Time-of-day-dependent rhythms in the transcriptional responsiveness of the rat heart to triiodothyronine

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INTRODUCTION AND AIM

Myocardial gene expression and metabolism fluctuate over the course of the day, in association with changes in energy supply and demand. Recently, time-of-day-dependent oscillations in myocardial processes have been linked to the intrinsic cardiomyocyte circadian clock. Triiodothyronine (T3) is an important modulator of cardiac form and function. The genomic actions of T3 are triggered after its interaction with thyroid hormone nuclear receptors that often dimerized with RXR or RORA. Some target proteins, such as PDK4, are regulated not only by the cardiomyocyte circadian clock, but also by T3, suggesting a potential interrelationship between the two mechanisms. Circulating levels of T3 and its intermediates exhibit a time-of-day-dependent oscillation. However, whether the sensitivity of T3 responsive tissues oscillate in a time-of-day-dependent manner is unknown. Thus, the purpose of the present study was to investigate whether the heart exhibits a diurnal variation in T3 responsiveness, at a transcriptional level, and/or whether T3 impacts the circadian clock in the heart.

PARTIAL RESULTS AND CONCLUSION

In general, the administration of T3 promoted a marked alteration in the expression of Bmal1, Ucp3 and Pdk4 (Figs. 1A-C), revealing a time-of-day-dependent responsiveness specially at the end of the dark phase for Bmal1 and Ucp3 (ZTs 21-24) and throughout the whole investigated period for Pdk4 (Figs. 2A-C). Our study shows that T3 might acts as a *Zeitgeber* for these genes, and lead to alteration of the cardiac functions, which may help to explain some metabolic and functional disorders observed in thyroid diseases.

Figure 1

![Figure 1](image1)

**Figure 1.** Effects of T3 on Bmal1, Ucp3 and Pdk4 mRNA expression in the rat heart. The animals received Vehicle or T3 injection (i.p. 12.5 μg/100 g) 4 h prior each *Zeitgeber* Time (ZT - ZT=06:00am). The animals were euthanized at the respective ZT, throughout 24 h. The hearts were excised and the mRNA expression was evaluated by RT-qPCR using Taqman probe specific for each target gene; *Cyclophilin* was used as a housekeeping gene. One and Two-Way ANOVA analysis were used to evaluate the time-of-day-dependent differential expression for each gene/group and their interactions.

Figure 2

![Figure 2](image2)

**Figure 2.** Induction analysis of mRNA expression. The induction was calculated by the difference between T3 and Vehicle values at respective ZT. n=5/ZT/group. ZT=Zeitgeber Time.

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