Effects of Naltrexone in an Animal Model of Hunger


Department of Psychology, University of Wisconsin-Eau Claire 54703

Introduction

Obesity is a leading cause of premature illness and death in the United States. We have developed a food deprivation discrimination task to investigate neurochemical and dietary factors that influence the discriminative stimulus associated with food deprivation. We trained rats to discriminate between 2 hr and 22 hr food deprivation in a two-lever choice procedure. Using this model we previously determined that intrahypothalamically administered PVN ghrelin and neuropeptide Y produced discriminative stimuli similar to those of 22 hours food deprivation. In the present study, we investigated the ability of drugs to reduce or eliminate the discriminative stimulus effects of 22 hours food deprivation. We examined the ability of naltrexone, sibutramine, and rimonabant to alter the stimulus effects associated with acute food deprivation. Naltrexone is an opioid antagonist that decreases food intake in animal models. Rimonabant is a cannabinoid antagonist that decreases eating in animal models and results in a 5-HT and noradrenaline uptake inhibitor. Sibutramine significantly decreases food intake in a variety of situations.

Method

Subjects and apparatus

Male Sprague-Dawley rats were housed in individual cages in a room with 12:12 light/dark cycle (lights on at 8:30 a.m.) and given continuous access to rodent chow (Harlan Teklad) and water unless noted.

Drugs

- Naltrexone (0.3-10 mg/kg) was dissolved in saline and administered s.c.
- Naltrexone (0.33-10 mg/kg) was dissolved in water and administered p.o.
- Rimonabant (0.3-15 mg/kg) was dissolved in 75% polyethylene glycol and administered s.c.
- Sibutramine (0.3-10 mg/kg) was dissolved in water and administered p.o.
- Sibutramine (0.3-10 mg/kg) was dissolved in saline and administered s.c.

Behavioral training

- Correct lever presses (e.g. left lever presses following 22 hour food deprivation and right lever presses following 2 hour deprivation) were reinforced with food pellet delivery under a FR-15.
- Incorrect lever presses resulted in an 8 second period of darkness.
- Training continued until subjects emitted greater than 80% condition-appropriate lever presses following the appropriate lever were reinforced. Drug tests all occurred under a FR-15.

22 hour deprivation generalization tests

Tests were conducted similar to the two cycle training sessions except for the following differences:

- At least 1 hour before a test session, subjects completed a one cycle training session.
- For test sessions, responses toward either lever were reinforced under the FR-15. Food and water intake was measured for 1 hour after test session.

Results

- The opioid antagonist naltrexone did not reduce the discriminative stimulus effects associated with acute food deprivation when administered either orally or subcutaneously.
- Naltrexone did not alter food intake when delivered orally compared to control conditions.
- The CB1 receptor antagonist rimonabant did not reduce the discriminative stimulus effects associated with acute food deprivation.
- The largest dose of rimonabant tested (10 mg/kg) significantly reduced response rates compared to response rates following 22 hr food deprivation and vehicle injection.
- Rimonabant (3.2 - 10 mg/kg) significantly reduced food intake compared to control conditions.
- In rats food deprived for 22 hours, naltrexone (3.2 mg/kg) produced a significant decrease in 22-hour deprivation-appropriate responding.
- Sibutramine produced dose-dependent decreases in lever pressing. Response rates following 1.2 and 10 mg/kg sibutramine were significantly lower than control response rates.
- Sibutramine (10 mg/kg) also produced a significant decrease in food intake for subjects food deprived for 22 hours.

Conclusion

- Naltrexone did not reduce the discriminative stimulus effects of acute food deprivation indicating that opioid mechanisms do not play an important role in the initiation of feeding.
- While rimonabant decreases food intake and the rate of responding, rimonabant did not alter the internal stimulus associated with acute food deprivation. Such data support the idea that CB1 receptors are not involved in food consumption stimulated by energy needs, but affect other feeding-related mechanisms.
- Sibutramine decreased the discriminative stimulus effects of acute food deprivation indicating that serotonergic and/or noradrenergic mechanisms play an important role in the initiation of feeding.

Acknowledgements

- Kell Container Corporation Scholarship for Faculty/Student Collaborative Research
- NIH Chemical Synthesis and Drug Supply Program
- University of Wisconsin-Eau Claire Faculty/Student Research Collaboration
- University of Wisconsin-Eau Claire Student Travel for the Presentation of Research Results
- University of Wisconsin-Eau Claire Summer Research Experiences for Undergraduates