Circadian control of brown adipose tissue activity by glucocorticoids

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Background: Brown adipose tissue (BAT) displays a strong circadian rhythm in metabolic activity (van den Berg, Cell Rep 2018). On the other hand, circadian disturbances affect BAT activity and result in weight gain (Kooijman, PNAS 2015). The aim of the current study was to investigate the role of the superimposed rhythm in the glucocorticoid corticosterone in the metabolic activity of BAT.

Methods: Wildtype and hyperlipidemic APOE*3-Leiden.CETP mice were subcutaneously implanted with pellets releasing a continuous low dose of corticosterone to flatten corticosterone rhythm. Alternatively, daily corticosterone injections were given to study the effect of hypercortisolism and adipose-specific GR KO mice were employed to investigate the underlying mechanism.

Results: Implantation of corticosterone-containing pellets resulted in constant and flattened circulating corticosterone, with slight hypercortisolism. Strikingly, flattened corticosterone rhythm caused a complete loss of circadian rhythm in the uptake of triglyceride-derived fatty acids by BAT in both male and female mice. In line with these data, lipoprotein lipase mRNA and protein were highly rhythmic in BAT of vehicle-implanted mice, but were blunted in mice with flattened corticosterone rhythm. In APOE*3-Leiden.CETP mice, long-term experimental flattening of corticosterone - and thus BAT activity rhythm - resulted in increased lipid deposition in adipose tissue depots and as a consequence weight gain. All described effects were independent of glucocorticoid receptor expression in (brown) adipocytes and not caused by hypercortisolism, but rather mediated by reduced sympathetic outflow to BAT as evidence by a blunted rhythm in norepinephrine production and reduced adrenergic signaling.

Conclusion: A physiological glucocorticoid rhythm is essential for rhythmic BAT activity and metabolic health. We anticipate that disruption of glucocorticoid rhythm, and thereby BAT activity rhythm, could partially underlie the relationship between rhythm disturbances and metabolic disease in humans.