YBX1 functions in the *Drosophila* fat body to regulate sleep

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Abstract

Metabolic dysfunction-associated stetatoic liver disease (MASLD) is a chronic liver condition caused by excessive fat buildup in the liver due to factors outside of alcohol consumption. While the exact causes and mechanisms underlying MASLD development are still not entirely understood, sleep dysfunction is associated with MASLD and increasing sleep may contribute to MASLD prevention. Y-box binding protein 1 (YBX1) is a highly conserved multifunctional DNA/RNA-binding protein that modulates many important cellular functions and previous research suggests that hepatic expression of YBX1 increases significantly in patients with MASLD and in mice exposed to a high-fat diet. Flies, like humans, develop symptoms associated with MASLD, including dysregulation of lipid and glucose metabolism, and many genes and metabolic pathways involved in human hepatic diseases are conserved in Drosophila, including YBX1. Ypsilon scachtel (YPS) is the Drosophila ortholog and is expressed in the liver-equivalent fat body. To determine the effects of YPS expression on sleep duration, we manipulated expression of YPS in the fat body and compared their sleep patterns to control flies. Silencing YPS in the fat body significantly increases both sleep duration and the length of individual sleep episodes, suggesting YPS may mediate sleep quality. To further understand the relationship between YPS expression, MASLD, and sleep, we are currently measuring sleep duration in flies fed a high-fat diet when YPS expression is manipulated in the fat body. Overall, this work will inform our understanding of how YPS expression in the fat body mediates MASLD development and its effects on sleep duration.

Background

Figure 1. The liver-equivalent fat body tissue present in *Drosophila*. Diagram adapted from Li *et al* 2022.

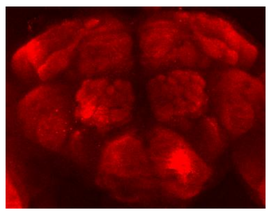

Figure 2 . R4-GAL4 is expressed in the fat body, not the brain. Lack of GFP fluorescence in the brain indicates no presence of R4-GAL4-expression neurons.

Figure 3. Drosophila Activity Monitoring (DAM) system. Sleep is measured starting at ZT = 0 over the course of a 3 day period.

Results

A high fat diet promotes sleep in *Drosophila*

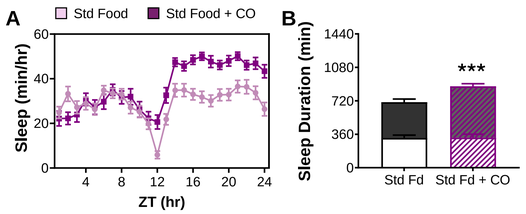

Figure 4. High-fat diet promotes sleep in *Drosophila.* **(A)** Sleep profile. (**B**) Flies fed 10% coconut oil significantly increase nighttime sleep duration.

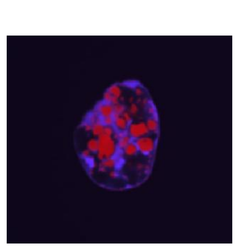

Figure 5. Lipid droplet accumulation in *Drosophila* fat body. Adult fat body tissue with lipid droplets labelled using Nile Red fluorescence (red), cell bodies labelled using DAPI fluorescence (blue).

Silencing YPS in the fat body promotes sleep

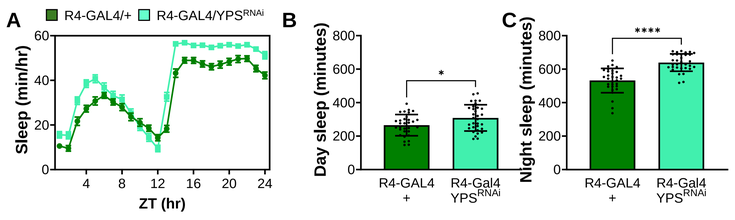

Figure 6. YPS regulates sleep in the fat body. (A, B) Silencing YPS increases day and night sleep. **(C)** Sleep profile of silenced YPS flies and control.

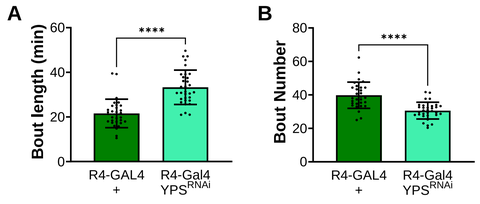

Figure 7. YPS mediates sleep by increasing sleep consolidation. (A) Silencing YPS significantly increases bout length. **(B)** Bout number is significantly reduced.

Results (continued)

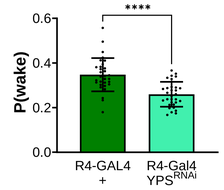

Figure 8. Analysis of sleep-wake transitions suggests silencing YPS promotes sleep quality. The probability of waking, P(wake), significantly decreases when YPS is silenced in the fat body.

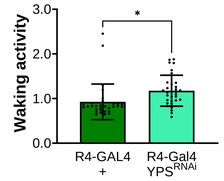

Figure 9. Changes in sleep are not due to inherent changes in activity. Waking activity, measured by beam crosses per waking minute, increases despite overall sleep increasing when YPS is silenced.

Conclusions

- Silencing YPS expression has significant effects on sleep patterns in *Drosophila*, increasing sleep duration and individual sleep episodes.
- High fat diets promote nighttime sleep in wild-type flies.
- Follow up experiments will characterize the effect of YPS expression on lipid accumulation in the *Drosophila* fat body.

References

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- Liao, Sifang,et al. (2021) Impact of High-Fat Diet on Lifespan, Metabolism, Fecundity and Behavioral Senescence in Drosophila. Insect Biochem and Mol Biol.
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