Obesity is the result of a caloric imbalance, where energy intake exceeds energy expenditure in an individual over time. While this imbalance may be addressed by reducing intake, weight gain in response to caloric intake varies widely between individuals, in part due to differences in spontaneous physical activity (SPA) [1]. Clinical studies and animal models strongly suggest that non-exercise activity thermogenesis (NEAT) generated through SPA is an important component in defense against weight gain [1-3]. Orexin A and B (hypocretin 1 and 2) are identified as important regulators of arousal and sleep-wake behavior, general activity, and ingestive behavior [4-8]. Recent studies indicate that orexin A (OXA) might play a role in determining SPA levels [2,3,9,10]. Our lab has shown differences in both OXA-induced SPA and in hypothalamic orexin receptor expression in obesity-prone and obesity-resistant rats [2]. In this study we investigated whether OXA influences body weight by contributing to SPA levels in rodents. We hypothesized that (1) OXA responsiveness and orexin receptor expression are correlated to SPA and body weight gain, that (2) blocking endogenous OXA would reduce SPA and increase weight gain, and (3) OXA injections would increase SPA and reduce body weight gain.

Methods

Experiment 1: Adult male Sprague-Dawley (SD) rats (n = 10). Charles River, Kingston, NY USA) were fitted with stainless steel guide canules aimed at the rostral lateral hypothalamic area (rLHA) Animals were subjected to a dose response experiment over a 2 week period in which each was injected with artificial cerebrospinal fluid (aCSF) or one of four concentrations of OXA (31.25, 62.5, 125, and 250 pmol, American Peptides, Sunnyvale, CA USA) in a randomised Latin square design, such that all animals received each treatment once, with one day recovery between injections. Food intake and SPA were monitored for 2 hours following each injection; body weight change was tracked for the duration of the experiment.

Experiment 2: Six week old male SD rats (n = 6) were individually housed and maintained on a low-fat diet (D12451B, Research Diets, New Brunswick, NJ USA) for 2 weeks. Weight gain during this period was tracked daily. After 2 weeks, animals were sacrificed, and microdissected rLHA tissue was subjected to RNA extraction. Relative orexin-1 (OX1R) and orexin-2 (OX2R) mRNA levels were determined by real-time RT-PCR analysis. All data were corrected for rat ribosomal protein L32 (Rpl32) mRNA levels.

Experiment 3: Adult male obesity-resistant (OR) rats (Charles River) were fitted with rLHA guide canules as in Experiment 1. Rats were subjected to a chronic application of aCSF (n = 3) or 10 pmol/10µl OXA antagonist SB 334867 (n = 4). Tocris Bioscience, Ellville, MO USA) for 5 days using an osmotic minipump 24-hour SPA was determined on the 5th day of the experiment.

Experiment 4: Adult male SD rats fitted with rLHA guide canules as in Experiment 1 were treated three times daily (1, 5, and 9 hours after lights-on) for 14 days with aCSF (n = 8) or 500 pmol OXA (n = 9). Final body weight was obtained on Day 15, but no treatment was given on this day.

Results

Introduction

Conclusion

References

Acknowledgements

Funding for these experiments provided by the US Department of Veterans Affairs Rehabilitation Research & Development and the Minnesota Craniofacial Research Training Program.