4-2022

A study of the DBP gene expression in the SCN under normal day length

Marie-Claire Boutrin Ph.D., MPH
Oakwood University, mboutrin@oakwood.edu

A study of the DBP gene expression in the SCN under normal day length

Kahylin Nesbitt, Feyikemi Oriola, Jamiah Thomas, Zenoviah Graham, Marie-Claire Boutrin, PhD, MPH

Oakwood University, School of Arts and Sciences,
Department of Biological Sciences
Huntsville AL, 35896

ABSTRACT

Circadian rhythms are internally driven cycles that are influenced by light and darkness exposures, and are controlled by clock genes. The master clock, also known as the suprachiasmatic nucleus, houses clock genes such as *Per1, Cry1, CLOCK, REVERB* and *Bmal*. The circadian clock sets the timing for many circadian rhythms that oscillate over a 24-hour period to regulate processes such as sleep/wake cycles, hormonal activity, body temperature, eating, and digesting. *DBP*, a clock gene, encodes for the D-Box Binding PAR BZIP Transcription Factor (DBP) protein that influences the circadian clock by positively regulating the *mPer1* promoter and amplifying the circadian clock of *mPer1*. Also, *DBP* regulates circadian and homeostatic aspects of sleep, including rapid eye movement sleep/paradoxical sleep. Jet lag is a circadian disorder that occurs when the body's internal clock is out of sync with environmental cues, such as light exposure from a new time zone. The purpose of this study was to investigate the effects of jet lag on *DBP* gene expression. SCN *DBP* gene expression levels were evaluated under normal day length, jetlag and control (non-jetlag) conditions at ZT10 and ZT14 time points in C57BL/6NCrl adult mice using qPCR. Our results showed downregulation in *DBP* gene expression when comparing ZT14 to ZT10 time points under both jet lag and non-jet lag conditions. Similarly, *DBP* expression levels were downregulated under jet lag conditions (compared to non-jet lag conditions) at ZT10 and ZT14 time points. Our findings suggest that *DBP* expression levels vary with time and are affected by jet lag under normal day length conditions. Gaining understanding on circadian molecular mechanisms will assist in the development of therapies targeting jet lag.

INTRODUCTION

Circadian rhythms are internally driven cycles controlled by clock genes and establish the body's circadian clock[1]. Bodily processes such as sleep/wake cycles, hormonal activity, body temperature, eating, and digesting are all influenced by 24-hour circadian rhythms, which are governed by the master clock.[2] The master clock, also known as the suprachiasmatic nucleus (SCN), houses clock genes such as *DBP, Per1, Cry1, CLOCK, REVERB*, and *Bmal*. *DBP* encodes for the D-Box Binding PAR BZIP Transcription Factor protein that influences the circadian clock by positively regulating the mPer1 promoter and amplifying the circadian clock of mPer1.[3] *DBP* can be found in the nucleus of clock-oscillating SCN cells.[4] It is also found in the liver, adrenal glands, and other tissues.[5,6,7] In addition, *DBP* was found to be a regulator of circadian and homeostatic aspects of sleep, including rapid eye movement sleep/paradoxical sleep.[8]

Jet lag is a desynchronization between the body's internal clock and environmental cues, such as light exposure.[9] Disruptions of circadian rhythms and desynchronizing of the circadian clocks were associated with disorders and diseases including Familial advanced sleep phase disorder (FASPD), metabolic syndrome, and tumor development.[10] Zeitgeber time (ZT) is used for assessing biological time in a LD cycle.[11] ZT0 is light-on and ZT12 is light-off under non-jet lag conditions.[11]

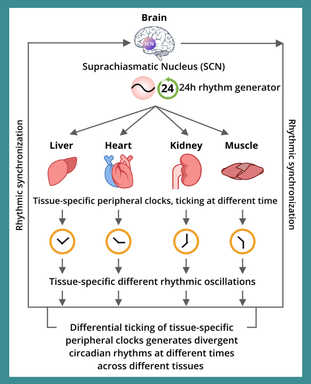


Figure 1: Representation of how the master clock influences the peripheral clocks.[12]

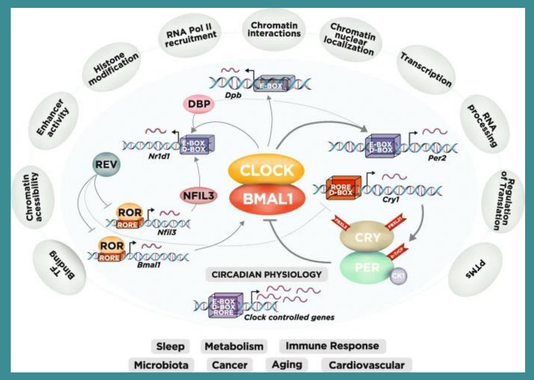
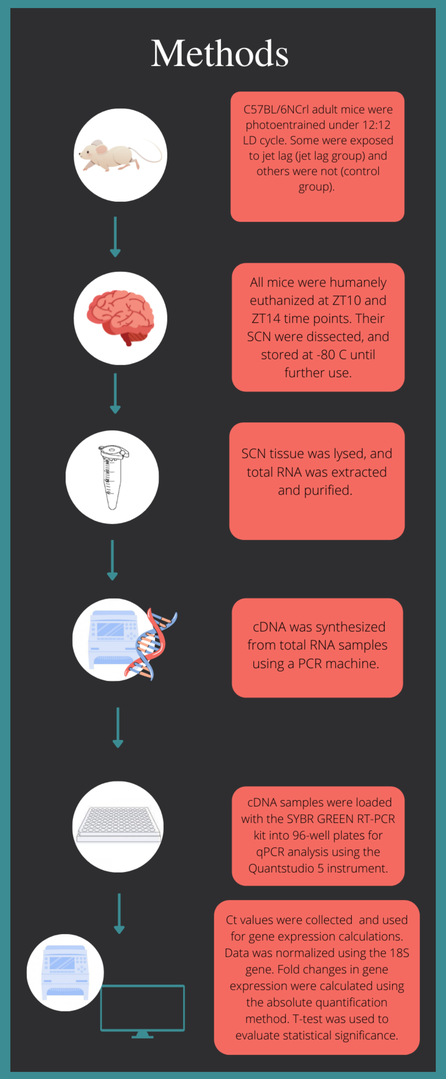


Figure 2: How *DBP* works together with other clock genes in the SCN.[1]

RESEARCH STATEMENT:

This study investigates *DBP* gene expression levels between the ZT10 and ZT14 time points, and the effect of jet lag on gene expression.



RESULTS

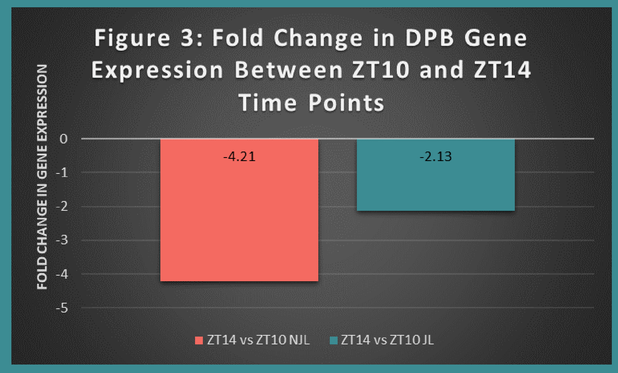


Figure 3: *DBP* gene expression was downregulated when comparing ZT14 to ZT10 time points under both jet lag and non-jet lag conditions.

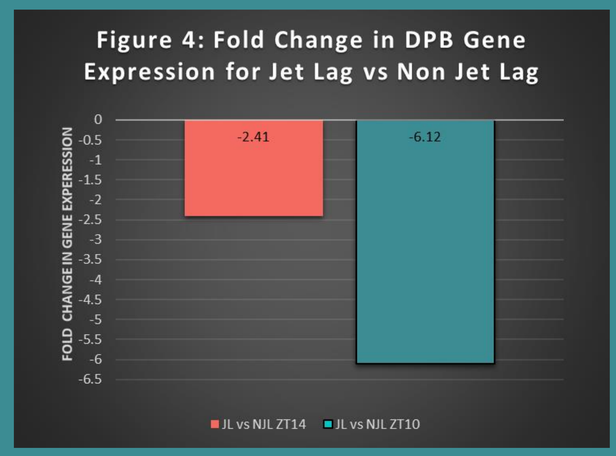


Figure 4: *DBP* expression levels were downregulated under jet lag conditions (compared to non-jet lag conditions) at ZT10 and ZT14 time points.

DISCUSSION

Our results comparing ZT10 to ZT14 timepoints under non-jet lag conditions are similar to previous findings, under the same conditions in the SCN.[11] Previous publication reported that *DBP* gene expression in the SCN was higher during the day (subjective day) and lower during the night (subjective night) in both the LD cycle.[11] Other studies also found that *DBP* mRNA exhibited a robust circadian expression in SCN neurons.[4] Our results follow this reported pattern of gene expression as we observed downregulation in *DBP* expression levels under jetlag conditions. T-tests determined that there was no statistical significance in the downregulation of *DBP* gene expression. One of the limitations of this study is sample size, which could partially explain the lack of statistical significance for our results.

CONCLUSIONS

DBP expression levels were shown to vary with time and were affected by jet lag under normal day-length conditions.

REFERENCES

1. Rijo-Ferreira, F., Takahashi, J.S. Genomics of circadian rhythms in health and disease. Genome Med 11, 82 (2019). https://doi.org/10.1186/s13073-019-0704-0
2. Walker, W.H., Walton, J.C., DeVries, A.C. et al. Circadian rhythm disruption and mental health. Transl Psychiatry 10, 28 (2020). https://doi.org/10.1038/s41398-020-0694-0
3. Yamaguchi, S., Mitsui, S., Yan, L., Yagita, K., Miyake, S., & Okamura, H. (2000). Role of DBP in the circadian oscillatory mechanism. Molecular and cellular biology, 20(13), 4773–4781. https://doi.org/10.1128/MCB.20.13.4773-4781.2000
4. Lopez-Molina, L., Conquet, F., Dubois-Dauphin, M., & Schibler, U. (1997). The DBP gene is expressed according to a circadian rhythm in the suprachiasmatic nucleus and influences circadian behavior. The EMBO Journal, 16(22), 6762-6771.
5. Tanaka, S., Ueno, T., Tsunemi, A. et al. The adrenal gland circadian clock exhibits a distinct phase advance in spontaneously hypertensive rats. Hypertens Res 42, 165–173 (2019). https://doi.org/10.1038/s41440-018-0148-8
6. Mazzoccoli, G., Francavilla, M., Pazienza, V., Benegiamo, G., Piepoli, A., Vinciguerra, M., ... & Takumi, T. (2012). Differential patterns in the periodicity and dynamics of clock gene expression in mouse liver and stomach. Chronobiology International, 29(10), 1300-1311.
7. Cooke, N. E., McLeod, J. F., Wang, X., & Ray, K. (1991). Vitamin D binding protein: genomic structure, functional domains, and mRNA expression in tissues. The Journal of steroid biochemistry and molecular biology, 40(4-6), 787-793.
8. Franken, P., Lopez-Molina, L., Marcacci, L., Schibler, U., & Tafti, M. (2000). The transcription factor DBP affects circadian sleep consolidation and rhythmic EEG activity. The Journal of neuroscience: the official journal of the Society for Neuroscience, 20(2), 617–625. https://doi.org/10.1523/JNEUROSCI.20-02-00617.2000
9. Waterhouse, J., Reilly, T., & Atkinson, G. (1997). Jet-lag. The Lancet, 350(9091), 1611-1616.
10. Andreani, T. S., Itoh, T. Q., Yildirim, E., Hwangbo, D. S., & Allada, R. (2015). Genetics of Circadian Rhythms. Sleep medicine clinics, 10(4), 413–421. https://doi.org/10.1016/j.jsmc.2015.08.007
11. J Yan, L., Miyake, S., & Okamura, H. (2000). Distribution and circadian expression of dbp in SCN and extra-SCN areas in the mouse brain. Journal of neuroscience research, 59(2), 291-295.
12. Chowdhury, Debajyoti & Wang, Chao & Lu, Ai-Ping & Zhu, Hai-Long. (2019). Understanding Quantitative Circadian Regulations Are Crucial Towards Advancing Chronotherapy. Cells. 8. 883. 10.3390/cells8080883.

ACKNOWLEDGEMENTS

This research was funded by the National Science Foundation (NSF) HBCU grant at Oakwood University.