

## Diet/Energy Balance Affect Sleep and Wakefulness Independent of Body Weight

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Obesity is highly prevalent in the United States and is strongly associated with excessive daytime sleepiness (EDS), even in individuals without obstructive sleep apnea or narcolepsy. Remarkably, obese patients who undergo bariatric surgery for weight loss report dramatic improvements in EDS before significant weight loss occurs, suggesting that other factors besides adiposity may contribute to daytime wake impairments. We hypothesize that energy balance (i.e., weight gain/loss) has independent effects on EDS and sleep/wake architecture. Rodent models of adiposity exhibit an EDS phenotype, evidenced by increased sleep time and fragmented sleep/wake states, which can be reversed by normalizing body weight. However, no study to date has tried to disentangle the relative contributions of diet/energy balance from body weight on sleep/wake architecture. To test this, we implemented a novel feeding paradigm that generates mice of equal body weight, but divergent energy balance. Adult mice were randomized to receive either regular chow (RC; 13.5% kcal from fat) or high fat diet (HFD; 45% kcal from fat) for eight weeks. After this chronic feeding, subsets of mice from each group were fed the opposite diet (a.k.a. diet switch), causing newly-fed HFD mice to gain weight and RC-fed mice to lose weight. Sleep/wake behavior was assessed at baseline (Week 0), pre-diet switch (Week 8), and post-diet switch (Week 9). At Week 9, absolute body weight was similar between diet switch conditions ( $p > 0.05$ ), but weight-loss mice exhibited significantly increased wake time ( $p < 0.05$ ) and consolidated sleep/wake bouts ( $p < 0.05$ ) compared to mice gaining weight. Multivariate analysis revealed that both body weight and energy balance contribute to total wake time ( $p < 0.01$  for both), while only energy balance related to bout fragmentation ( $p < 0.05$ ). Further, we compared how sleep/wake behavior changed from Week 8 to Week 9. We found that one week of diet switch caused significant, bi-directional changes to body weight, total sleep/wake time, and sleep/wake fragmentation, with acute HFD worsening and RC rescuing these respective metrics. Collectively, our study shows that acute changes to diet/energy balance is sufficient to drive sleep/wake abnormalities and may be stronger regulators of sleep/wake than body weight.