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Regulation of TNFα converting enzyme activity in visceral adipose tissue of obese mice

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ABSTRACT

Tumor necrosis factor α (TNFα) is a pro-inflammatory cytokine and one of the major mediators of obesity-induced insulin resistance. TNFα is generated through TNFα converting enzyme (TACE)-mediated cleavage of the transmembrane precursor pro-TNFα. Inhibition of TACE resulted in the improvement in glucose and insulin levels in diabetic animals, suggesting a crucial role of TACE activity in glucose metabolism. However, the regulation of TACE activity in insulin-sensitive tissues has not been fully determined. This study aimed to investigate the impact of TACE in insulin-sensitive tissues in the early stage of the development of obesity. C57BL6 mice were fed standard chow (B6-SC) or high-fat/high-sucrose diet (B6-HF/HS). KK-Ay mice were fed SC *ad libitum* (Ay-AL) or fed reduced amounts of SC (caloric restriction (CR); Ay-CR). As control for Ay-AL, KK mice fed SC *ad libitum* (KK-AL) were used. TACE activity in visceral adipose tissue (VAT), but not in liver or skeletal muscle, was significantly elevated in B6-HF/HS and Ay-AL compared with B6-SC and KK-AL, respectively. Phosphorylation of JNK and p38MAPK, but not ERK, in VATs from B6-HF/HS and Ay-AL was also significantly elevated. Ay-CR showed significantly lower TACE, JNK and p38MAPK activities in VAT and serum TNFα level compared with those of Ay-AL. In contrast, intraperitoneal injection of TNFα activated TACE, JNK and p38MAPK activities in VAT in KK mice. In conclusion, during the development of obesity, TACE activity is elevated only in VAT, and CR effectively reduced TACE activity and TACE-mediated pro-TNFα shedding in VAT.

1. Introduction

Obesity is a growing public health problem worldwide and causes insulin resistance, hypertension, impaired lipid metabolism and type 2 diabetes. Excessive caloric intake and reduced physical activities contributes to the development of obesity [1]. Increased adiposity leads to local tissue inflammation as a consequence of adipocyte hypertrophy and associated infiltration of macrophages [2,3]. Both events cause dysregulation of adipokine production (overproduction of deleterious adipokines such as tumor necrosis factor α (TNFα) and hyposecretion of defensive ones such as adiponectin) [2,3]. Lifestyle modification with caloric restriction (CR) reduces body weight (BW) and improves various metabolic parameters [1,4].

TNFα is a pro-inflammatory cytokine that involves the development of insulin resistance in obese rodents and humans. In obesity, increased plasma TNFα is not only the hallmark of insulin resistance but also a crucial determinant of adipokine dysregulation in adipocytes [2,3,5–7].

Precursor of TNFα, pro-TNFα, is located on cell surface as a 26 kDa membrane-anchored protein and is processed into a 17 kDa secreted form, mature TNFα, that is released to extracellular space as a functioning cytokine through cleavage by TNFα converting enzyme (TACE, also known as a disintegrin and metalloproteinase-17 (ADAM17)) [8,9]. TACE is naturally inhibited *in vivo* by tissue inhibitor of matrix metalloproteinase-3 (TIMP3). The balance between TACE and TIMP3 activities seems to determine serum TNFα levels, and a reduction of TIMP3 expression, indeed, resulted in an elevation of serum TNFα due to unrestricted TACE activity [10,11]. Activation of TACE is triggered by mitogen-activated protein kinases (MAPKs) including extracellular signal-regulated kinase (ERK) and p38MAPK [12–15].

After translation of TACE mRNA, immature TACE protein with its prodomain is present as an inactive zymogen in the endoplasmic reticulum (ER), and TACE becomes active when its inhibitory prodomain is removed in the Golgi apparatus (mature TACE (mat-TACE)) [16,17].

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Several reports revealed that inhibition of TACE activity by pharmacological TACE inhibitors resulted in improvement in insulin sensitivity and glucose metabolism in diabetic animals [11,18,19]. In addition, a temporal systemic TACE deletion *in vivo* showed the improved glucose metabolism under high-fat (HF) diet feeding [20]. Taken together, these results suggest a crucial role of TACE activity in insulin action and glucose metabolism.

However, the tissues responsible for TACE activation during the development of obesity are largely unknown. In this study, therefore, we investigated the TACE activity in insulin-sensitive tissues in two animal models of genetic hyperphagic and diet-induced obesity. We found that, at an early stage of the development of obesity, TACE activity elevated only in visceral adipose tissue (VAT), but not in liver or skeletal muscle. We further focused on VAT as a target of TACE activation, and investigated the effects of CR and TNFα administration on the activity and expression of TACE.

2. Material and methods

2.1. Animals and CR procedure

Mice were purchased from CLEA Japan (Tokyo, Japan). Five-week-old male C57BL/6J (B6), KK and KK-Ay mice were fed standard chow (SC: 4.6% fat, 51.0% carbohydrate and 24.9% protein by calories; CLEA Japan) *ad libitum* (AL) for a week, divided into experimental groups and housed individually. All procedures were approved by the Animal Care and Use Committee of Kumamoto University. The following three series of experiments were performed:

Study 1: The KK-Ay mice were randomized to CR-group (Ay-CR) or AL feeding-group (Ay-AL) (n = 6–12 each). The control KK mice were fed AL (KK-AL). Ay-AL and KK-AL were allowed a free access to food. To reduce the food intake and BW, the Ay-CR were given a reduced amount of SC (4.0 g/day) as previously described [21] with slight modifications. After 4 week-intervention with the respective diets, animals were subjected to the experiments. Before tissue harvest, animals were fasted for 16 h and the SC was given for 3 h, and then subjected to the experiments, otherwise indicated.

Study 2: Six-week-old B6 mice were randomized to two groups, fed SC (B6-SC) or fed high-fat/high-sucrose diets (B6-HF/HS) (n = 8–10 each). Animals were maintained with the indicated diet for 12 weeks and were subjected to experiments.

Study 3: Ten-week-old KK-AL were intraperitoneally (ip) injected with vehicle alone (phosphate-buffered saline (PBS)) or TNFα (100 μg/kg) twice (24 and 8 h before tissue harvest) [22].

Assessments for metabolic parameters, procedures for protein extraction, Western blotting and measurements of plasma and tissue TNFα concentration with an ELISA kit (Invitrogen, Camarillo, CA) were described previously [21–23]. Tissue membrane preparation was performed as previously described [24]. Antibodies were described previously [21–23], except for anti-TACE antibodies from Santa Cruz Biotechnology (sc-13973) and Abcam (ab2051).

2.2. Measurement of TACE activities

TACE activity was determined by using the SensoLyte 520 TACE activity Assay Kit (AnaSpec, San Jose, CA) according to the manufacturer's instructions.

2.3. Quantitative real-time RT-PCR (qRT-PCR)

The qRT-PCR analysis was performed as previously reported [21,23] with specific primer sets listed in Supplementary Table S1.

2.4. Data analysis

All data are presented as means ± SD and were analyzed by Student's t-test or one-way ANOVA, respectively. A P value <0.05 was considered statistically significant.

3. Results

3.1. TACE activity in VAT was up-regulated in obese mice

We first investigated the TACE activities in liver, skeletal muscle and VAT in obese mice models. TACE activities in liver and skeletal muscle in Ay-AL were not elevated compared with those in KK-AL. TACE activity of Ay-AL was significantly elevated only in VAT by 3.3-fold compared with that of KK-AL (Fig. 1A).

Ay-AL ate more than KK-AL throughout the treatment periods (Supplementary Fig. S1A). The CR procedure used in the present study reduced the BW of the Ay-CR to the comparable level of that of KK-AL after 1 week (Supplementary Fig. S1B). After 1 week, the BWs of Ay-CR and KK-AL were comparable and Ay-AL kept significantly greater BWs ($P < 0.05$) compared with those of the Ay-CR and KK-AL at every point investigated. Before the initiation of CR, the fasting and postprandial glucose levels, but not HbA1c, of Ay mice (Ay-AL and Ay-CR) were already higher than those of KK-AL (Supplementary Table S2), and no difference was observed in these parameters between Ay-AL and Ay-CR. After CR, fasting glucose, postprandial glucose and HbA1c levels were all reduced in Ay-CR compared with those in Ay-AL.

TACE activities in liver and skeletal muscle were comparable among KK-AL, Ay-AL, and Ay-CR (Fig. 1A), whereas elevated TACE activity in VAT in Ay-AL was significantly suppressed by 62% in Ay-CR (Fig. 1A).

Next, we examined the effect of HF/HS diet in B6 mice. The feeding of HF/HS diets for 12 weeks (B6-HF/HS) significantly increased BWs, fasting and postprandial glucose levels compared with those of B6 mice fed with standard chow (B6-SC) (Supplementary Table S3). TACE activity of VAT, but not in liver or skeletal muscle, elevated by 2.7-fold after 12-week feeding of HF/HS diet (Fig. 1B).

3.2. Elevated TACE activity in VAT of Ay-AL was induced by increased expression and processing of TACE protein

To investigate the molecular mechanisms of the regulation of TACE activity, we first evaluated the effects of obesity and CR on mRNA expression of TACE by qRT-PCR analysis. In Ay-AL, TACE mRNA expression was higher in liver and VAT, but was comparable in skeletal muscle, when compared with KK-AL. Ay-CR showed significantly lower TACE mRNA expression only in VAT, but showed

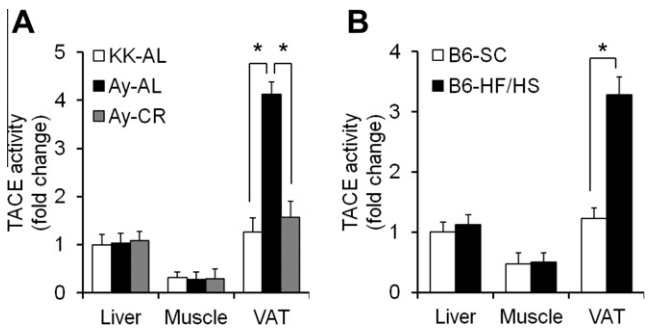

Fig. 1. Effects of the development of obesity or CR on tissue TACE activities. Tissue TACE activities were measured in KK-AL, Ay-AL and Ay-CR (A), or in B6-SC and B6-HF/HS (B). *$P < 0.05$ vs. indicated groups.

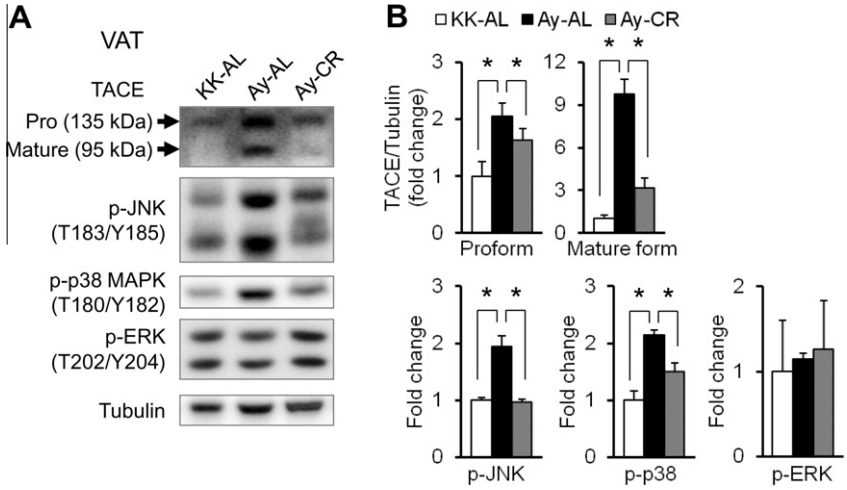

Fig. 2. Effects of CR on TACE protein expression and phosphorylation of JNK, p38MAPK and ERK in VAT. Western blot analysis for TACE, p-JNK, p-38MAPK and p-ERK are shown. Representative Western blots (A) and quantification data (B) are shown. $^{*}P < 0.05$ vs. indicated groups.

comparable TACE mRNA expression in liver and skeletal muscle when compared with those in Ay-AL (Supplementary Fig. S2A).

Next, we investigated the protein expression of TACE. TACE expression was higher in VAT (Fig. 2A upper panel, and 2B), but not in liver (Supplementary Fig. S3B and C) or skeletal muscle (Supplementary Fig. S3D and E), in Ay-AL compared with KK-AL. Similar results were observed in B6-HF/HS (Supplementary Fig. S4). Worthy to note, we easily detected the corresponding bands for TACE (135 kDa; TACE proform and 95 kDa; TACE mature form) in liver and VAT by Western blotting using 30 μg of tissue lysates per lanes. On the other hand, in skeletal muscle, we could not detect the corresponding bands of TACE (Supplementary Fig. S3A) by the same method as shown in Fig. 2. Therefore, we performed immunoprecipitation prior to Western blotting to concentrate TACE proteins from skeletal muscle lysates (200 μg of protein), and could detect the corresponding bands as shown in Supplementary Fig. S3D.

When compared with Ay-AL, in Ay-CR, both TACE mRNA and protein expression were significantly reduced in VAT (Supplementary Fig. S2A, Fig. 2A and B), which was not observed either in liver or muscle (Supplementary Figs. S2A and S3B–E).

TACE is activated by cleavage from proform (pro-TACE) to mature form (mat-TACE) [16,17]. The expression of pro-TACE in VAT was 2.1-fold higher in Ay-AL compared with that in KK-AL (Fig. 2A and B). On the other hand, mat-TACE protein was 9.8-fold higher in Ay-AL compared with that in KK-AL. In VAT of Ay-CR, both pro-TACE and mat-TACE were significantly lower (79% and 33%, respectively) compared with those of Ay-AL (Fig. 2A and B).

These results suggested that the elevated TACE activity in VAT of KK-Ay mice was caused by both increased TACE expression and enhanced processing of pro-TACE to mat-TACE, and that CR significantly reduced the expression and processing of pro-TACE in VAT.

3.3. Obesity-induced up-regulation of TACE activity in VAT was associated with elevated phosphorylation of JNK and p38MAPK

Next, we investigated the signaling pathways mediating obesity-induced TACE activation in VAT. Since we previously observed that phosphorylation of stress-activated kinases including c-Jun N-terminal kinase (JNK) and p38MAPK was elevated in several insulin-resistant obese rodents [21,23], we investigated the phosphorylation of JNK, p38MAPK and ERK, indicatives for the activation of these kinases. The higher phosphorylation of JNK and p38MAPK, but not of ERK, was observed in VAT of Ay-AL compared with that of KK-AL (Fig. 2A and B). Similar results were observed in B6-HF/HS (Supplementary Fig. S4). In Ay-CR, phosphorylation of both JNK and p38MAPK was significantly reduced in VAT compared with that in Ay-AL (Fig. 2A and B).

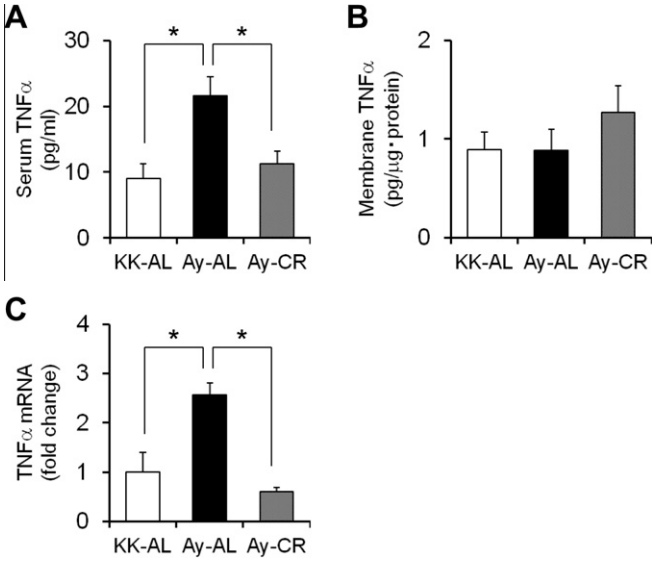

Fig. 3. CR reduces shedding of pro-TNFα in VAT. (A) Serum TNFα was measured in KK-AL, Ay-AL and Ay-CR. (B) TNFα located in the plasma membrane of VAT in the indicated animals was measured. (C) The mRNA expression of TNFα was investigated by qRT-PCR. $^{*}P < 0.05$ vs. indicated groups.

3.4. CR-mediated inhibition of TACE in VAT was associated with reduced serum TNFα concentration in KK-Ay mice

Since CR effectively suppressed TACE activity in VAT, we investigated the effect of CR on plasma TNFα level. Compared with KK-AL, higher plasma TNFα level was observed in Ay-AL. The plasma level of TNFα was dramatically reduced in Ay-CR (Fig. 3A). To confirm whether the observed reduction in plasma TNFα by CR was due to the suppression of the ectodomain-shedding of pro-TNFα on the cell surface in VAT, we measured the amounts of pro-TNFα in membrane fraction of VAT. Pro-TNFα located in membrane of VAT in Ay-CR was comparable to that in Ay-AL (Fig. 3B). TNFα

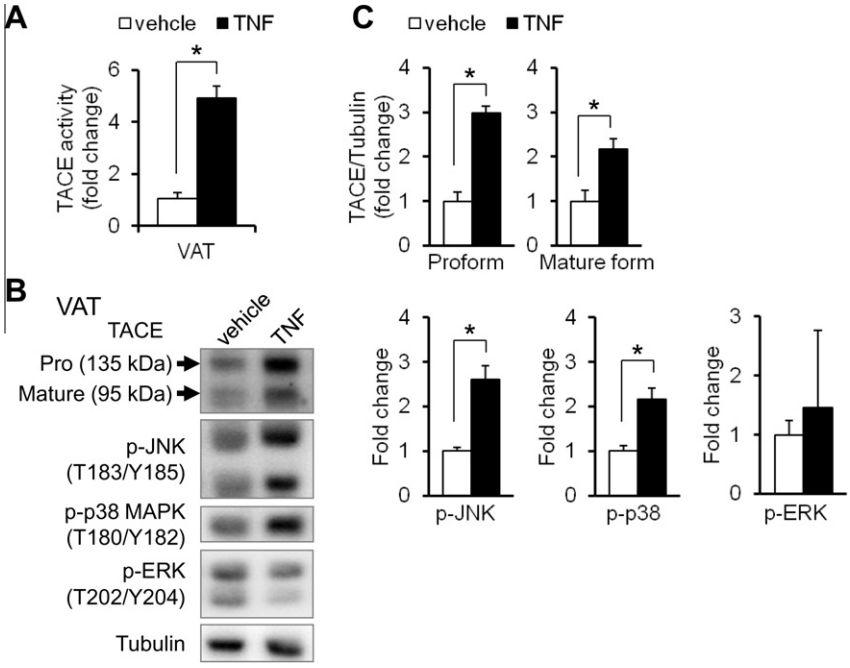

Fig. 4. Intraperitoneal injection of exogenous TNFα increases TACE activity and protein expression in VAT of KK mice. (A) TACE activity in VAT of KK mice treated with vehicle or TNFα. (B and C) Representative Western blots (B) and quantification data (C) are shown. $^{*}P < 0.05$ vs. vehicle.

mRNA expression was 2.5-fold elevated in Ay-AL compared with KK-AL, and CR significantly reduced TNFα mRNA expression in VAT (Fig. 3C). These results suggest that reduced plasma TNFα in Ay-CR may be due to both reduced TNFα expression and reduced TACE-mediated pro-TNFα shedding in VAT.

3.5. TNFα increased TACE activity and expression in KK mice

To further investigate whether TNFα could stimulate TACE activity in VAT *in vivo*, we investigated the effect of exogenously-injected TNFα (100 μg/kg) on TACE in VAT of KK mice. TACE activity was elevated by 4.7-fold (Fig. 4A), and the pro-TACE and mat-TACE proteins were elevated by 3.0-fold and 2.2-fold (Fig. 4B and C), respectively, by TNFα treatment compared with vehicle-treated. The TNFα stimulation also increased TACE mRNA expression in VAT by 2.9-fold (data not shown). Phosphorylation of JNK and p38MAPK, but not of ERK, was elevated by 2.6- and 2.2-fold, respectively (Fig. 4B and C), by the treatment compared with vehicle-treated. These results suggest that endogenously produced TNFα in VAT in obesity may up-regulate TACE expression and its activity via transcriptional and post-transcriptional mechanisms in VAT.

4. Discussion

The crucial roles of TNFα secreted from VAT in insulin resistance have been investigated [1–7]. TACE activity is an essential determinant factor in the generation of TNFα signals [7–9], because an interaction of TNF receptors on the cell surface and TNFα present in extracellular space produce the TNFα signals. Despite the importance of TNFα secreted from VAT on various obesity-related disorders, to date, understanding on TACE function in adipose tissue remain to be limited [25,26]. In addition, tissue-specific regulation of TACE activity and the protein expression of both pro-TACE and mat-TACE in insulin sensitive tissues have not been investigated, especially at early stage of the development of obesity. Therefore, we tried to elucidate TACE activity, mRNA expression and protein expression of both pro-TACE and mat-TACE in two animal models of obesity.

In the present study, we demonstrated, for the first time, the following findings. First, during the early period on the development of obesity, TACE activity increased only in VAT, but not in liver or skeletal muscle, and the induction of TACE mRNA expression responding to the development of obesity was evident in liver and VAT, and the extent of the response is the highest in VAT among the major insulin-sensitive tissues investigated. Second, a mild-strength CR procedure reduced TACE activity only in VAT of obese KK-Ay mice. Third, elevated phosphorylation of JNK and p38MAPK, but not of ERK, is associated with up-regulation of TACE activity and the shedding of pro-TNFα in VAT, and an increased serum TNFα in KK-Ay mice, all of which were inhibited by CR. Forth, administration of exogenous TNFα stimulated TACE activity in VAT in non-obese KK mice.

Expression of TACE in adipose tissue in obese animals or animals fed with HF-diet was previously reported [24,27–29] and several studies investigated the alteration in TACE expression and activity during the development of obesity [24,29]. Xu et al. found that TACE mRNA expression was increased but the activity was decreased in epididymal fat pad of 12-week-old ob/ob mice [24]. In another study, Fiorentino et al. showed that elevated TACE expression and activities in white adipose tissues in B6 mice fed a HF-diet for 20 weeks [29]. In the present study, we found that both Ay-AL fed SC for 4 weeks and B6 fed HF/HS for 12 weeks showed elevated expression of both TACE mRNA and protein and elevated TACE activity in VAT. For mRNA expression of TACE, their and our observations are in good agreement. For protein expression of TACE, we detected the obesity-induced up-regulation of TACE protein in 10-week-old KK-AL and B6 fed HF/HS-diet for 12 weeks, while Fiorentino et al. detected the obesity-induced up-regulation of TACE protein in B6 mice fed a HF-diet for 20 weeks [29]. The reason of difference between observations by Fiorentino et al. and us is not clear at this point, and may be due to a difference in diets to be loaded to B6 mice. For TACE activity, Xu et al. reported the reduced TACE activity in adipose tissue in ob/ob mice [24], while we and Fiorentino et al. detected elevated TACE activity in VAT of obese

animals [29]. Xu et al. used lysis buffer containing 1% NP-40 to prepare the tissue extracts and measured the TACE activity in the membrane fraction of the adipose tissue [24]. Fiorentino et al. and we used a same commercially available TACE activity assay kit, which recommend the use of 0.1% Triton X-100 as a detergent for sample preparation. Since the concentration-dependent inhibition of TACE activity by NP-40 detergent was recently reported [30], differences in used detergents and its concentration may be the reason for the discrepancy.

We investigated the regulation of TACE activity in the early stage of the development of obesity, while Fiorentino et al. used B6 mice fed a HF-diet for 20 weeks, which may represent an established state of obesity [29]. After establishment of obesity, elevated TACE activities may be detected in all of liver, skeletal muscle and white adipose tissues as described previously [29,31].

In the present study, we observed that increased TACE and decreased TIMP3 expression in VAT of obese mice (Fig. 2 and Supplementary Fig. S2C). These alterations may explain the elevated TACE activity in VAT of obese mice. In addition, we observed the increased p38MAPK phosphorylation in VAT of obesity. ERK and p38MAPK pathways are well known to induce TACE-mediated ectodomain shedding [12–16]. Very recently, it is reported that activation of either ERK or p38MAPK stimulates TACE activity through altering association of TACE dimmers with TIMP3 at cell surface [32]. Activation of p38MAPK in VAT of obesity may reduce the association of TACE dimmers and TIMP3.

JNK has been demonstrated to play a crucial role in obesity-induced insulin resistance and inflammation in obesity [33]. As for the impact of JNK on TACE activity, Kenchappa et al. reported the contribution of JNK3 on TACE mRNA induction in sympathetic neurons [34]. Since we observed that elevated JNK and p38MAPK activities in VAT of obese mice, we will investigate the impacts of JNK and p38MAPK on TACE activity, TACE dimerization and interaction of TACE and TIMP3 in VAT.

Among studies that investigated the impact of TACE on the development of obesity, glucose metabolism or insulin action [20,25,31,35], processing of TACE protein in insulin-sensitive tissues has not been investigated. We evaluated the protein expression of pro-TACE and mat-TACE, and found the enhanced processing from pro-TACE to mat-TACE in VAT of Ay-AL compared with that of control KK-AL. The enhanced processing of TACE in VAT was only observed in Ay-AL. This is also the first finding in obese animals to our knowledge, since no previous work described the pro-TACE, mat-TACE and processing of TACE in adipose tissue.

In the present study, we observed that CR reduced serum TNFα in KK-Ay mice. It is a good agreement with the previous numerous studies. Since CR could reduce oxidative stress and ER stress [21] as well as activities of JNK and p38MAPK in VAT of obesity [21,36], reduction in these stresses in VAT may also contribute to a reduction of TACE activity. Further study is required for the complete understanding of the CR-mediated TACE inhibition.

In conclusion, the present study explored the effects of the development of obesity and CR on TACE activity in insulin-sensitive tissues, and we have found that VAT was the only tissue to increase TACE activity to response to the development of obesity and CR, and that CR effectively reduced TACE activity and shedding of pro-TNFα in VAT of KK-Ay mice. Furthermore, the results presented in this study may provide insight into regulatory mechanisms of TACE activity in obesity.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2012.12.086.

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