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.

MATERIAL AND METHODS

For this study, euthyroid male Wistar rats were divided in two groups: Vehicle or T3 (supraphysiological dose, 12.5 μg/100 g), administered 4 h prior each *Zeitgeber* Time (ZT – ZT0=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.

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

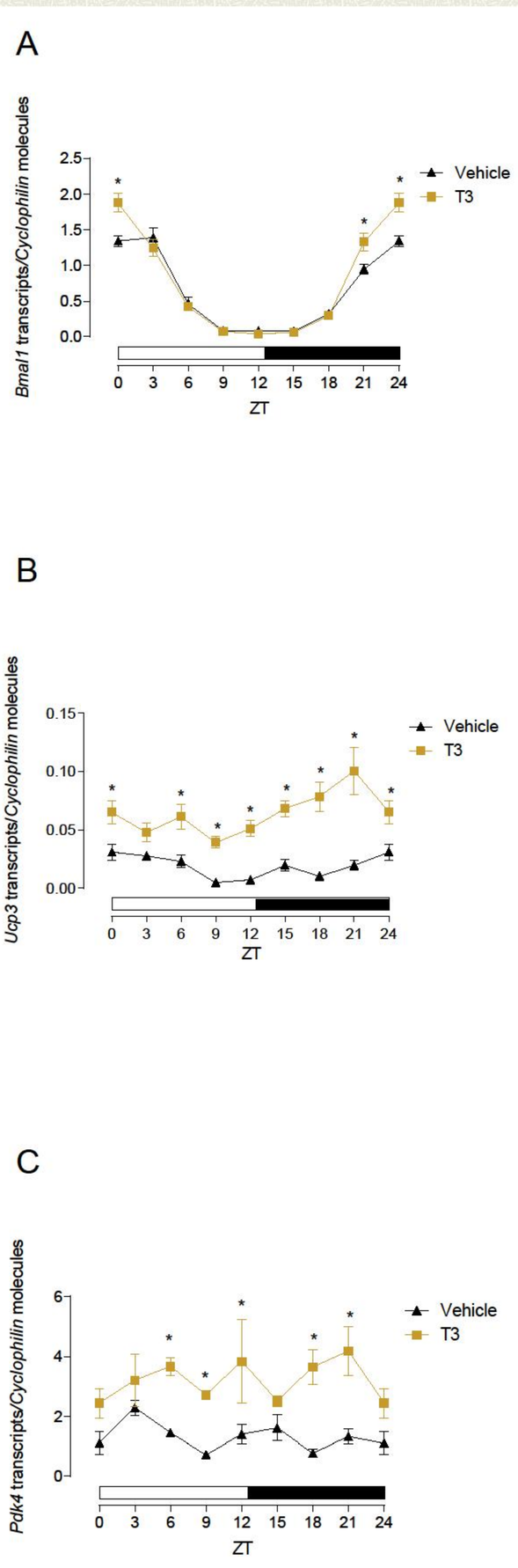

Figure 2

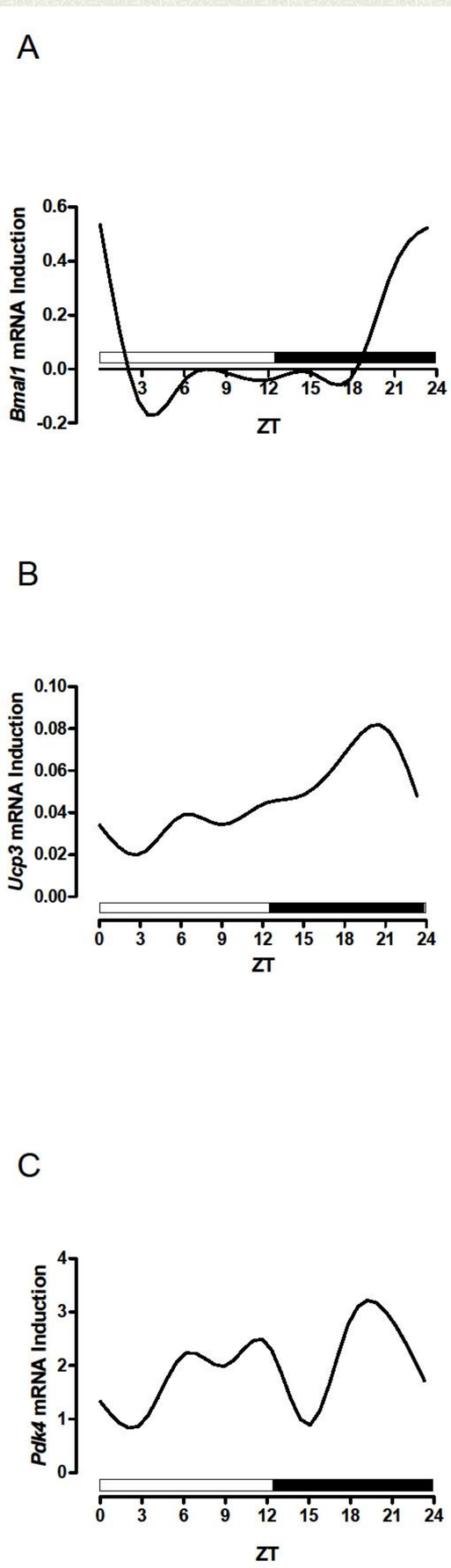

Figure 1. Effects of T3 on *Bmal1, Ucp3* and *Pdk4* mRNA expression in the rat heart. The animals received Vehicle or T3 injection (i.p. 12.5 μg/100 g) 4 h before each ZT. The ZT 24 was double plotted as ZT 0). Expression of *Bmal1, Ucp3* and *Pdk4,* A, B and C, respectively. The statistical analysis performed was One-way ANOVA, $P<0.05$, for both groups in all cases, and Two-way ANOVA, *$P<0.05$ vs vehicle. n=5/ZT/group. ZT=*Zeitgeber* Time.

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

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