UCP1 - a lever of the redox-metabolic seesaw in the regulation of lipid-buffering function of white adipose tissue

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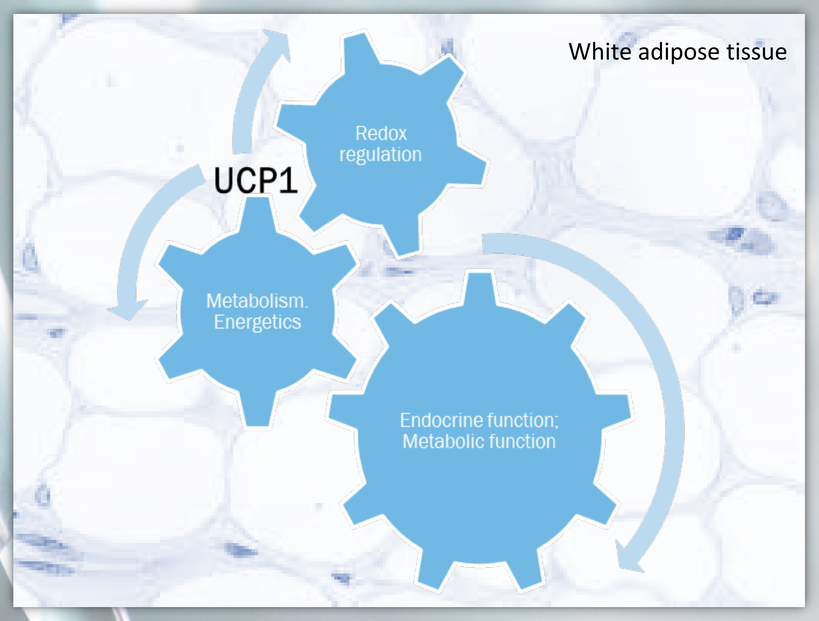
Oxidative stress, redox biology and antioxidants from plants to humans

BACKGROUND

In the absence of energy-demanding conditions, excess glucose and fatty acids end up as lipid reserves in the white adipose tissue (WAT). The lipid storage function of WAT maintains glucose and lipid homeostasis and provides fatty acids which can be mobilized as needed. Understanding molecular mechanisms that control such lipid-buffering capacity of WAT are essential in obesity and diabetes prevention and treatment. An ectopic occurrence of uncoupling protein 1 (UCP1) in WAT (known as *browning*) could be leveraged as a therapy for obesity, as UCP1 limits the synthesis of ATP and lipogenesis and restrains the production of superoxide in mitochondria. The physiological role of UCP1 in the lipid-buffering function of WAT is still unclear, as several prooxidative states (increased mitochondrial superoxide, hydroperoxide and lipid hydroperoxides and/or glutathione (GSH) depletion) *per se* upregulate UCP1 which in turn may limit deposition of lipids in WAT.



AIM

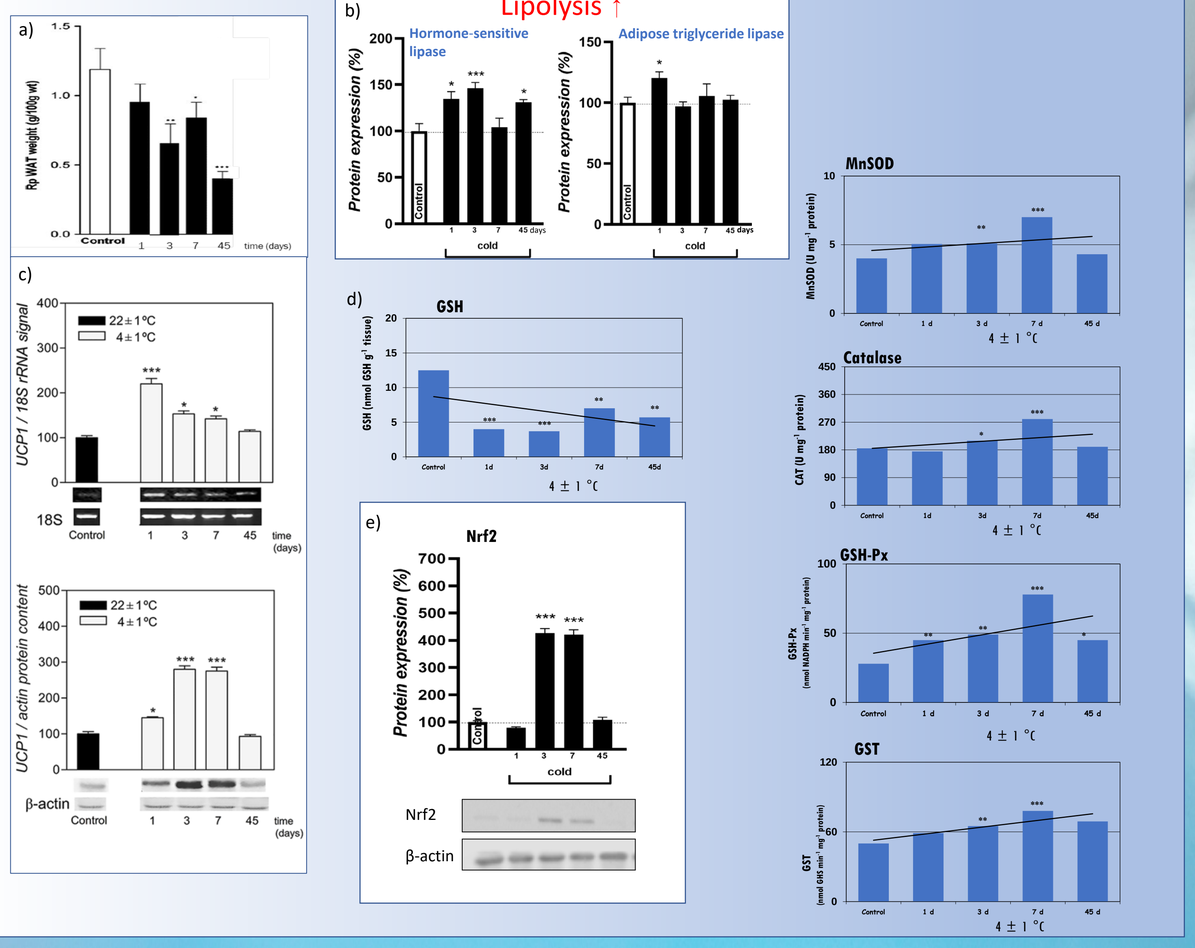
To clarify the physiological role of UCP1 in white adipose tissue we aimed to investigate the relation of UCP1 expression with the components of redox-adaptive homeostasis in two extreme states favouring lipid degradation or lipogenesis in WAT. Toward this aim, we investigated time-dependent changes in morphology and metabolic function of WAT, expression patterns of UCP1, glutathione (GSH) level, nuclear factor erythroid 2-related factor 2 (Nrf2) and its downstream antioxidant enzyme targets.

EXPERIMENTAL MODELS

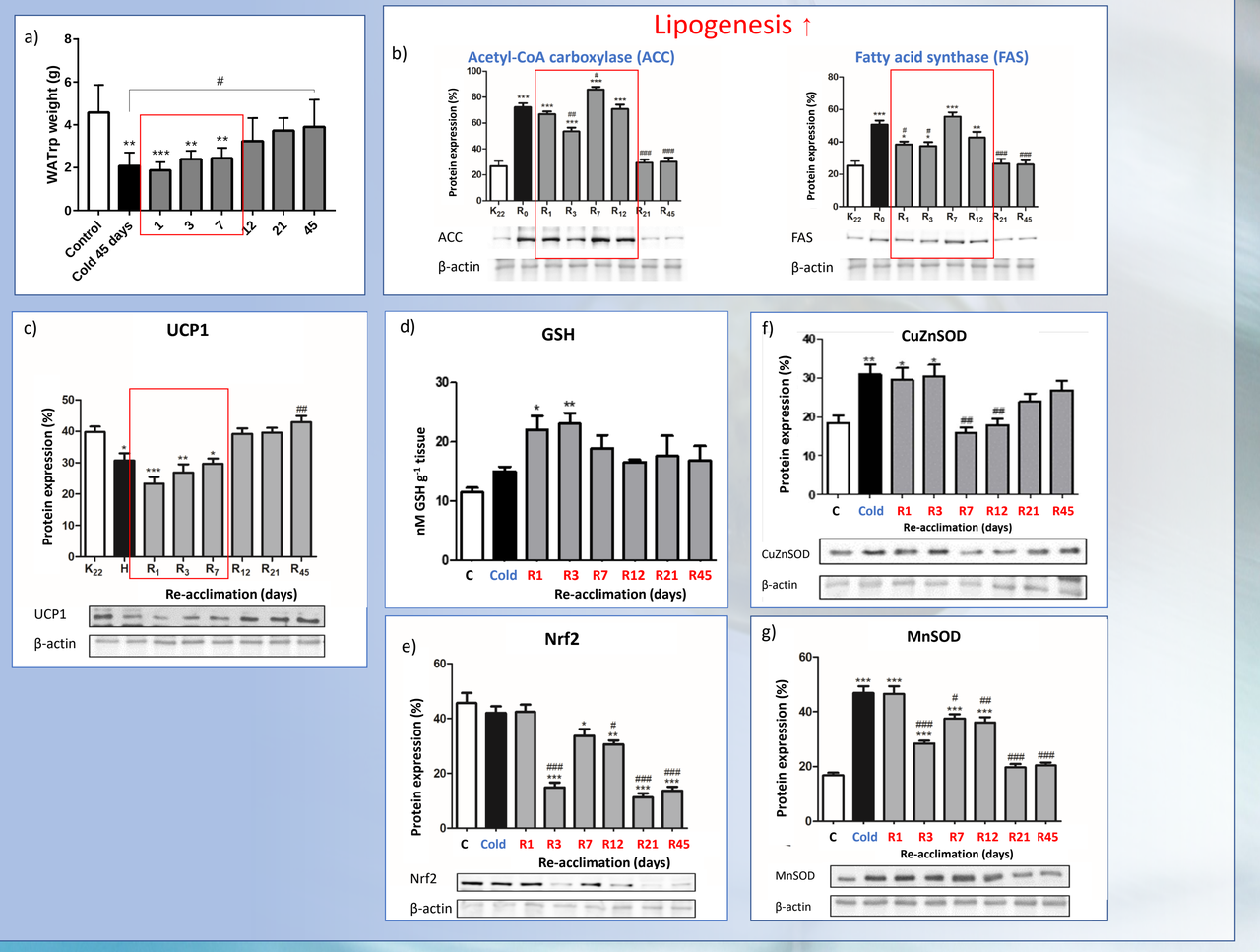
The relative tissue weight, key enzymes of triacylglycerol degradation and biosynthesis of FA, UCP1, GSH level, expression and or activity of Nrf2 and several antioxidant target enzymes were investigated in the retroperitoneal WAT (rpWAT) of adult male Mill Hill hybrid hooded rats following 1, 3, 7 and 45 days of cold (4 °C) acclimation and 1, 3, 7, 12, 21 and 45 days of re-acclimation to RT (24 °C) in rats previously exposed to cold for 45 days. The changes were compared to respective RT and/or cold-acclimated controls.

RESULTS

I Acclimation to cold



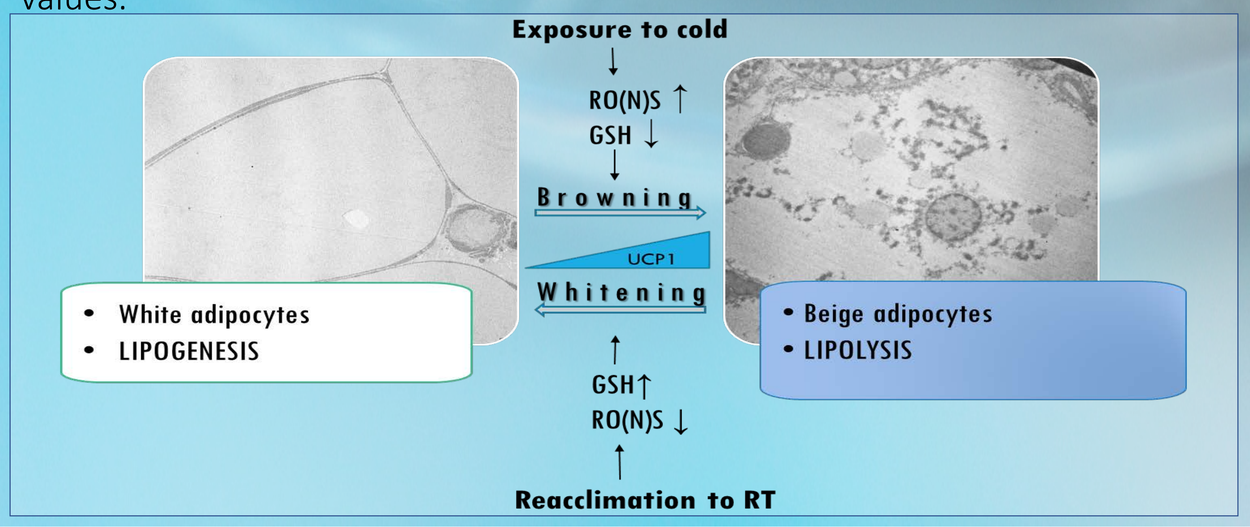
II Re-acclimation to RT



*comparison with RT-maintained control, *p < 0.05; **p < 0.01; ***p < 0.001; # comparison with cold-acclimated group, # < 0.05; ## p < 0.01; ### p < 0.001.

- Cold exposure induces regression of WAT weight (a) that involves increase of lipid mobilisation (b). In response to cold-induced lipid mobilization transient induction of UCP1 expression levels (c) concords with GSH depletion (d) and subsequent upregulation of Nrf2 (e) and its downstream antioxidant enzymes (such as MnSOD, catalase, GSH-Px and GST).

- The reverse sequence of molecular events was observed during the early (1-12. days) and late (12-45. days) periods of re-acclimation to RT. Namely, in the initial days of re-acclimation high lipogenesis (b) and redox threshold (higher GSH level (d), and higher expression levels of CuZnSOD and MnSOD (f and g)) correspond to lower levels of UCP1 protein expression (c). From the moment of restitution of lipid reserves (revealed by rpWAT mass(a)) and on, UCP1, GSH, and most antioxidant enzymes including SODs return to their RT control values.



CONCLUSION

The results emphasize UCP1 as lever of redox-metabolic seesaw fine-tuning of redox homeostasis for optimal regulation of lipid mobilization and deposition in white adipocytes.

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