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Injury-induced insulin resistance in adipose tissue

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ABSTRACT

Hyperglycemia and insulin resistance are common findings in critical illness. Patients in the surgical ICU are frequently treated for this 'critical illness diabetes' with intensive insulin therapy, resulting in a substantial reduction in morbidity and mortality. Adipose tissue is an important insulin target tissue, but it is not known whether adipose tissue is affected by critical illness diabetes. In the present study, a rodent model of critical illness diabetes was used to determine whether adipose tissue becomes acutely insulin resistant and how insulin signaling pathways are being affected. There was a reduction in insulin-induced phosphorylation of IR, IRS-1, Akt and GSK-3β. Since insulin resistance occurs rapidly in adipose tissue, but before the insulin resistance in skeletal muscle, it may play a role in the initial development of critical illness diabetes.

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1. Introduction

Insulin resistance is a major underlying feature of Type 2 diabetes and many other chronic metabolic abnormalities, including obesity, dyslipidemia, non-alcoholic fatty liver, polycystic ovary syndrome, and hypertension [1–5]. An acute form of hyperglycemia and insulin resistance, referred to as "critical illness diabetes", are common findings in patients following trauma, surgery, burn injury or infection [6–13]. The development of hyperglycemia in human critical illness diabetes has been considered an adaptive and beneficial response to stress. However, recent studies indicate that the development of hyperglycemia is associated with poor outcomes following critical illness [9,14–17], and intensive insulin therapy, used to reduce the hyperglycemia, reduces morbidity and mortality among at least a subset of this patient population [6,9,18,19].

The binding of insulin to the extracellular subunit of its receptor activates the insulin receptor tyrosine kinase activity, stimulates autophosphorylation, and induces the phosphorylation of a number of target proteins. These include the insulin receptor substrate proteins (IRS) which serve as docking proteins for several downstream signaling molecules, facilitating the activation of multiple insulin responsive signal transduction cascades [20,21]. The IRS/phosphatidylinositol 3-kinase (PI3K)/Akt pathway is the major signaling cascade that is activated following insulin binding and is involved in the regulation of metabolism by insulin [22–25].

White adipose tissue, liver, and skeletal muscle are the major targets of insulin action and play an important role in energy metabolism and insulin sensitivity. The development of insulin resistance in skeletal muscle following injuries has been studied [10,26–29] and there are a few studies on the development of insulin resistance in liver [11,12,29,30]. However, little is known about the development of insulin resistance in adipose tissue following injury. To address the question of whether adipose tissue becomes insulin resistant following injury and to determine the time course of any defects in insulin signaling, we assessed the phosphorylation of IR, IRS-1, Akt, and GSK-3β following experimental injury. Here we provide evidence that insulin resistance develops in adipose tissue as early as 15 min following hemorrhage and is characterized by impaired insulin-stimulated signaling via the IR/IRS/PI3K/Akt pathway.

2. Materials and methods

2.1. Animal model of critical illness diabetes

All procedures were carried out in accordance with the guidelines set forth in the Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals by the National Institutes of Health and were approved by the Institutional Animal Care and Use Committee of the University of Alabama at Birmingham. An animal model of rat critical illness diabetes, trauma and hemorrhage,

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was used in this study as previously described [10–12,27]. Male Sprague–Dawley rats (260–300 g, Harlan, Indianapolis, IN) were fasted 18–20 h before the experiment, but allowed water *ad libitum*. The rats were anesthetized with isoflurane inhalation (Mallinckrodt Veterinary, Mundelein, IL), a 5-cm ventral midline laparotomy was performed representing soft-tissue trauma and the abdomen was closed. Polyethylene-50 catheters (Clay–Adams, Parsippany, NJ) were placed in the right and left femoral arteries and the right femoral vein for bleeding, monitoring of mean arterial pressure (MAP), and fluid resuscitation, respectively. Trauma and hemorrhage (TH) rats were bled to a MAP of 35–40 mm Hg within 10 min (=initial bleed). Once the MAP reached 40 mm Hg, the timing of the hemorrhage period began and was maintained for the specified times. Trauma only (T) rats underwent the same surgical procedure (laparotomy and catheterization), but were not hemorrhaged.

2.2. Study design

Due to the considerable trauma incurred by anesthesia and opening of the abdominal cavity to perform the saline or insulin injections, it was impossible to have a completely untreated control group [10–12,27]. Thus, the baseline group was selected in these experiments to be the trauma only animals (T0′) that were subjected to anesthesia, laparotomy, and catheterization and then killed immediately. Additional trauma only animals (T groups) were subjected to these same procedures and then killed at 15 (T15′), 30 (T30′) and 60 min (T60′) after catheterization. Matched to these groups were the trauma and hemorrhage (TH) groups that were subjected to the same procedures as the T groups, but also subjected to hemorrhage and then killed at 15, 30 or 60 min after the initial bleed.

At the specified time point, the abdominal cavity was opened again, the portal vein exposed, and insulin (5 U in 0.5 ml saline) or saline alone (0.5 ml) was injected into the portal vein. Epididymal fat pads were removed 1.5 min following the injection and quickly frozen in liquid nitrogen.

2.3. Immunoblot analysis

Epididymal adipose tissue from each animal (approximately 0.25 g) was homogenized in 0.5 ml lysis buffer containing 50 mM Tris, pH 8.0, 150 mM NaCl, 50 mM NaF, 30 mM sodium pyrophosphate, 2 nM sodium orthovanadate, 0.1 μg/ml okadaic acid, 1% Igepal, 0.5% sodium deoxycholic acid, and 0.5× protease inhibitor cocktail (P2714; Sigma–Aldrich, St. Louis, MO). Tissue lysates were centrifuged twice at 12,000×*g* for 10 min. Protein concentrations were determined using the Bio-Rad DC assay (Bio-Rad Laboratories, Hercules, CA). For Western blotting, 20 μg of protein per lane was resolved by SDS–PAGE and transferred to nitrocellulose membranes [10–12,27]. The Western transfers were immunoblotted with polyclonal antiserum against phosphotyrosine (Y972) IR, phosphotyrosine (Y612) IRS-1 (Invitrogen's Biosource International, Carlsbad, CA), phosphoserine (S473) Akt, phosphoserine (S9) GSK-3β, and total-ERK (Cell Signaling Technology, Danvers, MA). Horseradish peroxidase-conjugated secondary antibody was added for detection of bound antibody by enhanced chemiluminescence (GE Healthcare, Piscataway, NJ). Each blot was stripped in Re-Blot Plus (Chemicon, Temecula, CA) before reprobing with a different antibody.

2.4. Statistical analysis

Enhanced chemiluminescent images of immunoblots were scanned and quantified using Zero D-Scan (Scanalytics, Fairfax, VA). All values are presented as mean density ± standard error. The values for the T and TH groups (in the absence and presence of insulin) are expressed as fold change compared to the T0 group in the absence of insulin (baseline). All data was analyzed by either Student's *t* test or one-way ANOVA, when appropriate, using the InStat statistical program by GraphPad Software (San Diego, CA).

3. Results

3.1. Time course of alterations in insulin signaling in adipose tissue following initiation of critical illness diabetes

The primary aim of this study was to determine whether adipose tissue becomes insulin resistant in a rat model of critical illness diabetes. Trauma and hemorrhage was performed and mean arterial pressure maintained at 35–40 mm Hg for 15 min (TH15′), 30 min (TH30′), and 60 min (TH60′), respectively. Western blot data (Fig. 1A) indicated that there was an almost complete loss of insulin-induced phosphorylation of insulin receptor tyrosine 972 (P-IR [Y972]), as early as 15 min following hemorrhage which persisted up to 60 min following hemorrhage. Quantified data from multiple animals demonstrated that there was no consistent difference in the fold induction of insulin-stimulated P-IR (Y972) in epididymal adipose tissue (Fig. 1B–D) following trauma only (T0′ vs T15′, T30′ and T60′), although following 30 min of trauma only (T30′; Fig. 1C), there was a transient increase in insulin-induced P-IR (Y972). Most importantly for this work, there was a consistent, large, and significant decrease in insulin-stimulated P-IR (Y972) in each of the trauma and hemorrhage (TH) groups (T0′ vs TH15′, TH30′, and TH60′; Fig. 1B–D). Total ERK levels are shown as a control for loading and transfer. All blots were re-probed with the antibody for total ERK in all the experiments presented below, but are not shown for brevity (Figs. 2–4).

Western blot analysis was performed at the same time points to examine the phosphorylation of tyrosine 612 of IRS-1 (P-IRS-1 [Y612]), which is important for the activation of the PI3-kinase/Akt pathway (Fig. 2A; [31]). In the trauma only groups there was little consistent change in insulin-induced P-IRS-1 (Y612: Fig. 2B–D). Again, most important for the present work, for each of the trauma and hemorrhage time points, there was a complete loss of insulin-induced tyrosine phosphorylation of IRS-1 (Y612) following the combination of trauma and hemorrhage.

To further evaluate the IRS/PI3K/Akt signaling cascade in adipose tissue, insulin-induced phosphorylation of Akt on serine 473 (P-Akt [S473]; Fig. 3) and GSK-3β on serine 9 (P-GSK-3β [S9]; Fig. 4), a downstream substrate of Akt, were also examined. Following trauma alone there was no significant change in insulin-stimulated P-Akt (S473). However, there was a complete loss of insulin-stimulated P-Akt (S473; Fig. 3A) as early as 15 min (TH15′), as well as at 30 and 60 min following the combination of trauma and hemorrhage (Fig. 3B–D). Likewise, as early as 15 min and at 60 min following the combination of trauma and hemorrhage following hemorrhage, there was a complete loss in insulin-induced P-GSK-3β (Fig. 4A–C). Thus, the data indicates a rapid onset of a severe epididymal adipose tissue defect of insulin induction of the IR/IRS/PI3K/Akt signaling pathway which occurred as early as 15 min following the initiation of an animal model of critical illness diabetes.

4. Discussion

The overall endocrine response to injury is not well understood. There are only a limited number of studies on insulin signaling defects in skeletal muscle and liver following injury [10–12,27–30,32,33]. Recently, we found that hepatic insulin resistance develops quickly in rats, within 15 min [11,12,27,30], while skeletal

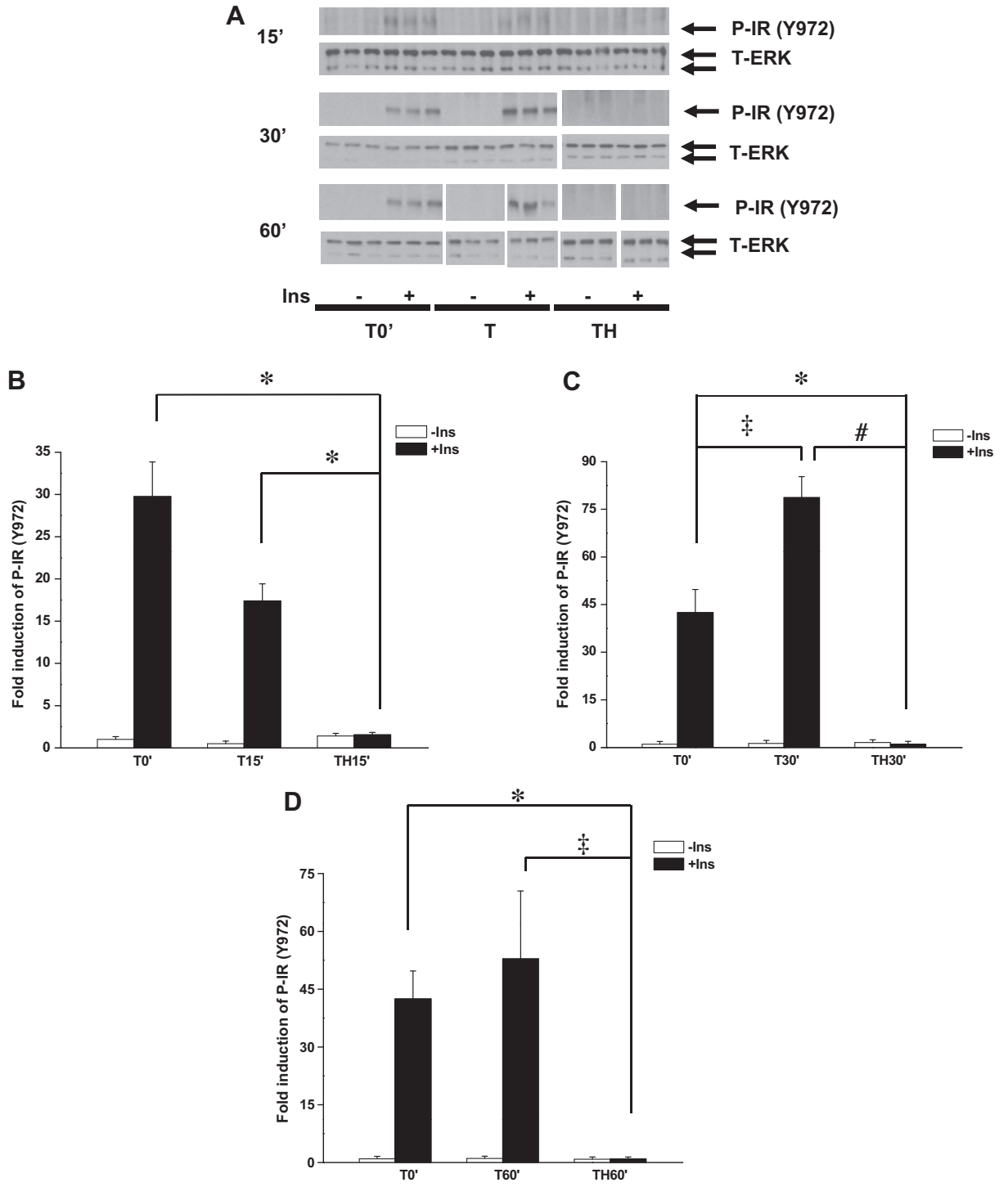

Fig. 1. Decreased insulin-stimulated tyrosine phosphorylation of the insulin receptor (IR) in rat epididymal adipose tissue following trauma and hemorrhage. Rats were subjected to trauma only (T), or trauma and hemorrhage (TH). At 0′, 15′, 30′ or 60′, either saline (-) or 5U insulin (+) was injected via the hepatic portal vein and the epididymal adipose tissue was removed after 1.5 min. Tissue lysates were subjected to Western blotting with antibody specific for phospho-IR tyrosine 972 (P-IR [Y972]). (A) Representative Western blots are presented. Breaks in the images indicate where samples were run on different portions of the same gel. (B–D) Autoradiographs were quantified by scanning densitometry. The phosphorylated protein levels in T0′ without insulin treatment were arbitrarily set to 1 and the data are presented as the means ± SEM, fold induction of P-IR (Y972) by insulin of three rats ($n = 3$) in each group. $^{\#}p < 0.001$; $^{*}p < 0.01$ and $^{\ddagger}p < 0.05$. For this and all figures, T, trauma only; TH, trauma and hemorrhage; Ins, insulin. Total ERK levels are shown as a control for loading and transfer. All blots were re-probed with the antibody for total ERK in all the experiments presented below, but are not shown for brevity.

muscle signaling defects develop more slowly (within 60 min) following trauma and hemorrhage [10,27]. While decreased insulin sensitivity in adipose tissue is well-established in chronic diseases [34–39], little is known about the acute adipose tissue response to critical illness diabetes. One study reported alterations in insulin signaling in adipose tissue following burn injury in rats, but these measurements were performed 3 weeks after the injury [29]. In the present study, an insulin signaling defect, as measured by decreased insulin receptor autophosphorylation, developed in adipose tissue following a time course similar to liver, but prior to that

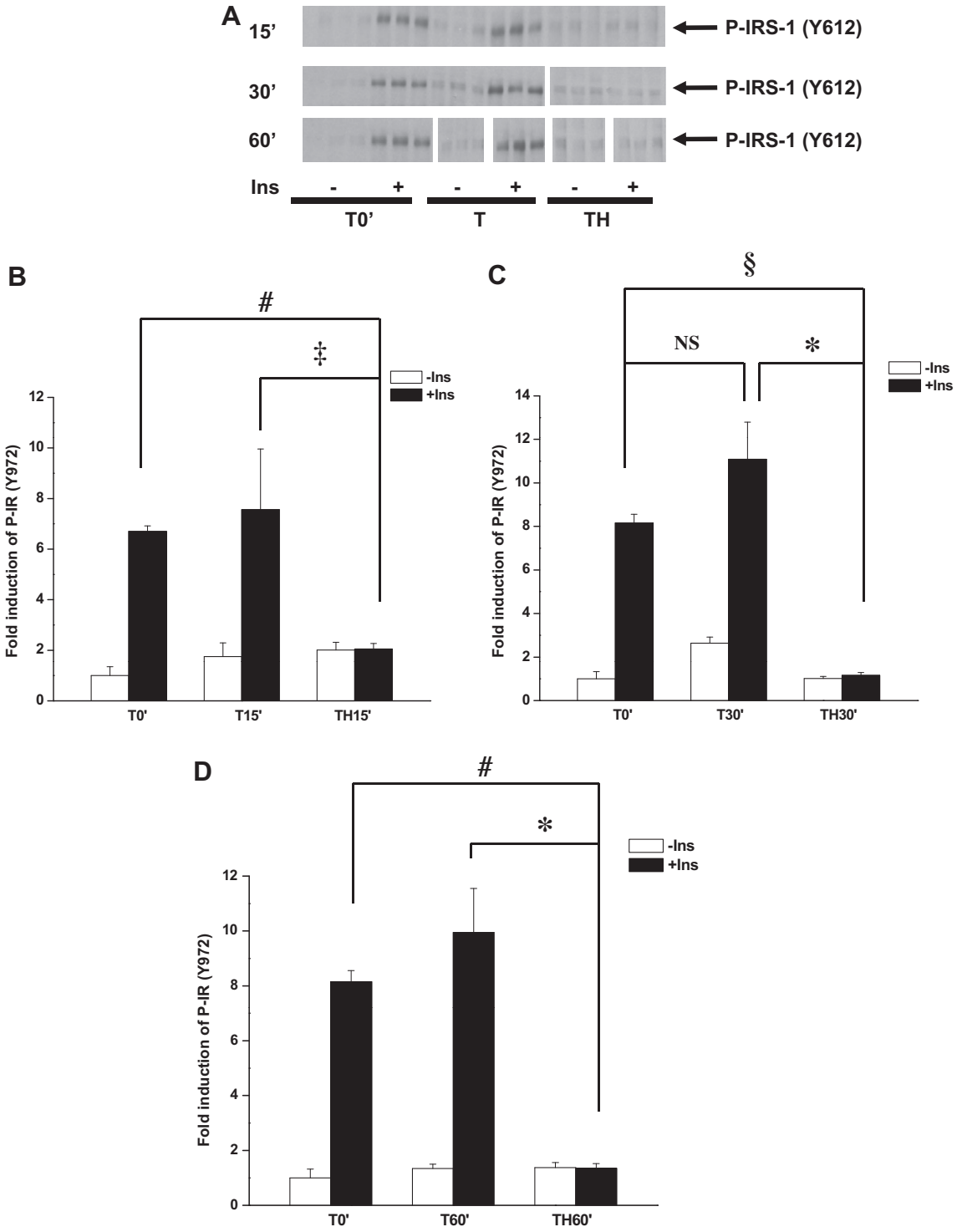

Fig. 2. Decreased insulin-stimulated tyrosine phosphorylation of IRS-1 in rat epididymal adipose tissue following trauma and hemorrhage. Rats were subjected to trauma only (T) or trauma and hemorrhage (TH) as described in Fig. 1 except tissue lysates were subjected to Western blotting with antibody specific for phospho-IRS-1 tyrosine 612 (P-IRS-1 [Y612]). (A) Representative Western blots are presented. Breaks in the images indicate where samples were run on different portions of the same gel. (B–D) Autoradiographs were quantified by scanning densitometry. The phosphorylated protein levels in T0′ without insulin treatment were arbitrarily set to 1 and the data are presented as the means ± SEM, fold induction of P-IRS-1 (Y612) by insulin of three rats ($n = 3$) in each group. $^{\S}p < 0.0001$; $^{\#}p < 0.001$; $^{*}p < 0.01$; $^{\ddagger}p < 0.05$ and NS, not significant.

in skeletal muscle. We also measured decreased activation/phosphorylation downstream of the insulin receptor, including insulin-stimulated phosphorylation of IRS-1, Akt and GSK-3β, possibly due to the decreased activation of the insulin receptor.

The present work indicates the potential importance of adipose tissue in critical illness diabetes. Adipose tissue can produce and secrete both cytokines and adipokines, which have been implicated in insulin resistance associated with chronic diseases, such as Type 2 diabetes and obesity [40–45]. Several of these cytokines and adipokines can directly or indirectly interfere with insulin signaling [30,46–53]. However, there is no information on protein or mRNA expression of adipose tissue cytokines and adipokines in

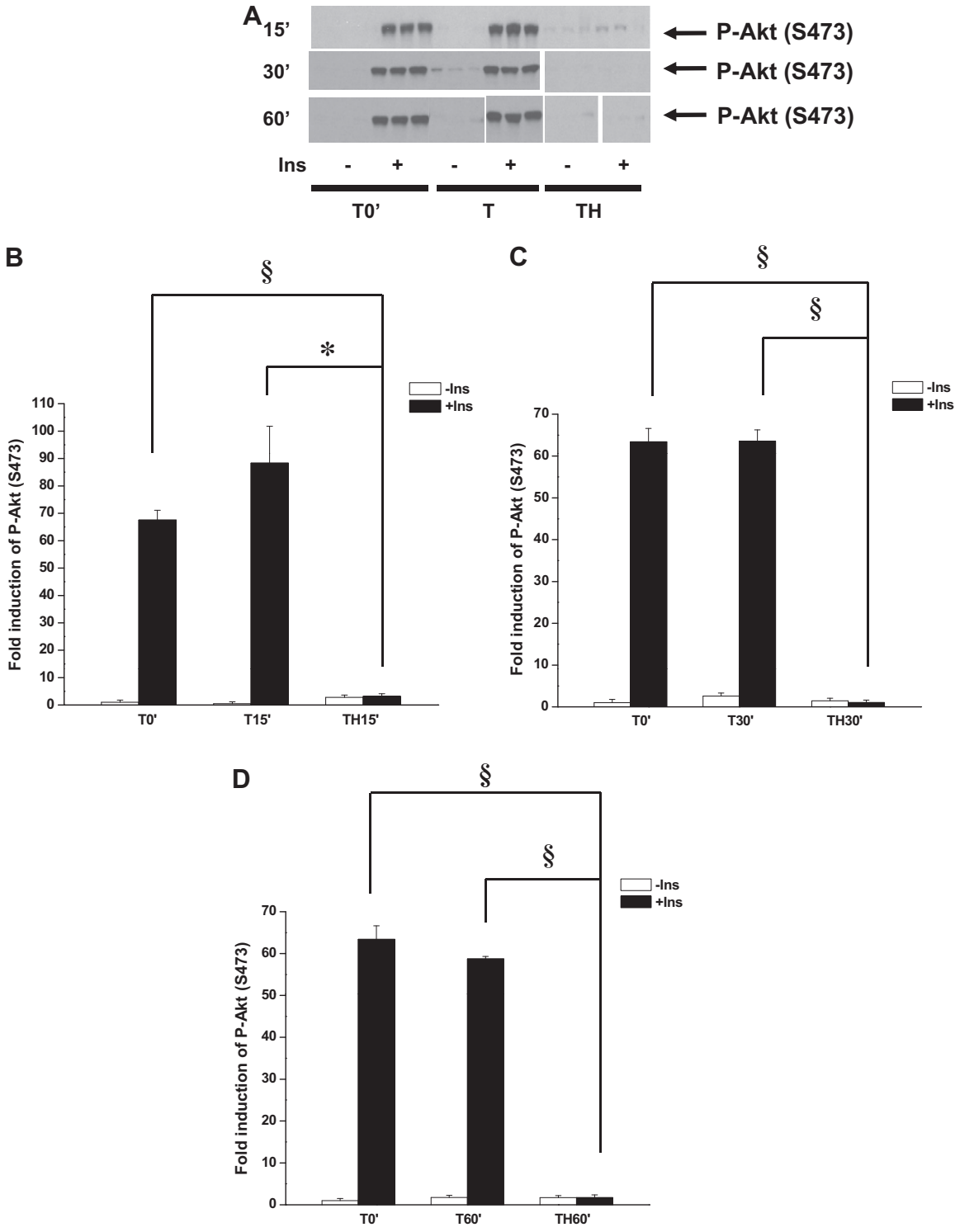

Fig. 3. Decreased insulin-stimulated serine phosphorylation of Akt in rat epididymal adipose tissue following trauma and hemorrhage. Rats were subjected to trauma only (T) or trauma and hemorrhage (TH) as described in Fig. 1 except tissue lysates were subjected to Western blotting with antibody specific for phospho-Akt serine 473 (P-Akt [S473]). (A) Representative Western blots are presented. Breaks in the images indicate where samples were run on different portions of the same gel. (B–D) Autoradiographs were quantified by scanning densitometry. The phosphorylated protein levels in T0′ without insulin treatment were arbitrarily set to 1 and the data are presented as the means ± SEM, fold induction of P-Akt (S473) by insulin of three rats ($n = 3$) in each group. $^{\S}p < 0.0001$ and $^{*}p < 0.01$.

critical illness diabetes, and since there are changes in adipose tissue insulin responsiveness, future experiments are planned to determine this. For instance, we previously demonstrated that circulating TNF-α, and hepatic levels of TNF-α mRNA and protein, increase by 90 min following the combination of trauma and hemorrhage [11,30], but changes in adipose tissue TNF-α expression is unknown.

Numerous studies suggest that intensive insulin therapy, to reduce the hyperglycemia often observed in the critically ill, can be beneficial, reducing morbidity and mortality [9,54–59]. However,

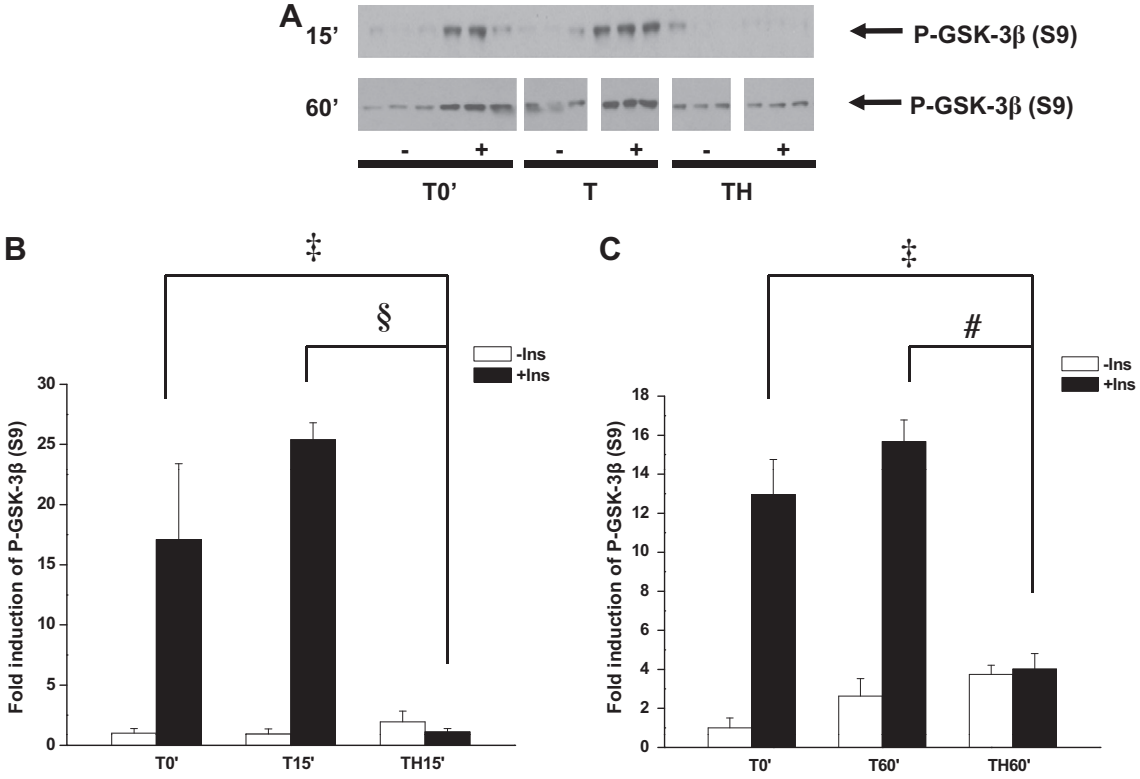

Fig. 4. Decreased insulin-stimulated serine phosphorylation of GSK-3β in rat epididymal adipose tissue following trauma and hemorrhage. Rats were subjected to trauma only (T) or trauma and hemorrhage (TH) as described in Fig. 1 except tissue lysates were subjected to Western blotting with antibody specific for phospho-GSK-3β serine 9 (P-GSK-3β [S9]). (A) Representative Western blots are presented. Breaks in the images indicate where samples were run on different portions of the same gel. (B,C) Autoradiographs were quantified by scanning densitometry. The phosphorylated protein levels in T0′ without insulin treatment were arbitrarily set to 1 and the data are presented as the means ± SEM, fold induction of P-GSK-3β [S9] by insulin of three rats ($n = 3$) in each group. $^{\S}p < 0.0001$; $^{\#}p < 0.001$ and $^{\ddagger}p < 0.05$.

there can also be an increase in hypoglycemic incidents, and it is not clear if all patients will benefit from intensive insulin therapy [60–62]. Even though intensive insulin treatment to reduce hyperglycemia is now the norm in many ICU's, little has been learned about the causes of the acute insulin resistant state that leads to the hyperglycemia, which tissues are involved, and the cellular mechanisms which result in the acute insulin resistance of critical illness diabetes. Our additional studies suggest that there are likely different causative factors and cellular mechanisms for the acute development of insulin resistance in the three main insulin target tissues, liver, skeletal muscle and adipose tissue. The present study indicates that adipose tissue may play a role in the acute insulin resistant state in an animal model of critical illness diabetes.

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