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RESEARCH ARTICLE

Reversible remodeling of lung tissue during hibernation in the Syrian hamster

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SUMMARY

During hibernation, small rodents such as hamsters cycle through phases of strongly suppressed metabolism with low body temperature (torpor) and full restoration of metabolism and body temperature (arousal). Remarkably, the repetitive stress of cooling–rewarming and hypoxia does not cause irreversible organ damage. To identify adaptive mechanisms protecting the lungs, we assessed histological changes as well as the expression and localization of proteins involved in tissue remodeling in lungs from Syrian hamsters at different phases of hibernation using immunohistochemical staining and western blot analysis. In torpor (early and late) phase, a reversible increased expression of smooth muscle actin, collagen, angiotensin converting enzyme and transforming growth factor-β was found, whereas expression of the epidermal growth factor receptor and caveolin-1 was low. Importantly, all these alterations were restored during arousal. This study demonstrates substantial alterations in protein expression mainly in epithelial cells of lungs from hibernating Syrian hamsters. These structural changes of the bronchial airway structure are termed airway remodeling and often occur in obstructive lung diseases such as asthma, chronic obstructive pulmonary disease (COPD) and lung fibrosis. Unraveling the molecular mechanism leading to reversal of airway remodeling by the end of torpor may identify possible therapeutic targets to reduce progression of this process in patients suffering from asthma, chronic obstructive pulmonary disease and lung fibrosis.

Key words: hibernation, torpor, hypothermia, lung, remodeling, *Mesocricetus auratus*.

INTRODUCTION

Hibernation, the state of metabolic depression and inactivity in animals during winter, is a phenomenon that is observed in many mammals, including primates (Dausmann et al., 2004). Hibernation of small rodents is characterized by two phases: torpor and arousal. In torpor, a marked drop in metabolic activity results in a substantial drop in body temperature and inactivity in animals (Geiser, 2004). Torpor phases are interspersed with intermittent short arousal periods, during which metabolic rate and body temperature normalize (Kortner and Geiser, 2000). Remarkably, despite the repetitive cycles of cooling and rewarming, hibernating animals do not show gross signs of organ damage (Arai et al., 2005). Hibernating animals have been used to study the effects of low temperature and hypoxia on body organs and the strategies adopted to cope with these (Carey et al., 2003). In these studies, a main focus has been to identify mechanisms that these animals employ to protect their internal organs from injury during hypothermia and rewarming (Bouma et al., 2010; Henning et al., 2002; Sandovici et al., 2004). Elucidation of the mechanisms involved in this natural model of organ protection could be relevant to human medicine (Zancanaro et al., 1999).

The Syrian golden hamster (*Mesocricetus auratus*) is a hibernator belonging to the rodent family. During torpor, hibernating hamsters drop their metabolic rate and heart rate instantaneously, which, by passive cooling, leads to body temperatures of a few degrees above environmental temperature. At an ambient temperature of 5°C this results, within 26 h, in a final body temperature of ~6–8°C (Fig. 1) during torpor. In torpor, many physiological processes are substantially suppressed, including breathing rate, which drops from 84±20 (Rubin et al., 1978) to 5–7 breaths min^{-1}. Typically, the arousal period starts after 3–4 days of torpor and the body temperature rises to the normal value of ~37°C (Fig. 1). These cooling–rewarming cycles of hibernation take place repeatedly throughout the winter. Thus, it is of interest to study lung tissue during different phases of hibernation.

Only a few studies have addressed changes in the lungs in hibernators. During hibernation of the golden mantled ground squirrel, isolated alveolar type II cells of torpid animals were found to have a higher *in vitro* secretion of pulmonary surfactant than those of warm, active squirrels (Ormond et al., 2003a), which supports a previous finding in cold-acclimated Richardson's ground squirrels (Melling and Keough, 1981). It was suggested that the higher production of surfactant is an adaptation to the temperature fluctuations experienced by these animals, because it is necessary to prevent the adhesion of alveolar surfaces during long periods without ventilation (Daniels et al., 1998). Importantly, the long-term inhalation of cool air is associated with the induction of lung injury and airway remodeling in endurance athletes. Winter sports athletes spend many hours per week training in cold and dry air, and it has been observed that they particularly display respiratory symptoms

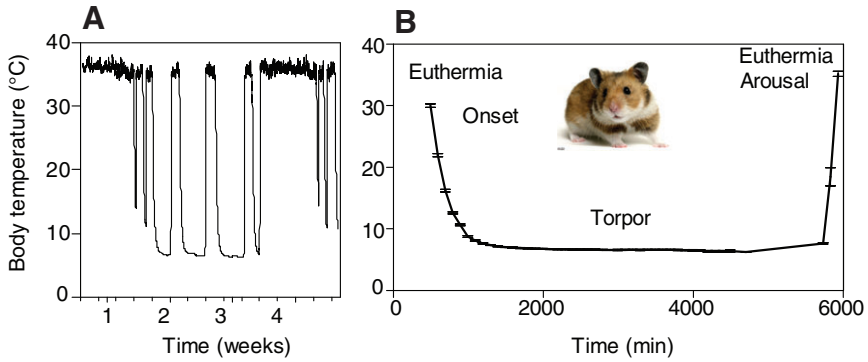

Fig. 1. Example of body temperature of a Syrian hamster in hibernation. (A) A 4-week body temperature recording acquired with an intraperitoneal temperature logger showing the onset of the hibernation. Note the cycle of torpor (low body temperature) and arousal (high body temperature in between torpor bouts). The ambient temperature of the climatic room was set at 5±1°C. During torpor animals cool down to near environmental temperature. (B) A single torpor–arousal cycle during hibernation, illustrating the major phases of the hibernation cycle of the Syrian hamster. Euthermic animals have a body temperature of 37°C. After the onset of torpor animals cool down to near environmental temperatures and body temperature in deep torpor is approximately 1–2° above the ambient temperature of 5°C. after several days of torpor (ranging from 1 to 6 days at an ambient temperature of 5°C in Syrian hamsters) animals spontaneously rewarm to normal physiological body temperatures (arousal).

and airway hyper responsiveness (Bougault et al., 2009; Karjalainen et al., 2000; Sue-Chu et al., 1999). Additional studies on temperature fluctuations during hibernation in lung are absent; hence, we investigated changes in lung histology in the hibernating Syrian hamsters. We hypothesized that animals exposed to low environmental temperature show signs of lung remodeling. However, in view of the adequate restoration of physiology during arousal, we further hypothesized that the expected remodeling in this hibernation model would be transient. Thus, we examined lungs from hibernating animals at the beginning and end of torpor and arousal phases and compared them with summer euthermic animals. We focused on expression and localization of proteins implicated in remodeling, i.e. α-smooth muscle actin (SMA), collagen, epidermal growth factor receptor (EGFR), caveolin-1, transforming growth factor β (TGF-β) and angiotensin converting enzyme (ACE) (Bottoms et al., 2010; Cho et al., 2004b; Elias et al., 1999; LeCras, 2009). Our results demonstrate a rapid reversible remodeling of lung during the hibernation cycle.

MATERIALS AND METHODS

Animals and hibernation induction

For this study 20 (male and female) golden Syrian hamsters (*Mesocricetus auratus* Waterhouse 1839), ~11 months old, were obtained from our local breeding colony. Food and water were available *ad libitum* throughout the experiment. Hay was provided as nesting material and cage enrichment. A summer control group of four animals was maintained in a photoperiod of 14 h:10 h light:dark and a temperature of 20±1°C until they were examined. Other animals were transferred to a separate climate-controlled room and hibernation conditions were applied. Briefly, hamsters were housed in a short-day photoperiod of 8 h:16 h light:dark for 5 weeks. Temperature was maintained at 21±1°C. After 5 weeks, ambient temperature was reduced to 5±1°C and lighting conditions were changed to continuous dim red light (<0.5 lux). These conditions triggered the majority of animals to enter hibernation, and were maintained until the animals were killed. General movement of all the animals was continuously monitored with passive infrared detectors. Activity was accumulated in 2 min time bins using a PC-based recording system. Activity patterns were used for the discrimination of torpid and euthermic phases. Periods with >24 h of inactivity were considered to be torpid phases. Animals were allowed to hibernate for several weeks in order to maximize torpor bout duration. Subsequently, animals were killed at different timepoints in the hibernation cycle. Animals were killed on day 1 after entering torpor (torpor early; N=4), on day 3 during deep torpor (torpor late; N=4), 1.5 h after onset of arousal (arousal early; N=4) and 8 h after reaching euthermia (arousal late; N=4). Summer euthermic animals (N=4) served as controls. The experiments were approved by the Animal Experiments Committee of the University of Groningen, The Netherlands (DEC#4746).

Lung tissue preparation

Animals were killed by means of an intraperitoneal injection of an overdose of 1.5 ml 6% sodium pentobarbital. Upon sacrifice, lungs obtained from each state were either flash frozen in liquid nitrogen for western blot analysis or fixed and embedded in paraffin blocks for pathohistological analysis. Flash-frozen lungs from different stages of hibernation were homogenized (20% w/v) in ice-cold RIPA buffer [1% Igepal ca-630 (octylphenyl-polyethylene glycol), 1% SDS, 5 mg ml^{-1} sodium deoxycholate, 1 mmol l^{-1} sodium orthovanadate, 10 mmol l^{-1} β-mercaptoethanol, 40 μg ml^{-1} phenylmethylsulfonyl fluoride (PMSF), 100 μg ml^{-1} benzamidine, 500 ng ml^{-1} pepstatin A, 500 ng ml^{-1} leupeptine and 500 ng ml^{-1} aprotinin in PBS] (Meijering et al., 2009).

Antibodies

SMA (MO 851; Dako, Glostrup, Denmark), EGFR (Santa Cruz SC-03, Santa Cruz Biotechnology, Santa Cruz, CA, USA), ACE (Santa Cruz SC-12187), TGF-β (Santa Cruz SC-146) and caveolin-1 (Santa Cruz SC-849) were used for western blot and immunolocalization in tissue sections.

Morphological and immunohistological evaluation

Lung samples were fixed and embedded in paraffin, cut into 3 μm sections, deparaffinized and stained with hematoxylin–eosin and periodic acid–Schiff staining for general examination of lung morphology (Hocher et al., 1999). For pathohistological evaluation, the lung samples were fixed and embedded in paraffin, cut into 3 μm sections, deparaffinized and submitted to antibody staining for the mentioned proteins. Sections were incubated with primary antibodies (1:100) with 1% bovine serum albumin (BSA) for 1 h and subsequently washed three times with PBS. Next, sections were

incubated with secondary antibodies (1:100) with 1% BSA and 1% hamster serum for 1 h and subsequently washed three times with PBS. Dako AEC+high sensitivity substrate chromogen was used to visualize the stain.

The percentage of lung area containing SMA was calculated using morphometric analysis using Leica Qwin image analysis software (Leica Microsystems, Rijswijk, the Netherlands) (Blacquiere et al., 2009). To demonstrate the localization of each protein in lung sections a Nikon 50i light microscope with a Paxcam camera add on was used to capture the areas mainly around the bronchioles, veins and the alveoli of the same size.

Collagen analysis

To evaluate the localization of collagen as a molecule present during remodeling in lung tissue, the paraffin blocks were cut in 3 µm sections, deparaffinized and stained with Sirius Red and Fast Green (Cho et al., 2004a). The concentration of collagen was spectrophotometrically measured in lung tissues. In brief, lungs were lysed on dry ice using RIPA buffer. Collagen was isolated from 50 µg of lung lysates by 50 µl of 0.5 mol l^{-1} acetic acid at 4°C overnight. 1 ml of either Sirius Red reagent, which binds to collagen, or Fast Green reagent, which binds to non collagenous proteins, were added to each extraction. The samples were vortexed for 2 min and mixed for 30 min at room temperature. Afterwards, the samples were centrifuged for 5 min at 10,000 ***g*** and unbound dye was washed with 1 ml 0.1 mol l^{-1} HCl. Subsequently, 1 ml 0.5 mol l^{-1} NaOH was added to each sample and the tubes were vortexed to release the bound dyes. The color intensity for Sirius Red and Fast Green were measured at 540 and 570 nm, respectively, using a microplate reader (Jimenez et al., 1985). A collagen standard curve was used to determine the concentration of collagen in each sample. Collagen content was expressed as µg 50 µg^{-1} lung protein.

Western blot analysis

The expression of proteins was investigated for each hibernation stage by western blot analysis. In lung lysates, the protein concentration was determined by the Bradford protein assay (Bradford, 1976). For each sample, 20 µl of loading buffer (10% SDS, 50% glycerol, 0.33 mol l^{-1} Tris-HCl pH 6.8, 0.05% Bromophenol Blue) was added to every 50 µg of protein and loaded onto pre-made 4–20% gels (gels originated in Australia; Thermoscientific, Rockford, IL, USA; 15 wells #25224) for electrophoresis at 100 V (80 min). Each gel was subsequently blotted onto a nitrocellulose membrane. Proteins on the nitrocellulose membranes were detected with specific primary antibodies (1:1000) overnight at 4°C, washed three times with Tris-buffered saline plus Tween solution and treated with the related secondary antibody (1:1000, 2 h at room temperature). The membranes were later developed using super signal West Dura substrate, and GeneSnap (version 6.07; Syngene, Cambridge, UK) was used to acquire images. The results were analyzed using GeneTools version 3.08 (Syngene).

Statistics

Statistical analyses were performed using a one-way ANOVA (P<0.05) with Tukey's test (GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego, CA, USA), unless indicated otherwise.

RESULTS

To investigate the possibility of remodeling in hibernating hamsters, the expression of SMA and collagen were investigated by western blot. SMA expression gradually increased during torpor, with the highest concentration in late torpor and a drop during arousal, as shown in Fig. 2E,F. Immunohistological stainings showed the expression of SMA in all phases of hibernation around the airways and in blood vessels as shown in Fig. 2A–D.

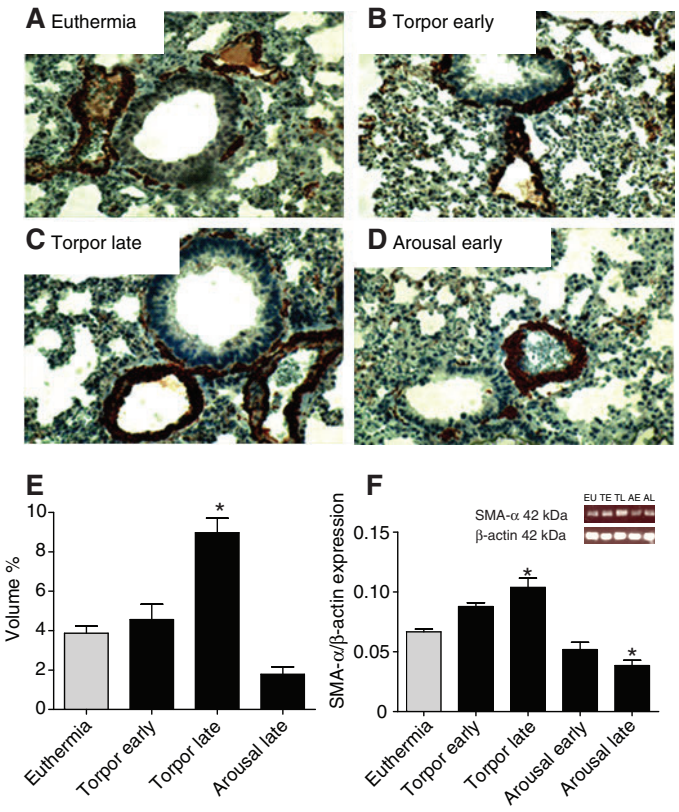

Fig. 2. Expression of α-smooth muscle actin (SMA) in lung tissue of hibernating hamsters. (A–D) SMA-expressing cells were dispersed throughout the lung tissue but were mainly present around the airways and blood vessels. Original magnification ×40. (E,F) The number of SMA-expressing cells (E) and SMA protein expression (F) were highest during late torpor and were reduced to euthermic levels during late arousal. Protein levels are expressed relative to that of β-actin. The inset in F shows representative western blot for SMA and β-actin. TE, torpor early; TL, torpor late; AE, arousal early; AL, arousal late; EU, euthermia. Values are means ± s.e.m. *Significantly different from euthermia, P<0.05, N≥3 per group.

High expression of SMA was accompanied by a high expression of collagen, as measured by the quantitative Sirius Red–Fast Green spectrophotometrical method (Fig. 3E). The expression rose during early torpor followed by a drop during late torpor. The staining was mainly present around airways and in blood vessels during early torpor as shown in Fig. 3A–D.

The expression of EGFR, one of the molecules that promote lung tissue remodeling in asthma, was also measured in the different phases of hibernation, by western blot. Quantitative analysis of EGFR revealed the lowest concentration at the late phase of torpor followed by gradual upregulation after arousal (Fig. 4D). EGFR expression was mainly localized in the epithelium of the airways as shown in Fig. 4A–C.

ACE is responsible for the conversion of angiotensin I to angiotensin II and is involved in lung vascular remodeling (Kuba et al., 2006). Quantitative analysis demonstrated a higher expression of this protein at the onset of torpor, downregulation at the late phase

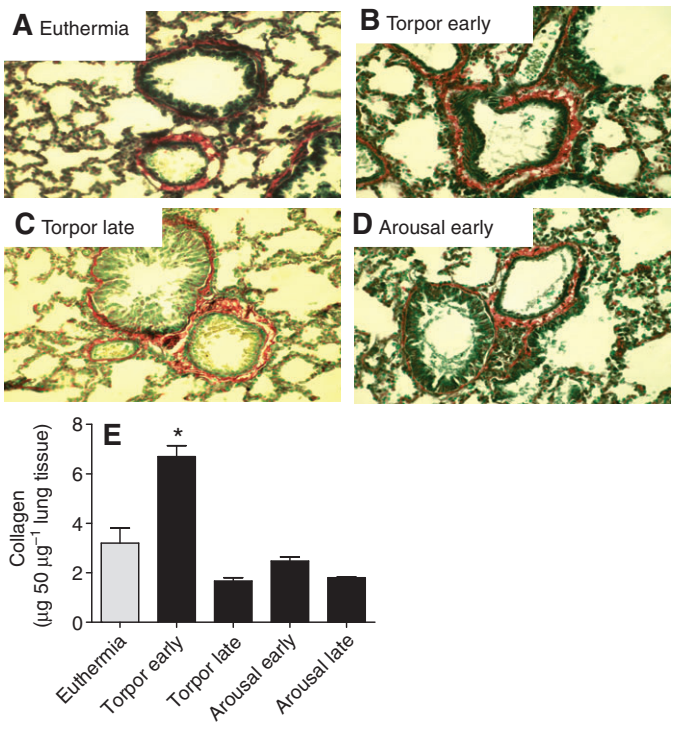

Fig. 3. Sirius Red–Fast Green staining of collagen in lung tissue of hibernating hamsters. (A–D) Collagen was expressed mainly around the airways and blood vessels during all phases of hibernation. Original magnification ×40. (E) Quantification of collagen expression in the lung, which was highest during torpor. Values are means ± s.e.m. *Significantly different from euthermia, $P<0.05$, $N\geq3$ per group.

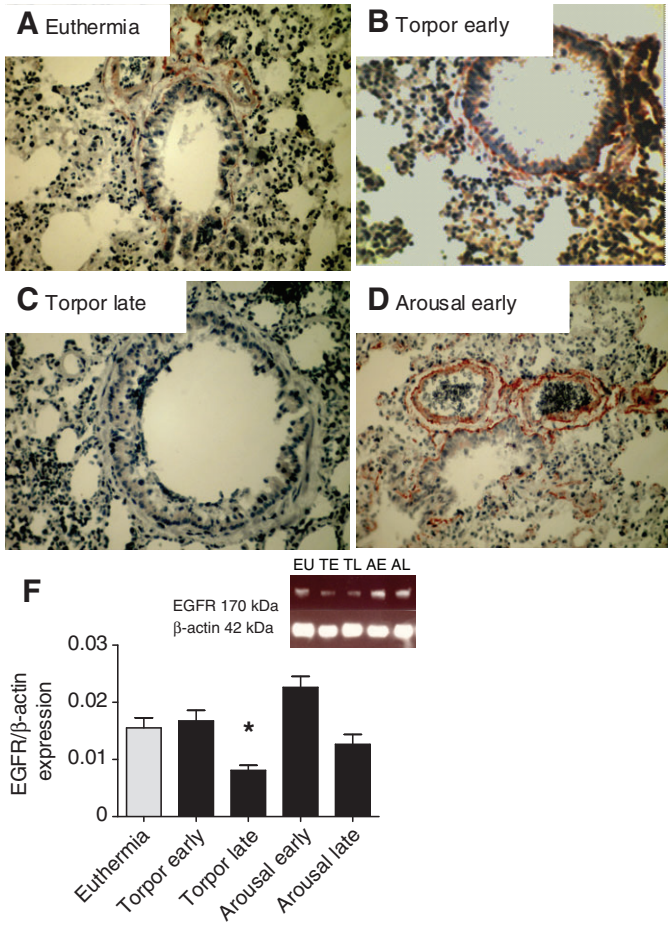

Fig. 4. Epidermal growth factor receptor (EGFR) staining in lung tissue of hibernating hamsters. (A–D) EGFR was expressed mainly around the blood vessels and airways and highest expression was found during early arousal (D) Original magnification ×40. (E) Quantification of protein expression, normalized to that of β-actin. The inset in E shows representative western blot for EGFR and β-actin. TE, torpor early; TL, torpor late; AE, arousal early; AL, arousal late; EU, euthermia. Values are means ± s.e.m. *Significantly different from euthermia, $P<0.05$, $N\geq3$ per group.

of torpor followed by a change to the euthermic level during arousal (Fig. 5A). High expression of TGF-β, another marker for tissue remodeling, was also found during early torpor and also at early arousal, which was then reduced to the euthermic level at the late arousal phase (Fig. 5B).

Caveolin-1 expression, as part of the TGF-β signaling pathway was also measured (Le Saux et al., 2008b). The expression was reduced to half of the euthermic expression during the late torpor phase, and it reached its highest point during early arousal (Fig. 6D). The immunolocalization demonstrates the changes mainly in the epithelial cells of the alveoli and vasculature, as shown in Fig. 6A–C.

DISCUSSION

We report here on two important observations in the lungs of hibernating Syrian hamster. First, during torpor, animals show marked lung remodeling as evidenced by substantial changes in collagen and SMA and in the expression of remodeling-related proteins. Second, the torpor-related lung remodeling was completely reversed during arousal, a phenomenon not described before.

Scientists still question the actual definition of airway remodeling but medical dictionaries explain it as the structural changes in the number, mass, size and/or composition of the airway tissues that is manifested by an increase in collagen and SMA. Interestingly, the changes in the lungs that we found in the torpor phase of hibernating hamsters are similar to lung remodeling seen in asthma (Ten Hacken et al., 2003; Vignola et al., 2003). In asthma, airway remodeling includes alterations of the epithelial cell layer with goblet cell hyperplasia, thickening of basement membranes, peri-bronchial and peri-bronchoalveolar fibrosis, smooth muscle cell hyperplasia and increase of activated fibroblasts and myofibroblasts with deposition of extracellular matrix such as collagen. It is initiated as a repair process in response to airway wall injuries caused by inflammation; however, dysregulation of this process leads to airway remodeling. Thus, hibernating animals could serve as a model to identify mechanisms of reversible lung remodeling.

There is very limited data on changes in lung during hibernation. Hibernating ground squirrels have been suggested to significantly increase surfactant production, which might prevent alveolar collapse during long non-ventilatory periods between breaths (Ormond et al., 2003b). However, it is not clear whether this occurs in the whole animal, as results were obtained in *in vitro* isolated epithelial type II cells. Thus, the current study is the first to identify *in vivo* changes in the lung of hibernating animals.

The main characteristics of lung remodeling observed during torpor in the Syrian hamster are the increase in collagen and SMA. Regarding expression of collagen, this was increased in the early phase of torpor and reached a euthermic level at the end of torpor.

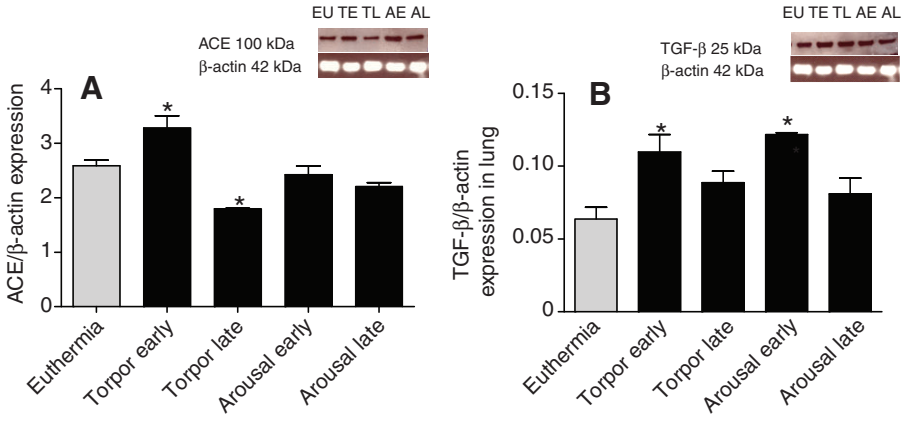

Fig. 5. Expression of angiotensin converting enzyme (ACE; A) and transforming growth factor β (TGF-β; B) in lung tissue of hibernating hamsters. Protein expressions were normalized to that of β-actin. The insets show representative western blots for ACE, TGF-β and β-actin. TE, torpor early; TL, torpor late; AE, arousal early; AL, arousal late; EU, euthermia. Values are means ± s.e.m. *Significantly different from euthermia, $P<0.05$, $N\geq3$ per group.

Collagen is an extracellular matrix protein, fundamental in the maintenance of lung structure and function. A dispersed collagen deposition was found in the lungs, mainly around the bronchi and blood vessels, which is typical of a remodeling pattern. Although the mechanism is not clear, the substantial increase in collagen content in early torpor may be related to changes occurring in some of the remodeling-associated proteins, as it coincides with upregulation of TGF-β and ACE and the downregulation of caveolin-1. TGF-β has been implicated in collagen deposition in the lung (Murata et al., 1997). Moreover, a decreased expression of caveolin-1 has been associated with enhanced TGF-β signaling and increased collagen deposition (Le Lay and Kurzchalia, 2005). However, ACE has been described to inhibit collagenase activity (Brilla et al., 1994), a process expected to induce collagen deposition. Thus, changes in the expression of these proteins in lung match the observed increase in lung collagen content.

Hibernation also clearly affects SMA, a second important protein in lung remodeling. The expression of SMA is augmented during early torpor with a further increase in late torpor. In lung tissue of our hamsters in torpor, increased SMA protein expression was mainly found around bronchi and blood vessels, again indicative of remodeling. *In vivo* and *in vitro* studies have demonstrated that smooth muscle contributes to an epithelial–mesenchymal trophic unit, which is activated during tissue injury and repair and is driven by both changes in inflammatory cells and damaged epithelium (Dekkers et al., 2009). The process underlying the observed higher SMA expression in our model is currently unknown, but subject for further studies. Possibly, it is related to an increase in TGF-β signaling during early torpor, which subsequently may induce smooth muscle cell growth (Holgate, 2008). Alternatively, the observed high expression of collagen during early torpor may have induced the proliferation of smooth muscle cells, as found in *in vitro* experiments performed on cells obtained from asthmatic and non-asthmatic subjects (Johnson et al., 2004).

Caveolin-1 expression is lower during torpor phase, which could be an inducing factor in the process of remodeling. Caveolae are vesicular organelles that are considered an organizing unit of cellular signal transduction (Norkin and Kuksin, 2005; Simons and Ikonen, 1997) and have a role in endothelial cell migration (Navarro et al., 2004). Caveolin-1-deficient mice show lung abnormalities, with thickened alveolar septa and hypercellularity, and they are exercise intolerant (Razani et al., 2001). Caveolin-1 inhibits the

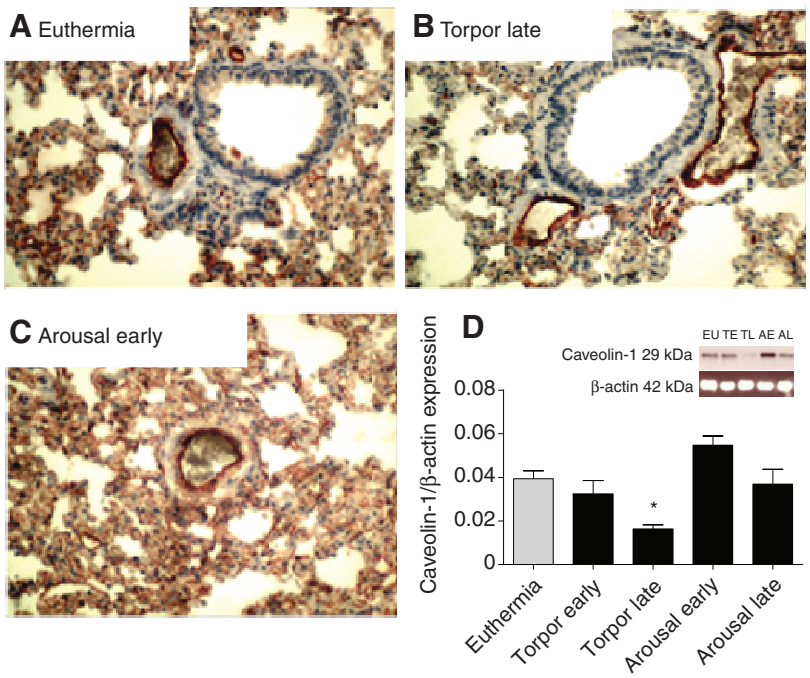

Fig. 6. Expression of caveolin-1 in lung tissue of hibernating hamsters. (A–C) Caveolin-1 was mainly located in endothelium and epithelial cells of the airways. (D) Quantification of protein expression showed that expression was lowest during late torpor and highest during early arousal. Protein expression was normalized to that of β-actin. The inset in D shows representative western blot for caveolin-1 and β-actin. TE, torpor early; TL, torpor late; AE, arousal early; AL, arousal late; EU, euthermia. Values are means ± s.e.m. *Significantly different from euthermia, $P<0.05$, $N\geq3$ per group.

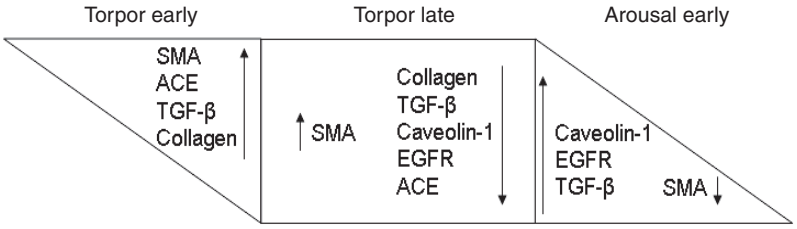

Fig. 7. Summary of changes in the expression of several proteins involved in lung remodeling during hibernation in the hamster. The expression of the proteins in lungs during the euthermic phase was set as control and the arrows indicate the change in expression of each protein compared with the euthermic level.

activity of TGF-β, perhaps by forming membrane invaginations that enfold TGF-β receptors (Le Saux et al., 2008a); however, a higher expression of TGF-β has shown to downregulate caveolin-1 expression in cultured endothelial cells (Igarashi et al., 2009). In our experiment lower expression of caveolin-1 was accompanied by higher expression of TGF-β as a remodeling marker. Caveolin-1 downregulation induces lung remodeling (Jasmin et al., 2004). Thus a downregulation of caveolin-1 and upregulation of TGF-β could facilitate the binding of this growth factor to its receptor, which could result in higher expression of collagen and SMA during the torpor phase in hamster lung.

The downregulation of EGFR around the bronchioles and alveoli, as found in late torpor animals, may represent an additional protective mechanism in lungs against permanent remodeling. EGFR controls a wide variety of biological processes, including cell proliferation, differentiation, survival and migration. EGFR is induced following lung injury and its deactivation is accompanied by suppression of remodeling in lungs (Kramer et al., 2009). High EGFR expression also leads to production of excess mucus and mucin, which contributes to the obstruction of the bronchioles, and remodeling with an asthmatic phenotype (Burgel and Nadel, 2004; Nadel, 2001) Thus, a downregulation of this protein during torpor may contribute to the reversibility of remodeling in this organ.

Our results suggest that during the torpor phase there is an ongoing change in expression of proteins involved in lung remodeling, despite a substantial suppression of metabolism during this phase (Storey, 2010). For example, while the expression of collagen decreases during torpor, the expression of SMA shows a gradual increase. Changes in protein expression during torpor is in line with the previous finding that there is a substantial post-transcriptional regulation of proteins during torpor–arousal cycles of hibernation (Shao et al., 2010). It has also been shown that proteolysis is depressed during torpor (Velickovska et al., 2005). Thus, even though protein synthesis is suppressed throughout torpor, it is not stopped. Our data seem to suggest that for almost all of the proteins examined, during torpor the rate of protein synthesis in lungs is higher that the rate of its degradation.

We observed that hibernation induces lung remodeling in hamster lungs similar to cold-air-induced remodeling in humans. However, this remodeling was observed to be rapidly reversible in hibernators, which is probably not the case in humans. Exposure to cold air seems to trigger the development of asthma and is an established factor for persistent remodeling in lungs as noticed in countries with a cold climate and in athletes in cold weather (Sarin et al., 2006; Shephard, 2004). Some of the respiratory problems in asthma involve the drying of the mucosa lining of the respiratory system, which is also brought about by prolonged inhalation of cold air, leading to or worsening lung remodeling (Barnes, 2002).

Importantly, all of the lung remodeling features observed in torpor in hamsters were reversed by the end of the arousal period. As outlined above, the changes in EGFR and ACE might be key elements to prevent or reverse permanent lung remodeling. The underlying mechanisms of lung remodeling and its reversibility, however, still remain unresolved. Another mechanism that could be of relevance to reversibility of lung remodeling is caloric restriction during torpor. Possibly, the extended fasting or caloric restriction of hibernating animals counteracts remodeling, as food deprivation has already been found to cause a decrease in lung collagen content in rats in early and late postnatal periods (Faridy, 1970; Sahebjami, 1993).

Airway remodeling is currently believed to largely account for the disease mechanisms of asthma and asthma-related disorders such as fibrosis or chronic obstructive pulmonary disease (Barnes, 2002). Increases in airway smooth muscle mass represents probably the main mechanism causing airway hyperresponsiveness, and changes in the extracellular matrix may stimulate smooth muscle growth and contribute to the mechanics of airway obstruction (Ramos-Barbon et al., 2004). Our findings in hibernating hamster lungs (Fig. 7) may help to unravel potential new avenues to prevent lung remodeling in humans.

In summary, this is the first report demonstrating substantial remodeling of lung tissue during hibernation in the Syrian hamster. Lung remodeling in hibernation shows marked similarities to asthmatic airway remodeling. Importantly, the airway remodeling of hibernation was fully reversible upon rewarming, a phenomenon not described earlier. Identification of the mechanism(s) responsible for the observed rapid reversibility of the remodeling could have consequences for chronic airway hyper-reactivity and airway obstruction and/or hypertrophy in human lung diseases such as asthma, chronic obstructive pulmonary disease and lung fibrosis, providing promising pharmaceutical targets for prevention and reversal of permanent lung remodeling.

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