High-fat diet disrupts daily physiology through protein S-palmitoylation

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***Abstract*:**

Poor food quality and irregular mealtime compromise health. We and others previously reported that nutrient-sensitive posttranslational modifications (PTMs) on proteins mediate the impact of mealtime on circadian biology. Here, we report daily rhythms of S-palmitoylation, a lipid-derived PTM that modulates membrane anchoring of proteins due to changes in hydrophobicity, in *Drosophila* tissues. We observe that daily S-palmitoylation rhythms are responsive to changes in nutrient intake by subjecting flies to high-fat diet (HFD). Lipidomics and enzymatic activity assays revealed HFD compromises lipogenesis pathways that supply substrates for S-palmitoylation. We then adopted quantitative proteomics to obtain daily profiles of site-specific S-palmitoylation in head tissues and identify proteins that are regulated by rhythmic S-palmitoylation. 305 out of 4690 modified peptides displayed rhythmic S-palmitoylation in flies fed with regular diet, while HFD disrupted these rhythms. These rhythmic peptides are enriched for proteins involved in synaptic signaling and other nervous system processes. Indeed, we observed altered sleep time and increased seizure in flies with mutation in genes that regulate S-palmitoylation. Furthermore, these flies display reduced blood-brain-barrier permeability, a sign of disrupted nervous system homeostasis. This study provides new insights into the metabolic regulation of daily physiology and sheds light on the deleterious effects of HFD.

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