Transcutaneous carbon dioxide attenuates impaired oxidative capacity in skeletal muscle in hyperglycemia model

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Abstract. Hyperglycemia impairs oxidative capacity in skeletal muscle. Muscle oxidative capacity is regulated by peroxisome proliferator-activated receptor-γ co-activator-1α (PGC-1α). Transcutaneous carbon dioxide (CO₂) enhances PGC-1α expression in skeletal muscle. Therefore, the aim of this study was to clarify the effects of CO₂ therapy on muscle oxidative capacity impaired by streptozotocin (STZ)-induced hyperglycemia. Eight-week-old male Wistar rats were randomly divided into 4 groups: control, CO₂ treatment, STZ-induced hyperglycemia, and STZ-induced hyperglycemia treated with CO₂. STZ-induced hyperglycemia resulted in a decrease of muscle oxidative capacity and decreased PGC-1α and cytochrome c oxidase subunit 4 (COX-4) expression levels; while, application of transcutaneous CO₂ attenuated this effect, and enhanced the expression levels of endothelial nitric oxide synthesis (eNOS). These results indicate that transcutaneous CO₂ improves impaired muscle oxidative capacity via enhancement of eNOS and PGC-1α-related signaling in the skeletal muscle of rats with hyperglycemia.

Key words: Carbon dioxide — Muscle oxidative capacity — Hyperglycemia

Abbreviations: cGMP, cyclic guanosine monophosphate; COX-4, cytochrome c oxidase subunit 4; CS, citrate synthase; eNOS, endothelial nitric oxide synthesis; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; PBST, phosphate-buffered saline with 0.1% Tween 20; PGC-1α, peroxisome proliferator-activated receptor-γ co-activator-1α; SIRT1, sirtuin 1; STZ, streptozotocin.

Introduction

Hyperglycemia induces widespread tissue dysfunction and deleterious complications (Blake and Trounce 2014). Especially, hyperglycemia impairs not only muscle protein synthesis but also oxidative capacity in the skeletal muscle (Py et al. 2002; Frier et al. 2008; Fortes et al. 2015; Ono et al. 2015). Muscle oxidative capacity is an important factor determining exercise capacity (Adams and Schuler 2011). It is critically regulated by mitochondrial function represented by adenosine triphosphate synthesis through the tricarboxylic acid cycle. Muscle oxidative capacity depends on mitochondrial enzymatic activity and biogenesis (Short et al. 2003; White and Schenk 2012), both of which are decreased by hyperglycemia in diabetes (Patti et al. 2003; Boushel et al. 2007; Fujimaki and Kuwabara 2017; Wang et al. 2018), leading to the decrement of exercise capacity. Therefore, attenuation of hyperglycemia-induced impairment of muscle oxidative capacity is important to maintain exercise capacity.

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 Peroxisome proliferator-activated receptor-γ co-activator-1α (PGC-1α) is known as a master regulator of oxidative capacity in the skeletal muscle (Wende et al. 2005; Calvo et al. 2008; Wenz et al. 2009; Tadaishi et al. 2011), and regulates mitochondrial enzymatic activity and biogenesis (Ventura-Clapier et al. 2008). Indeed, in a previous study, PGC-1α transgenic mice showed an increase in muscle oxidative capacity (Lin et al. 2002). In addition, endurance exercise induced an increase in muscle oxidative capacity via an increase in PGC-1α expression (Russell et al. 2003; Geng et al. 2010). These reports strongly suggest that PGC-1α plays a key role in enhancing muscle oxidative capacity. On the other hand, a decrease in PGC-1α expression has been shown to lower muscle oxidative capacity (Leone et al. 2005; Vainshtein et al. 2015). It has been reported that low muscle oxidative capacity in diabetes is associated with decreased PGC-1α expression (Nagatomo et al. 2011; Wang et al. 2018). Therefore, it would be beneficial to attenuate the decrease in PGC-1α expression in order to suppress the decline of muscle oxidative capacity due to hyperglycemia.

Physical exercise is a principal method to improve low muscle oxidative capacity in diabetes (Lumb 2014). However, it is physically difficult for some diabetic patients due to their complications and exercise intolerance. Therefore, it is necessary to develop an alternative treatment, which is effective even for diabetic patients with exercise intolerance. Carbon dioxide (CO₂) therapy has long been used in Europe as an effective treatment for cardiac disease and skin lesions (Riggs 1960; Goodman et al. 1975; Wells 1999). Exposure to CO₂ elevates blood flow and microcirculation in many tissues as well as partially increases O₂ pressure in the local tissues, a phenomenon known as the Bohr effect (Riggs 1960; Wells 1999; Jensen 2004; Izumi et al. 2015). Also, it is well known that CO₂ therapy induces peripheral vasodilatation, thereby increasing tissue blood flow (Hartmann et al. 1997; Sakai et al. 2011). The transfer of CO₂ across the skin might have beneficial local vasomotor effects without causing systemic hemodynamic modifications (Savin et al. 1995). In addition, the effects of CO₂-enriched water on subcutaneous microcirculation are regulated by peripheral vasodilatation, which results from increased parasympathetic and decreased sympathetic nerve activity (Toriyama et al. 2002). Together, these reports indicate that CO₂ therapy has a positive impact on microcirculation. A blood flow-induced mechanical factor enhances the expression level of endothelial nitric oxide synthesis (eNOS) in vascular endothelial cells (Harrison et al. 1996; Fleming and Busse 2003). eNOS is one of three NOS isoforms, which plays a major role in many physiological functions, such as regulating vascular tone (Huang et al. 1995; Duplain et al. 2001) and insulin sensitivity (Vincent et al. 2003). Additionally, nitric oxide synthesized by eNOS can increase PGC-1α protein expression in skeletal muscle via activation of cyclic guanosine monophosphate (cGMP) and consequently promote mitochondrial biogenesis and function (Nisoli et al. 2003, 2004; Le Gouill et al. 2007; Ventura-Clapier et al. 2008; Lira et al. 2010). On the other hand, it has been reported that application of CO₂ therapy up-regulates eNOS and cGMP expression in skeletal muscle via an increase in blood flow (Irie et al. 2005; Izumi et al. 2015). Moreover, the expression of positive regulators of oxidative capacity, including PGC-1α and sirtuin1 (SIRT1) is enhanced by transcutaneous application of CO₂ therapy (Oe et al. 2011). These results raise the possibility that transcutaneous CO₂ might enhance PGC-1α expression via increase in blood flow-induced eNOS signaling. Therefore, we hypothesized that application of transcutaneous CO₂ therapy attenuates the impaired muscle oxidative capacity in diabetes via up-regulation of eNOS and PGC-1α signaling. In the present study, we investigated the effect of CO₂ therapy on muscle oxidative enzymatic activity and protein expression of eNOS, PGC-1α, and cytochrome c oxidase subunit 4 (COX-4) using type 1 diabetes rodent model generated by a single injection of streptozotocin (STZ), a compound that displays a preferential toxicity toward pancreatic β-cells.

Materials and Methods

Animals

Eight-week-old male Wistar rats (Japan SLC, Shizuoka, Japan) were used. These animals were randomly divided into 4 groups: control (CON/CO₂ (–); n = 5), CO₂ treatment (CON/CO₂ (+); n = 5), STZ-induced diabetes (STZ/CO₂ (–); n = 5), and STZ-induced diabetes treated with CO₂ (STZ/CO₂ (+); n = 5). All animals were housed at a temperature of 22 ± 2°C with 12/12 h light/dark cycle and provided standard rodent chow and water ad libitum. Diabetes was induced by a single intravenous injection of 50 mg/kg STZ (Wako, Osaka, Japan) dissolved in citrate buffer. The blood glucose levels were measured 2 days after injection, and animals with blood glucose levels more than 250 mg/dl were used as a model for diabetes. Rats in both the STZ groups were injected with STZ, and the rats in both CON groups were injected with the same volume of citrate buffer. This study was approved by the Institutional Animal Care and Use Committee and carried out according to the Kobe University Animal Experimentation Regulations. All experiments were conducted in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (National Research Council 1996).

Transcutaneous CO₂ therapy

All animals were anesthetized with isoflurane (Wako, Osaka, Japan), and the hair on their hind limbs were shaved. CO₂ hydrogel, which enhances transcutaneous CO₂ absorption (NeoChemir Inc Kobe, Japan) as previously described (Oe et
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al. 2011), was applied on their hind limbs without anesthesia. The CO₂ adaptor was attached to the limbs and sealed. In the CON/CO₂ (+) and STZ/CO₂ (+) groups, 100% CO₂ gas (Mizushima Sanso, Kobe, Japan) was administered into the adaptor for 30 min, as previously described (Oe et al. 2011). This treatment was started from 5 days after injection of STZ and performed 5 times a week for 8 weeks.

Fasting blood glucose

After a fasting period of 12 h, the blood samples were obtained from the caudal vein. The blood glucose levels were measured using a portable blood glucose analyzer (Glutest Neo Super; Sanwa Kagaku Kenkyusho Co. Ltd., Nagoya, Japan) and monitored every 2 weeks.

Surgical procedure

After 8 weeks, rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.). The soleus muscle was removed and weighed, and then the muscle tissue was rapidly frozen using isopentane cooled in dry ice and stored at –80°C until further biochemical analysis.

Citrate synthase (CS) activity

The activity of CS, a key mitochondrial enzyme in the tricarboxylic acid cycle, is used as an indicator of oxidative capacity of the skeletal muscle. The sample was homogenized in 10 mM Tris (pH 7.4), 175 mM KCl, and 2 mM EDTA. The homogenates were frozen, thawed thrice, and then centrifuged at 15,000 \times g for 10 min at 4°C. The supernatants were collected and used for measuring the CS activity by Sere’s method (Sere 1969). Briefly, supernatants were reacted with 5 mM oxaloacetate acid after addition of 100 mM Tris (pH 7.4), 3 mM acetyl-CoA, and 1 mM 5,5’-dithiobis [2-nitrobenzoric acid], and the absorbance was measured at 412 nm for 5 min.

Western blotting

Portions (approximately 10 mg) of each soleus muscle were homogenized in RIPA lysis buffer containing 1 mM Na₃VO₄, 1 mM NaF, and protease inhibitor cocktail (1:100, P8340; Sigma Chemicals, Perth, WA, USA). Total supernatant protein concentrations were determined according to Bradford method using a protein assay kit (Bradford 1976) (Bio-Rad Laboratories, Hercules, CA, USA) before loading onto either 7.5 or 15% sodium dodecyl sulfate-polyacrylamide gels. Proteins were blotted onto polyvinylidene difluoride membranes, which were then blocked for 1 h with 5% skimmed milk in phosphate-buffered saline with 0.1% Tween 20 (PBST). Membranes were incubated with antibodies against PGC-1α (1:200 in PBST, sc-13067; Santa Cruz Biotechnology, Santa Cruz, CA, USA), COX-4 (1:1000 in PBST, #4850; Cell Signaling Technology), or eNOS (1:1000 in PBST, #5880; Cell Signaling Technology) overnight at 4°C and then incubated in a solution with horseradish peroxidase-conjugated anti-mouse or rabbit secondary antibody (1:1000 in PBST; GE, Healthcare, Waukesha, WI, USA) for 1 h. Proteins were detected using EzWestLumi Plus kit (ATTO, Tokyo, Japan). Finally, images were analyzed with an LAS-1000 (Fujifilm, Tokyo, Japan) using a chemiluminescent image analyzer and quantified using the Multi-Gauge Image Analysis Software program (Fujifilm) against a relative concentration of GAPDH (1:1000 in PBST, #97166; Cell Signaling Technology) as an internal control.

Statistical analysis

All data are presented as mean ± standard error of mean (SEM). The differences were assessed by two-way analysis of variance (ANOVA) followed by Tukey’s post hoc test. All data of time-dependent changes of blood glucose levels were assessed by two-way repeated measured ANOVA followed by Tukey’s post hoc test. Results were deemed statistically significant at \( p < 0.05 \).

Results

Body mass and soleus muscle mass

There was no significant difference in body mass and muscle mass between the STZ/CO₂ (-) and STZ/CO₂ (+), and the CON/CO₂ (-) and CON/CO₂ (+) groups, respectively. The mean body mass and soleus muscle mass were significantly decreased due to induction of hyperglycemia (8 weeks) (Table 1).

|               | CON       | STZ       |
|---------------|-----------|-----------|
|               | CO₂ (-)   | CO₂ (+)   | CO₂ (-)   | CO₂ (+)   |
| Body mass (g) | 320.4 ± 8.0 | 320.0 ± 10.4 | 217.2 ± 19.9* | 220.4 ± 16.0* |
| Muscle mass (g)| 122.8 ± 4.6 | 126.4 ± 5.0 | 90.0 ± 7.3* | 88.0 ± 7.0* |

Main effects of STZ were assessed by two-way ANOVA, \( p < 0.05 \) is considered statistically significant. Values are presented as mean ± SEM. * significantly different from CON with same intervention, at \( p < 0.05 \). CON, control; STZ, streptozotocin.
Protein expression levels of PGC-1α, COX-4, and eNOS

Representative images of Western blots for PGC-1α, COX-4, and eNOS expression in the soleus muscle are shown in Figure 3. There were no significant differences in the protein content of PGC-1α, COX-4 and eNOS between both the CON groups. The protein level of eNOS was significantly higher in the STZ/CO2 (+) group than that in the STZ/CO2 (−) group. The protein levels of PGC-1α and COX-4 were significantly lower in the STZ/CO2 (−) group than those in the CON/CO2 (−) group, but significantly higher in the STZ/CO2 (+) group than those in the STZ/CO2 (−) group.

Discussion

The novel finding of the present study was that application of transcutaneous CO2 therapy attenuated the decrease in CS activity in the skeletal muscle of rats with STZ-induced hyperglycemia. Furthermore, the protein expression levels of eNOS, PGC-1, and COX-4 were higher in the STZ/CO2 (+) group compared with those in the STZ/CO2 (−) group. These observations indicated that application of transcutaneous CO2 to rats with STZ-induced diabetes improved the impaired muscle oxidative capacity via enhancement of eNOS and PGC-1a-related signaling in hyperglycemic skeletal muscle.

Many studies have reported that PGC-1α is an important regulator of oxidative capacity in skeletal muscle (Zechner et al. 2010; Tadaishi et al. 2011; Kang et al. 2012). In the present study, the activity of CS, an indicator of oxidative capacity, and expression of COX-4, an enzyme of the mitochondrial respiratory chain, in the skeletal muscle were decreased in rats with STZ-induced hyperglycemia (Figure 2), which is consistent with previous reports (Py et al. 2002; Roberts-Wilson et al. 2010; Padrão et al. 2012; Wang et al. 2018). Additionally, the expression level of PGC-1a in the STZ/CO2 (−) group was significantly decreased compared with that in the CON/CO2 (−) group (Figure 3). Thus, the hyperglycemia-related decline in skeletal muscle oxidative capacity could be due to the down-regulation of PGC-1α.

It has been reported that shear stress associated with an increase in blood flow increases the expression level of eNOS (Yang et al. 2013), which can also be achieved by administration of α1-adrenergic receptor antagonist prazosin, an inducer of vasodilation (Baum et al. 2004), and exercise (Lloyd et al. 2001; Vassilakopoulos et al. 2003; Egginton 2009; Lee-Young et al. 2010). These reports suggest that blood flow appears to be a strong modulator of eNOS levels. On the other hand, Izumi et al. (2015) showed that CO2 therapy promotes blood flow in the subcutaneous tissues,
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and up-regulates the expression of eNOS in the hind limb of ischemic rats. Kindig et al. (1998) showed that STZ-induced hyperglycemia in rat results in a decrease in the proportion of capillaries in the skeletal muscle, due to which the blood flow within the skeletal muscle may be impaired. In the present study, an increase in the expression level of eNOS was observed in the STZ/CO₂ (+) group, but not in the CON/CO₂ (+) group. Our results, combined with previous findings, suggest the possibility that CO₂ therapy might influence eNOS expression only under conditions of reduced blood flow. Therefore, the increased eNOS expression in the STZ/CO₂ (+) group might be associated with enhanced blood flow within the skeletal muscle, consistent with a previous report showing the positive effect of CO₂ therapy in a hind limb ischemia model.

eNOS is a key factor for the enhancement of muscle oxidative capacity via up-regulation of PGC-1α expression. In a previous study, application of CO₂ to a hind limb ischemia model enhanced eNOS expression in the skeletal muscle (Irie et al. 2005; Izumi et al. 2015). Additionally, application of transcutaneous CO₂ to sedentary rats for 12 weeks increased the mRNA level of PGC-1α and SIRT1 and mitochondria number (Oe et al. 2011). Our results showed an increase in the protein expression of PGC1α as well as eNOS by application of transcutaneous CO₂ therapy to rats with STZ-induced hyperglycemia. On the other hand, application of transcutaneous CO₂ had no influence on the protein expression levels of PGC-1α and eNOS in the CON/CO₂ (+) group. This result suggested that the increase in expression of PGC-1α in the STZ/CO₂ (+) group was mediated by increased blood flow and resultant up-regulation of eNOS. Therefore, the effects of transcutaneous CO₂ on muscle oxidative capacity in hyperglycemic rats could be involved in the up-regulation of PGC-1α thorough an increase in eNOS expression.

In the present study, application of transcutaneous CO₂ decreased the fasting blood glucose levels in rats with STZ-induced hyperglycemia. It has been reported that an increase in PGC-1α expression improves impaired glucose metabolism (Puigserver 2005). Here, the expression level of PGC-1α was increased in the STZ/CO₂ (+) group compared to that in the STZ/CO₂ (–) group. Hence, our results suggest that application of transcutaneous CO₂ can improve hyperglycemia via increase of glucose metabolism mediated by increased PGC-1α expression.

In conclusion, this study demonstrates a novel effect of transcutaneous CO₂ on the impaired muscle oxidative capacity of rats with STZ-induced hyperglycemia. Application of transcutaneous CO₂ improved hyperglycemia-related decline in muscle oxidative capacity, as shown by an increase in CS activity and increased expression levels of COX4 and PGC-1α, which contributed to the amelioration of hyperglycemia. These results indicate that transcutaneous CO₂ therapy can be used to improve hyperglycemia-induced muscle metabolic dysfunction.

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