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ORIGINAL ARTICLE

Taurine chloramine modulates the expression of adipokines through inhibition of the STAT-3 signaling pathway in differentiated human adipocytes

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Abstract To examine the possible role of taurine chloramine (TauCl) in modulating the expression of adipokines in adipose tissue associated with obesity, we evaluated the effect of TauCl in human differentiated adipocytes in response to IL-1β. To study the physiological effects of TauCl on adipokine expression, differentiated adipocytes were treated with IL-1β in the presence or absence of TauCl at concentrations ranging from 200 to 600 μM for 7 days. Cell culture supernatants and total RNA were analyzed by ELISA and real-time PCR, respectively, to determine protein and mRNA levels of adipokines, including adiponectin, leptin, IL-6, and IL-8. Levels of proteins involved in relevant signaling pathways were investigated by western blotting. Stimulation with IL-1β significantly decreased levels of adiponectin and leptin in adipocytes, but increased levels of IL-6 and IL-8 in a dose-dependent manner. Treatment with TauCl significantly reversed the modulation of adipokine expression by inhibiting STAT-3 signaling in IL-1β-stimulated adipocytes, independent of MAPK signaling. TauCl treatment more significantly modulated the expression of adipokines in adipocytes stimulated with IL-1β than that of non-stimulated adipocytes, suggesting that TauCl plays a significant role in modulating the expression of adipokines under inflammatory conditions. In conclusion, TauCl and other taurine derivatives that inhibit the STAT-3 signaling pathway can modulate expression of adipokines and thus may be useful as therapeutic agents for obesity-related diseases.

Keywords Taurine chloramine · Adipokines · STAT-3 signaling · Obesity

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Introduction

Obesity is a global epidemic associated with significant morbidity and mortality (Holes-Lewis et al. 2013). Obesity is associated with several complications including heart disease, stroke, type-2 diabetes mellitus, sleep apnea, and certain types of cancer. Obesity causes chronic low-grade inflammation in adipose tissue, and several obesity-linked diseases appear to be induced through common mechanisms that produce persistent low-grade inflammation. The exact reasons for the chronic immune response to obesity remain unclear; however, there is strong evidence to suggest that the innate inflammatory system may link obesity and disease (Lumeng 2013). Obesity-related adipose tissue inflammation is characterized by infiltration and activation of immune cells such as macrophages, natural killer (NK) cells, natural killer T (NKT) cells, mast cells, eosinophils and neutrophils. Activated immune cells in adipose tissue

overproduce cytokines and chemokines, while adipose tissue also secretes adipokines such as adiponectin, leptin, TNF-α, IL-8, and IL-6 (Adamczak and Wiecek 2013). Dysregulated production and secretion of these adipokines as a result of adipose tissue dysfunction can contribute to the pathogenesis of obesity-linked complications (Ouchi et al. 2011; Scarpellini and Tack 2012).

Among immune cells, neutrophils have been a primary focus because of their abundance and diverse functions at sites of inflammation (Mohr et al. 1981; Wipke and Allen 2001). Once activated, neutrophils secrete various signaling mediators including reactive oxygen intermediates, nitric oxide, and hypochlorous acid (HOCl) (Davies et al. 1993; Edwards and Hallett 1997). In particular, HOCl, which is produced through the myeloperoxidase–H_2O_2–Cl system during neutrophil phagocytosis, reacts with amino acids, carbohydrates, nucleic acids, and lipids, and thus contributes to the mutagenic and cytotoxic effects of phagocytes on microbial pathogens (van der Veen et al. 2009). After clearance of pathogens, accumulated HOCl should be removed because it can affect the host tissue at high concentrations. In this way, activated neutrophils may have developed homeostatic mechanisms for neutralizing cytotoxic HOCl by producing high levels of taurine, which is one of the most abundant free intracellular amino acids present in mammalian tissue and blood cells. Specifically, taurine reacts with HOCl to form taurine chloramine (TauCl), which acts as a scavenger of HOCl (Thomas et al. 1985). Importantly, TauCl is endogenously produced by immune cells during inflammation and has been shown to play a major role in down-regulating the expression of inflammatory mediators such as chemokines, cytokines, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) in several cell types (Kim et al. 1996; Kontny et al. 2003; Marcinkiewicz et al. 1998; Schuller-Levis and Park 2004). Furthermore, we previously showed that TauCl significantly inhibits the differentiation of preadipocytes into adipocytes, suggesting that TauCl may be potentially developed into a drug for obesity-related diseases (Kim et al. 2013b).

In this study, we investigated whether TauCl modulates the expression of adipokines in adipocytes under inflammatory stimulation and identified the relevant signaling pathways involved.

Materials and methods

Preadipocyte cell culture and adipocyte differentiation

Human preadipocytes were purchased from Cell Applications (San Diego, CA, USA) and maintained using a Preadipocyte Growth Medium Kit (Cell Applications). Preadipocytes were seeded into 6-well plates (1.5×10^5 cells/well in 2 ml of media) or 60-mm dishes (2.5×10^5 cells/60-mm dish in 2 ml of media) and cultured until confluent. For differentiation, the culture medium was changed to Adipocyte Differentiation Medium (Cell Applications), and cells were cultured for 2 weeks, during which time the media for each plate was changed every 2 days. Differentiated adipocytes were further cultured in serum free media for 7 days in the absence or presence of TauCl and either stimulated with IL-1β or under no stimulation. Finally, cells were used for RNA extraction, and the culture media from each sample were collected and stored at −80 °C.

Real-time quantitative polymerase chain reaction (PCR) analysis

Complementary DNA was synthesized from 1 μg total RNA in 20 μl reverse transcription reaction mixtures containing 5 mmol/l $MgCl_2$, 1× RT buffer, 1 mmol/l dNTP, 1 U/μl RNase inhibitor, 0.25 U/μl AMV reverse transcriptase, and 2.5 μmol/l random 9-mers as described previously (Kim et al. 2007). For real-time quantitative PCR analysis, reactions were carried out using a LightCycler PCR system (Roche Diagnostics, Meylan, France). DNA-binding SYBR Green I dye was used to detect PCR products, and a serial dilution was used to generate each standard curve. Each 20 μl reaction mixture contained 1 × LightCycler-DNA Master SYBR Green I, specific primers, and 2 μl cDNA. After denaturation for 2 min at 95 °C, primers specific for adiponectin, leptin, IL-6, IL-8, or β-actin were amplified by 40 reaction cycles at 95 °C for 5 s, 55–60 °C for 10 s (annealing) and 72 °C for 13 s. Product specificity was determined by melting curve analysis as described in the LightCycler manual. Results are expressed as the ratio of gene transcript to β-actin transcript, with the quantity of transcripts in each sample expressed as copy number. The ratios of adiponectin, leptin, IL-6, and IL-8/β-actin mRNA were assigned a value of 100 %, and the corresponding results were calculated as relative percentages. Primers were synthesized by Bioneer Co. Ltd. (Seoul, Republic of Korea), and their sequences are listed in Table 1.

Western blot analysis

Differentiated human adipocytes in 60-mm dishes were serum-starved overnight and stimulated by IL-1β (1 ng/ml) for 2 h. The stimulated cells were then harvested at various time points to evaluate changes in cell signaling proteins as a function of time. Cells were also stimulated with IL-1β for 45 min or 90 min in the presence or absence of taurine chloramine (TauCl). Cell lysates were prepared as previously described (Kim et al. 2013b), separated by 10–12 %

Table 1 PCR primer sequences

Primer name	Primer sequence	Product size (bp)
IL-6 sense	5′-CCA GTA CCC CCA GGA GAA GA-3′	182
IL-6 antisense	5′-YYG TTT TCT GCC AGT GCC TC-3′	
IL-8 sense	5′-ACT TTC AGA GAC AGC AGA GC-3′	264
IL-8 antisense	5′-GTG GTC CAC TCT CAA TCA CT-3′	
Leptin sense	5′-CGC AGT CAG TCT CCT CCA AA-3′	168
Leptin antisense	5′-GGT TCT CCA GGT CGT TGG AT-3′	
Adiponectin sense	5′-AGG GAG ACA TCG GTA AAA CC-3′	160
Adiponectin antisense	5′-ATG GGC ATG TTG GGG ATA GT-3′	
β-Actin sense	5′-TCA TGA GGT AGT CAG TCA GG-3′	305
β-Actin antisense	5′-CTT CTA CAA TGA GCT GCG TG -3′	

SDS-PAGE, and transferred to Hybond-ECL membranes (Amersham, Arlington Heights, IL, USA). The membranes were first blocked with 6 % non-fat milk dissolved in Tris-buffered saline/Tween (TBST) buffer (10 mM Tris–Cl pH 8.0, 150 mM NaCl, 0.05 % Tween 20). The blots were then probed overnight at 4 °C with various rabbit polyclonal antibodies, namely, inhibitor of κB (IκB)α, p-ERK1/2, p-P38, p-Jun N-terminal kinase (JNK), p-Akt/Akt, p-STAT-3/STAT-3, or β-actin (Cell Signaling Technology, Beverly, MA, USA), all of which were diluted to 1:1,000 in TBS. Next, the blots were incubated with 1:1,000 dilutions of a goat anti-rabbit IgG secondary antibody coupled with horseradish peroxidase. The blots were developed using the ECL method (Amersham). For re-probing, blots were incubated in stripping buffer (100 mM 2-mercaptoethanol, 2 % SDS, 62.5 mM Tris–HCl pH 6.7) at 50 °C for 30 min with occasional agitation.

Measurement of gene expression by enzyme-linked immunosorbent assay (ELISA)

Levels of adiponectin, leptin, IL-6 and IL-8 in cell culture supernatants were determined with an ELISA kit according to the manufacturer's recommended protocol (R&D Systems, Inc., Minneapolis, MN, USA).

Statistical analysis

All in vitro experimental data are expressed as the mean ± standard error of the mean (SEM) of quadruplicate samples. Differences between groups were compared using the Mann–Whitney test. Prism software 4 (Graphpad Software, San Diego, CA) was used for statistical analysis and graphing. All P values <0.05 were considered statistically significant.

Results

Effect of inflammatory stimuli on fully differentiated adipocytes

To mimic the conditions of adipocytes under inflammatory stimuli, fully differentiated human adipocytes were treated with IL-1β for 24 h. Expression levels of the adipokines adiponectin, leptin, IL-6, and IL-8 from culture supernatants were analyzed by ELISA (Fig. 1a). The levels of adiponectin and leptin decreased in response to IL-1β in a dose-dependent manner. In contrast, levels of IL-6 and IL-8 increased in response to IL-1β in a dose-dependent manner. Consistent with these results, the mRNA expression of adiponectin and leptin decreased in a time-dependent manner, while the mRNA levels of IL-6 and IL-8 peaked at 3 h but decreased gradually thereafter (Fig. 1b).

Effect of TauCl on the production of adipokines in adipocytes treated with inflammatory stimuli

To determine whether TauCl modulates the expression of adipokines in adipocytes under inflammation conditions, TauCl was added to differentiated adipocytes stimulated with IL-1β (1 ng/ml) and cultured for 7 days. After 7 days, the cultured supernatants were assayed for expression of adiponectin, leptin, IL-6, and IL-8. At concentrations ranging from 200 to 400 μM, TauCl treatment significantly reversed the decreases in adiponectin and leptin expression in IL-1β-stimulated adipocytes (Fig. 2a). In addition, treatment with TauCl significantly reversed the elevated production of IL-6 and IL-8 in a dose-dependent manner. In contrast, TauCl treatment did not significantly affect the expression of adipokines in non-stimulated adipocytes at concentrations of 200–400 μM (Fig. 2b). Indeed, only with 600 μM TauCl were the levels of leptin, IL-6, and IL-8 significantly decreased, while adiponectin levels were not inhibited. These results indirectly suggest that TauCl might be specifically involved in the modulation of the expression of adipokines through the inhibition of signaling pathways in IL-1β-stimulated adipocytes.

Signaling pathways through which TauCl modulates levels of adipokines in IL-1β-stimulated differentiated adipocytes

To elucidate the signaling pathways by which TauCl inhibits levels of adipokines in IL-1β-stimulated differentiated adipocytes, differentiated adipocytes were stimulated with IL-1β for 2 h, and the cells were harvested to evaluate the time course of activation of the ERK, JNK, P-38, IκB, and Akt signaling pathways in IL-1β (1 ng/ml)-stimulated adipocytes (Fig. 3a). Adipocytes were also stimulated with

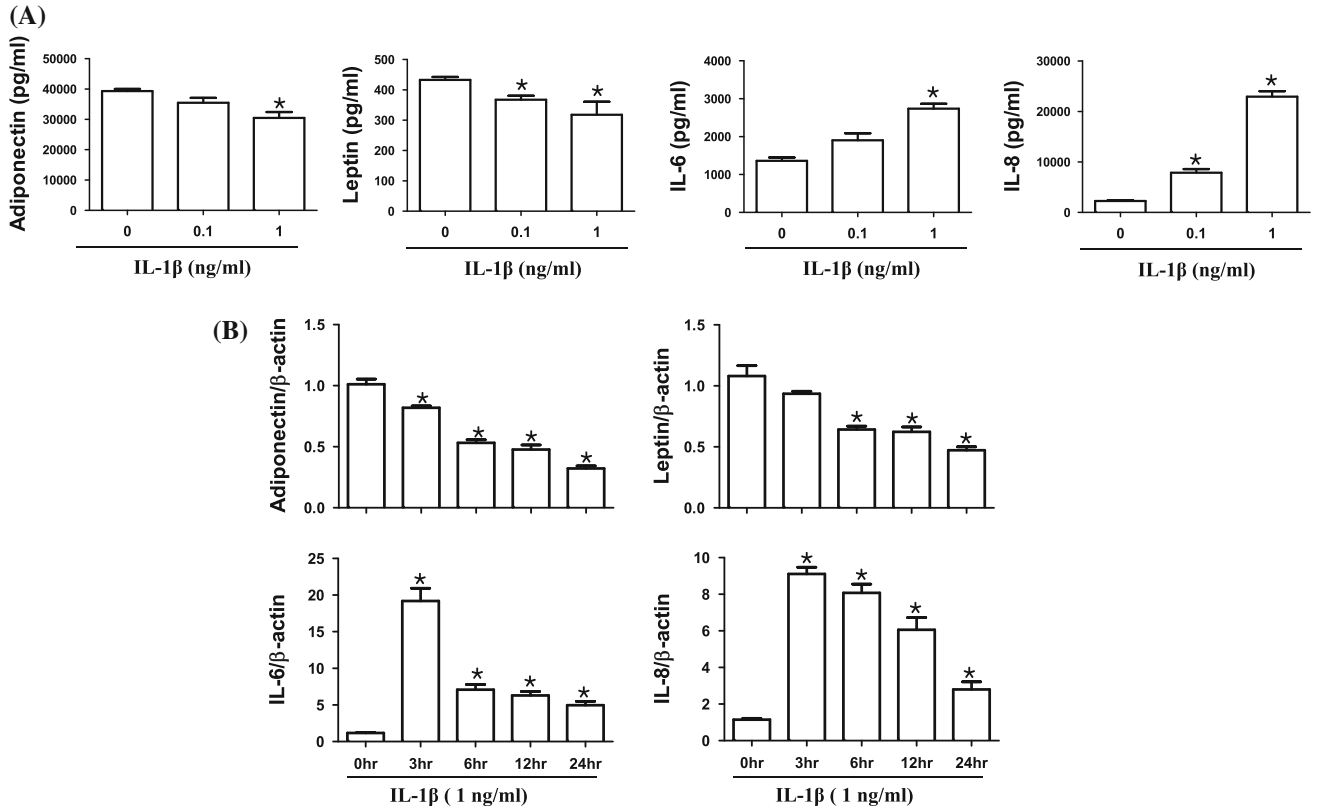

Fig. 1 Effects of inflammatory stimuli on in vitro production of adipokines in differentiated human adipocytes. **a** Adipocytes were stimulated with IL-1β (0.1 or 1 ng/ml) for 7 days. Culture supernatants were collected, and levels of adipokines were determined by ELISA. **b** Real-time PCR data showing mRNA expression of adipokines in adipocytes in response to IL-1β stimulation for 24 h as a function of time. Data are representative of three independent experiments performed in quadruplicate. Values are expressed as the mean ± SEM. $^*P < 0.05$ versus no treatment with IL-1β

IL-1β for 45 min in the presence or absence of TauCl at various concentrations (Fig. 3b). TauCl did not significantly affect the MAPK signaling pathways in IL-1β-stimulated adipocytes, suggesting that TauCl does not modulate adipokine levels through the MAPK and PI3 K/Akt signaling pathways in adipocytes under inflammation. We next analyzed if TauCl inhibits the STAT-3 signaling pathway (Fig. 4). As shown in Fig. 4a, phosphorylation of the STAT-3 signaling pathway was activated after 90 min of IL-1β stimulation, while MAPK signaling pathways were activated after 45 min of IL-1β stimulation. In contrast, TauCl greatly decreased the phosphorylation status of STAT-3 in a dose-dependent manner, suggesting that TauCl may modulate the expression of adipokines in IL-1β-stimulated adipocytes through inhibition of the STAT-3 signaling pathway.

Discussion

We investigated whether TauCl modulates the expression of adipokines in differentiated adipocytes. When differentiated human adipocytes were treated with IL-1β in vitro, the levels of expression of adiponectin and leptin were decreased, while those of IL-6 and IL-8 were increased in a dose-dependent manner. In addition, TauCl treatment significantly reversed the change in the expression of adipokines in IL-1β-stimulated adipocytes. STAT-3 signaling pathways appeared to play a prominent role than MAPK signaling pathways in mediating the effects of TauCl on adipokine expression in adipocytes under inflammatory stimulation. These results partly confirmed the observations of a previous study showing that IL-1β acts as an autocrine/paracrine stimulator of IL-6 release in human adipocytes (Flower et al. 2003). Consistent with our results, the addition of TauCl was previously shown to significantly inhibit the production of IL-6, TNF-α, and IL-8 in LPS-treated adipose explant cultures (Marcinkiewicz and Kontny 2012).

Adipose tissue is ubiquitously present in humans. Adipocytes, the dominant cell type of adipose tissue, secrete highly bioactive substances known as adipokines or adipocytokines. There is increasing evidence that adipokines have an active role in inflammatory, matrix-destructive, and fibrotic processes in rheumatic diseases (Gomez et al.

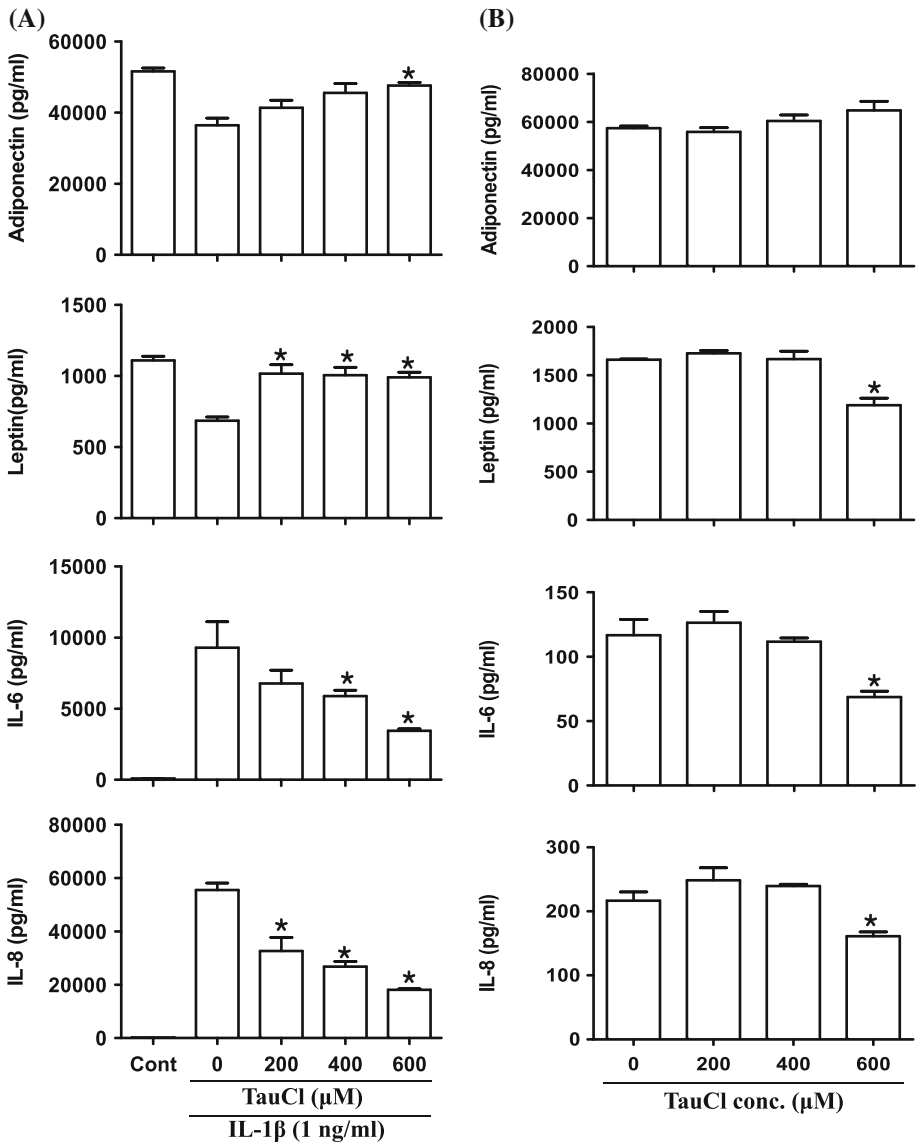

Fig. 2 Comparative effect of TauCl on the production of adipokines in **a** IL-1β-stimulated or **b** non-stimulated adipocytes. Differentiated adipocytes were cultured in serum-free media for 7 days in the absence or presence of TauCl either under stimulation by IL-1β or under no stimulation. Production levels of the adipokines adiponectin, leptin, IL-6, and IL-8 were measured by ELISA. Data are representative of three independent experiments performed in quadruplicate. Values are expressed as the mean ± SEM. $^{\#}P < 0.05$ versus no stimulation of IL-1β, $^{*}P < 0.05$ versus no treatment with TauCl in IL-1β-stimulated adipocytes

2009; Neumann et al. 2011). For example, increased production of adipokines can be detected in the synovial fluid of patients with rheumatoid arthritis (RA). Likewise, the abnormal proliferations of fibroblast-like synoviocytes (FLSs) as well as excessive production of cytokines and MMPs by these cells are important potential targets for therapeutic intervention in RA (Firestein 1998). Thus, the anti-inflammatory effects of TauCl were previously investigated for their potential to downregulate proinflammatory cytokines and MMPs in FLSs, which resulted in the discovery that synovial fluid neutrophils of RA patients exhibit impaired generation of TauCl (Kontny et al. 2002). Together, these findings provide insight into the role of TauCl in inflammatory diseases.

To the best of our knowledge, this study is the first to describe how TauCl regulates the expression of adipokines in adipocytes under inflammatory stimulation. TauCl also exhibits anti-inflammatory effects in IL-1β-stimulated differentiated human adipocytes. Furthermore, the molecular mechanisms by which TauCl modulates adipokines in adipocytes under inflammatory stimulation have not yet been studied. In our study, MAPK signaling pathways were activated in differentiated adipocytes by IL-1β stimulation, while TauCl did not inhibit the signaling pathways of IL-1β-stimulated adipocytes. The janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathways mediate the actions of numerous cytokines and hormones, which have profound effects on adipocyte development and function (Richard and Stephens 2011). In particular, STAT-3 signaling is abundantly activated in preadipocytes and adipocytes (Cernkovich et al. 2008; Deng et al. 2000). Thus, we investigated whether TauCl was involved in inhibition of the STAT-3 signaling pathway. TauCl downregulated STAT-3 signaling in IL-1β-

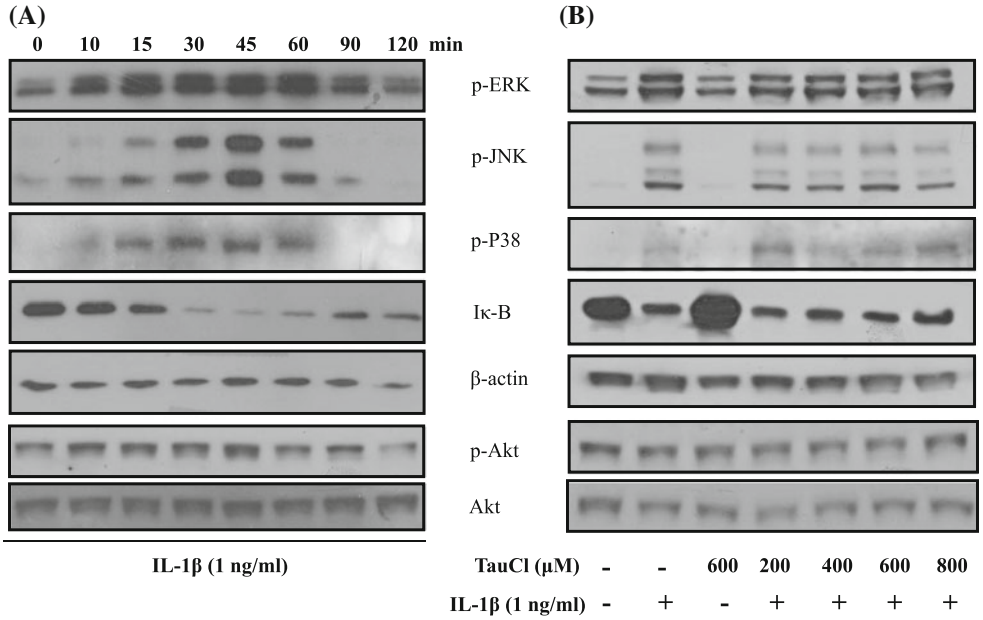

Fig. 3 Effect of TauCl on various signaling pathways in IL-1β-stimulated adipocytes. **a** Time course of ERK, JNK, P-38, IκB, and Akt signaling pathway activation in IL-1β (1 ng/ml)-stimulated adipocytes. **b** Adipocytes were stimulated with IL-1β (1 ng/ml) for 45 min in the presence or absence of TauCl at various concentrations. The data shown are representative of three independent experiments

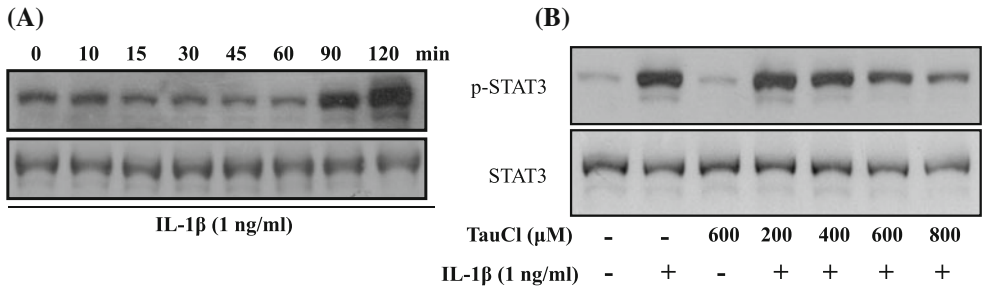

Fig. 4 Effect of TauCl on STAT-3 signaling in IL-1β-stimulated adipocytes. **a** Time course of activation of STAT-3 signaling pathway in IL-1β (1 ng/ml)-stimulated adipocytes. **b** Adipocytes were stimulated with IL-1β (1 ng/ml) for 90 min in the presence or absence of TauCl at various concentrations. The data shown are representative of three independent experiments

stimulated adipocytes in a dose-dependent manner, suggesting that TauCl may modulate the expression of adipokines through inhibition of STAT-3 phosphorylation. In contrast, a previous study showed that TauCl inhibits the activity of major transcriptional regulators such as NF-κB and AP-1 in IL-1β-activated fibroblast-like synoviocytes (FLSs) (Kim et al. 2007; Kontny et al. 2000). However, TauCl does not appear to inhibit the activity of NF-κB and AP-1 in IL-1β-stimulated adipocytes because it did not affect MPAK signaling pathways. These observations may also suggest that the effects of TauCl are more cell specific than previously thought, even though other antioxidants (e.g., dimethyfumarate, oleanolic acid) mimic the effects of TauCl on adipocyte metabolism and differentiation via inhibition of STAT-3 phosphorylation/translational activity (Kang et al. 2013; Kim et al. 2013a).

Criticism of this study may be raised with respect to whether differentiated adipocytes are an appropriate model of adipocytes found in adipose tissue. In the system employed in our study, the differentiated adipocytes exhibited greatly increased production of adiponectin and leptin compared to preadipocytes, while the production of IL-6 and IL-8 was significantly decreased after differentiation of preadipocytes into adipocytes. Likewise, IL-1β stimulation of differentiated adipocytes resulted in decreased production of adiponectin and leptin and increased expression of IL-6 and IL-8. The patterns of expression in adipocytes upon proinflammatory stimulation were consistent with the characteristics of adipocytes in adipose tissue (Fawcett et al. 2000; Hoch et al. 2008; Kappes and Loffler 2000). Together, these observations support the functional resemblance between in vitro differentiated adipocytes and fat cells in adipose tissue. In addition, concerns may be raised as to whether the physiological concentration of TauCl (200–600 μM) is effective for inhibition of inflammation in adipose tissue. While the physiologic concentrations of TauCl have not yet been determined, we can assume that this compound may accumulate and reach high local concentrations in the mM range during an inflammatory response (Kontny et al.

2000). Indeed, taurine is present in most mammalian tissue and human blood cells at concentrations of 10–20 mM, while its concentration in plasma and other physiologic fluids reaches values of 50–100 μM (Learn et al. 1990). Furthermore, TauCl is much more stable that taurine, with a decomposition rate of <5 % per hour at 37 °C (Grisham et al. 1984). We also verified that our results were not due to cytotoxicity as a result of the high concentrations of TauCl used in our experiments. Specifically, differentiated adipocytes exhibited no signs of cytotoxicity following treatment with a range of concentrations of TauCl (200–800 μM) (data not shown).

We also compared the effect of TauCl on the expression of adipokines in adipocytes under inflammatory stimulation with that of non-stimulated adipocytes. TauCl treatment effectively modulated the expression of IL-6, IL-8, adiponectin, and leptin in IL-1β-stimulated adipocytes compared with non-stimulated adipocytes. These results suggest that TauCl may contribute significantly to the modulation of adipokine expression in adipocytes in response to inflammatory stimuli. Our results also suggest that the mechanism of action of TauCl is based on a specific reaction such as inhibition of signaling pathways activated by IL-1β rather than a cytotoxic or nonspecific reaction. Likewise, TauCl is thought to play a significant role in modulating the expression of inflammatory cytokines at sites of inflammation.

Conclusions

TauCl is produced endogenously by immune cells such as neutrophils and macrophages and may modulate the expression of adipokines in adipocytes. In doing so, TauCl likely plays a role in controlling inflammation. Thus, TauCl and other taurine derivatives that inhibit STAT-3 signaling may be potential therapeutic agents for obesity-related diseases.

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Conflict of interest The authors declare that they have no conflict of interest.

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