Differential entrainment susceptibility of central and peripheral circadian clocks affects energy metabolism in Pitx3-deficient Aphakia mice

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Introduction

Most organisms adapt their physiology and behavior to daily light/dark cycles due to an internal circadian timing system. This system is governed by the hypothalamic suprachiasmatic nucleus (SCN) which is synchronized to the light input reaching the SCN directly from the retina. SCN translates this information to entrain molecular clocks in peripheral organs, which are essential to adapt metabolic activity to circadian variations. The synchronizing function of these molecular clocks is based on autoregulatory feedback loops of gene expression of clock genes, e.g., Per1 and Per2, which are part of the negative limb. Several studies confirm that peripheral clocks can be entrained by other cues like feeding. Therefore, time-restricted feeding (TRF) can change the phase of circadian gene expression in the peripheral organs regardless of the NSC activity.

GOALS: We investigated the relative importance of the input pathway relying light information to the SCN for the function of central and peripheral clocks and for the circadian regulation of energy metabolism.

Methods

ANIMAL MODEL: Pitx3-deficient Aphakia (Pitx3(Ak)) mice characterized by a congenital defect that severely disrupts eye development.

MEASUREMENTS:
- INDIRECT CALORIMETRY AND MOTOR ACTIVITY
- CLOCK GENE EXPRESSION BY qRT-PCR
- GLUCOSE BLOOD LEVELS
- ELECTRORETINOGRAPHY AND ANTICONVULSIVE TRACING

Blood glucose oscillations in Pitx3(Ak) mice

TRF does not entrain clock gene expression in the NSC in Pitx3(Ak) mice

TRF entrains partially the circadian clock in the liver in Pitx3(Ak) mice

Conclusions

- Pitx3Ak mice present a complete absence of circadian rhythms in metabolic parameters, motor activity and expression of clock genes (Per1 and Per2) in the NSC and the liver.
- Time-restricted feeding partially restores the circadian rhythms in metabolic parameters, motor activity and gene expression.
- Pitx3Ak mice present a lack of retinal function and its axonal projections do not reach the NSC.