, compared with a 2.7-fold increase in the muscle of OS rats; after acute exercise this increase was of 6.2-fold in the muscle of OE rats, suggesting that exercise improves insulin-induced IRS-1/PI3-K association in these rats (Fig. 1D) \( (P < 0.05) \). Finally, there was a \(-30\%\) decrease in Akt protein levels in the muscle of old rats that was reversed by acute exercise (Fig. 1E). The increase in insulin-induced Akt serine phosphorylation was less evident in OS rats, and exercise partially reversed this alteration.

The phosphate/protein ratio increased by 9.6-fold in control animals, compared with a 3.1-fold increase in the muscle of OS rats; after acute exercise this ratio increased by 8.8-fold in the muscle of OE rats, suggesting that exercise improves insulin-induced Akt serine phosphorylation in these rats (Fig. 1E) \( (P < 0.05) \). There was no difference in basal levels of Akt serine phosphorylation between the three groups (data not shown).

3.3. A single bout of exercise inhibits Ser307 phosphorylation of IRS-1, JNK activity and IkBα degradation in aged rats

Among the serine residues that become phosphorylated in response to risk factors of insulin resistance, Ser307 has been studied extensively and has become a molecular indicator of insulin resistance (Eldar-Finkelman and Krebs, 1997; Aguirre et al., 2002; Hirosumi et al., 2002; Lee et al., 2003). In muscle of old rats there was a 5.6-fold increase in IRS-1ser307 phosphorylation, when compared with control rats and, after exercise, IRS-1ser307 was significantly reduced (Fig. 2A) \( (P < 0.05) \). JNK activation was determined by monitoring phosphorylation of JNK (Thr183 and Tyr185) and p-c-Jun (Ser63), which is a substrate of JNK. In old rats, there was a 4.8-fold increase in JNK phosphorylation when compared with control rats, which was decreased at 16 h after a single bout of exercise (Fig. 2B upper panel) \( (P < 0.05) \). The JNK protein levels were not different between the groups (Fig. 2B lower panel). Consistent with JNK
activation, p-c-Jun was 4.6-fold higher in the muscle of OS rats, compared to control rats, and a significant decrease was observed after acute exercise (Fig. 2C) (P < 0.05).

We also examined the IKK-NF-κB pathway, an important regulator of insulin signaling, in obesity and inflammation-induced insulin resistance. The main function of the IKK complex is the regulation of insulin signaling, in obesity and inflammation-induced insulin resistance. The aging led to a decrease in IkBα expression in the muscle of control and old rats. The aging led to a decrease in IkBα protein expression levels in the muscle of OS rats that was 3.2-fold compared to control rats, and this alteration was reversed by a single bout of exercise (Fig. 2D) (P < 0.05).

3.4. A single bout of exercise decreased the expression of PTP1B and increased the expression of SIRT1 in aged rats

Aging increased the expression of PTP-1B in the skeletal muscle of old rats by 3.2-fold compared to control rats, a phenomenon that was reversed by acute exercise (Fig. 3A). It is well established that PTP1B can interact with and desphosphorylate the insulin receptor (Ropelle et al., 2006; Picardi et al., 2008). To further investigate the effect of acute exercise on this association in aged rats, we evaluated IRβ/PTP1B interaction in the skeletal muscle from OE rats. In aging rats there was an increase in the IRβ/PTP1B association/IRβ expression by 4.4-fold in the gastrocnemius muscle, when compared with control rats and, in the muscle of OE rats, IRβ/PTP1B association/IRβ expression was markedly decreased, when compared with OS rats (Fig. 3B) (P < 0.05).

4. Discussion

It is established that insulin resistance occurs with aging (Fink et al., 1983; Goodman et al., 1983; Yoshimasa et al., 1988; Kono et al., 1990; Barnard et al., 1992; Gulve et al., 1993; Reed et al., 1993). This decline in insulin action has been attributed to chronological age itself and/or to a variety of secondary factors associated with the aging process, such as an increase in body fat and/or in central adiposity, and a reduction in spontaneous physical activity (Shimokota et al., 1991; Rimbert et al., 2004; Amati et al., 2009). In accordance with these previous data, our results show an increase in body weight (accumulation of epididymal adipose tissue), decreased whole-body insulin sensitivity and impairments in insulin signaling in the skeletal muscle of Wistar old rats when compared with young rats. Additionally, the results of this study show that just one session of exercise is able to circumvent the negative effects of aging/obesity, extending a finding described for an animal model of obesity and also in humans (Ropelle et al., 2006; Schenk and Horowitz, 2007).

Exercise is widely perceived to be beneficial for glycaemic control in patients with insulin resistance and type 2 diabetes. Increased physical exercise has been linked to improved glucose homeostasis and enhanced insulin sensitivity. After an acute bout of exercise, insulin sensitivity is enhanced in insulin-sensitive tissues, such as skeletal muscle, adipose, liver and hypothalamus (Aoi et al., 2004; Peres et al., 2005; Flores et al., 2006; Ropelle et al., 2006, 2009; Pauli et al., 2008). The molecular mechanism for enhanced insulin-mediated glucose uptake with exercise training maybe partly related to increased expression and activity of key

![Image](https://via.placeholder.com/150)

**Fig. 2.** Effect of acute exercise on IRS-1 serine phosphorylation, JNK activity, IkBα degradation and JNK protein levels in muscle of controls, OS and OE rats. Tissue extracts were immunoblotted (IB) with anti-IRS-1 antibody (A upper panel), anti-IRβ antibody (A lower panel), anti-phospho JNK antibody (B upper panel), anti-JNK antibody (B lower panel), anti-phospho-c-Jun antibody (C) and anti-IkBα antibody (D) in control, OS and OE rats. Immunoblot was performed employing anti-beta-Actin antibody as the loaded protein (lower panels in C and D). The results of scanning densitometry were expressed as arbitrary units. Bars represent means ± SEM of eight rats. *P < 0.05, versus control and #P < 0.05, OS versus OE.

![Image](https://via.placeholder.com/150)

**Fig. 3.** PTP1B protein level in OS and OE rats was compared with control group (A upper panel). In addition, to determine the IRβ–PTP1B association the tissue extracts were immunoprecipitated (IP) with anti-IRβ followed by immunoblotting (IB) with anti-PTP-1B antibody (B upper panel). The expression of IRβ was evaluated in all groups. For this, the tissue extracts were immunoblotted (IB) with anti-IRβ (B lower panel); SIRT1 protein level in OS and OE rats also was compared with control group (C upper panel). Finally, immunoblot was performed employing anti-bet alpha-Actin antibody as the loaded protein (lower panels in A and C). The results of scanning densitometry were expressed as arbitrary units. Bars represent means ± SEM of eight rats. *P < 0.05, versus control and #P < 0.05, OS versus OE.
proteins known to regulate glucose metabolism in skeletal muscle and liver (Chibalin et al., 2000; Aoi et al., 2004; Ropelle et al., 2006, 2009). In our study, results showed that old rats exhibited decreased whole-body insulin sensitivity, as indicated by reduced glucose disappearance rate during an insulin tolerance test. However, old rats subjected to an acute exercise protocol displayed improvements in whole-body insulin sensitivity and this was associated with an improvement in insulin signaling in the skeletal muscle.

Nevertheless, the measurement of insulin sensitivity through the insulin tolerance test is a whole body measurement, while insulin signaling was enhanced in skeletal muscle. A limitation of our study, was that we do not provide any evidence that glucose uptake was enhanced in the skeletal muscle. However, a previous study in our laboratory using a hyperinsulinaemic–euglycaemic clamp procedure showed that diet-induced obese (DIO) rats presented a significant reduction in glucose uptake in the skeletal muscle when compared to the control group (Ropelle et al., 2006). Conversely, 16 h after a single bout of exercise, insulin induced an increase in glucose uptake of 33.8% in the muscle of exercised DIO rats, when compared to DIO rats. Thus, it is possible that in exercised old rats, there is also an increased glucose uptake in skeletal muscle in association with the improvement in insulin signaling.

Moreover, various defects in insulin action have been reported in animals during aging (Carrascosa et al., 1989; Kono et al., 1990; Kern et al., 1992; Nadiv et al., 1992; Gulve et al., 1993). However, the exact mechanisms involved in insulin resistance have not been adequately defined. Different components of insulin signaling have been measured in skeletal muscle with exercise training in aged rats (Arias et al., 2001). In accordance with previous data (Rocha et al., 2003), a significant reduction in insulin-induced IR, IRS-1 and Akt phosphorylation in the gastrocnemius muscle was observed in old rats, when compared with rats submitted to an acute exercise protocol. The improvement in insulin signaling pathways is related to an increase in protein expression of IR/IRS-1/Akt. These important adaptations in the insulin signal pathway in the skeletal muscle at 16 h after a single bout of exercise were able to improve insulin sensitivity in exercised old rats.

Is it well established that exercise-induced enhancement of glucose disposal is preserved in 25-month-old rats (Han et al., 1998). Other investigators have evaluated the effect of exercise training on the abundance of insulin signaling proteins, including the insulin receptor, IRS-1, PI3-K, and Akt, in the muscle of young and adult rats (Chibalin et al., 2000; Nagasaki et al., 2000). Previous research with young rats (that were approximately 4–27 weeks old) has indicated that exercise training can result in increased insulin receptor (Chibalin et al., 2000) and PI3-K abundance in skeletal muscle (Nagasaki et al., 2000).

However, differing results (no change, increased, or decreased levels) have been reported for insulin signaling in the skeletal muscle after exercise (Chibalin et al., 2000; Nagasaki et al., 2000; Arias et al., 2001). These apparently contradictory results maybe related to the protocol of exercise and changes in physiological and metabolic parameters in each model. Furthermore, another important methodological consideration is the nature of the insulin stimulus. In our study the rats were infused with a supra-maximal insulin dose through the portal vein, as opposed to an intraperitoneal injection or in vitro stimulation. It is important to mention that the doses of insulin used were 3–4 times higher than the dose required for maximal insulin signaling, suggesting a possibility of spare insulin signaling under these conditions.

In addition, it should be taken into consideration that insulin resistance is a metabolic situation that is related to several molecular mechanisms that act in parallel to down-regulate insulin signaling. Since exercise is an efficient way to improve insulin sensitivity, it is possible that it may also act in other mechanisms of insulin resistance. In this setting, an inflammatory network in ageing has been highlighted associated with insulin resistance (Krabbe et al., 2004; Arkan et al., 2005; Vasto et al., 2007). IKK-β and JNK are serine/threonine kinases activated by diverse stimuli, including cytokines, stress, and fatty acids and can inhibit insulin signaling (Hotamisligil et al., 1996; Hirosumi et al., 2002; Prada et al., 2005; Ropelle et al., 2006, Nieto-Vazquez et al., 2008). In the present study, we indirectly assessed IKK activation through IkBα protein expression in the muscle of rodents. The aging led to a decrease in IkBα protein expression and increased expression JNK in the skeletal muscle of old rats compared to control rats, and this alternation was reversed by a single bout of exercise. Our results are in accordance with other studies that show that acute exercise decreases JNK and IKK signaling in the context of obesity (Ropelle et al., 2006; Schenck and Horowitz, 2007). Likewise, JNK phosphorylation was reduced after resistance exercise in old men (Williamson et al., 2003). Notably previous studies have shown that acute exercise increases JNK activity (Aronson et al., 1997; Fuji et al., 2004), which is in contrast to our study and others (Ropelle et al., 2006; Schenck and Horowitz, 2007) findings of reduced JNK activity after exercise. A temporal difference in analysis is the likely explanation for these discrepancies, as well as others (Ropelle et al., 2006; Schenck and Horowitz, 2007) measured JNK some hours after exercise, while JNK was measured immediately after exercise in the other studies.

Previous studies, on cell-based experiments, demonstrated that IRS-1 Ser307 phosphorylation is a negative modulator of insulin action (Aguirre et al., 2002; Gao et al., 2002). However, very recently using knockin mice (which Ser307 was replaced with alanine) Copps et al. demonstrated that when these mice were fed a high-fat diet they developed more severe insulin resistance than control mice, suggesting that IRS-1 Ser 307 phosphorylation is a positive regulator of insulin action (Copps et al., 2010). Thus, the role of IRS-1 Ser phosphorylation in insulin sensitivity deserves further investigation.

Additionally, as a negative regulator of the insulin signal transduction cascade, protein tyrosine phosphatase 1B (PTP-1B) has been shown to function as a key insulin receptor phosphatase (Ventre et al., 1997; Greene et al., 2003). PTP-1B is a major PTP implicated in the regulation of insulin action, including in the insulin-resistant state (Seeley et al., 1996; Elchelby et al., 1999), which acts to reverse tyrosine kinase activity (Asante-Appiah and Kennedy, 2003). PTP-1B-deficient mice are more sensitive to insulin (Elchelby et al., 1999) and diabetic mice treated intraperitoneally with PTP-1B antisense oligonucleotides have lower PTP-1B protein levels in liver, leading to decreases in fat, plasma insulin, and blood glucose levels (Zinker et al., 2002). These findings indicate that inhibition or downregulation of PTP-1B is an effective strategy for improving insulin sensitivity. Our results show a decreased expression of PTP-1B, at 16 h after acute exercise in old rats in parallel with an increase in IR autophosphorylation, which certainly contribute to improved insulin sensitivity.

Recently, Sun et al. showed that SIRT1 is down-regulated in insulin-resistant cells and tissues and that knockdown or inhibition of SIRT1 induces insulin resistance (Sun et al., 2007). Furthermore, increased expression of SIRT1 improved insulin sensitivity, especially under insulin-resistant conditions. Similarly, resveratrol, a SIRT1 activator, enhanced insulin sensitivity in vitro in a SIRT1-dependent manner and attenuated high-fat-diet-induced insulin resistance in vivo. Further studies demonstrated that the effect of SIRT1 on insulin resistance is mediated by repressing PTP1B transcription at the chromatin level (Sun et al., 2007). Taken together, the finding that SIRT1 improves insulin sensitivity has implications toward resolving insulin resistance and type 2 diabetes. In our study, exercised old rats showed increased
expression of SIRT1, when compared with old rats. Thus, it is possible that this reduction in PTP1B in exercised rats maybe prevented after acute exercise, and is accompanied by an increase in muscle triglyceride synthesis. These data suggest that, after a bout of exercise, the flux of fatty acids toward triglyceride synthesis within muscle reduce the accumulation of fatty acid metabolites and suppressed the pimprolafina-
tory response in skeletal muscle, as evidenced by decreased phosphorylation and activation of JNK and increased abundance of inhibitor of IκBα and IκBβ (Schenk and Horowitz, 2007; Liu et al., 2007). Although, in the present study, we did not measure triglycerides, our data showed a reduction of the JNK and IκK-β/NFκB pathway in skeletal muscle in aging rats after an acute exercise protocol, which might contribute to improved insulin action.

In conclusion, our data reinforce the hypothesis that multiple mechanisms are involved in insulin resistance in aging rats and, that interestingly, a single bout of exercise attenuates different modulators of the insulin signaling pathway, resulting in improvement in insulin sensitivity. Thus, the beneficial effects of exercise to reverse obesity induced insulin resistance appear to be preserved in aging.

Acknowledgments

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