EFFECTS OF 2G ON ADIPOSITY, LEPTIN, LIPOPROTEIN LIPASE (LPL) AND UNCOUPLING PROTEIN-1 (UCP1) IN LEAN AND OBESE ZUCKER RATS

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INTRODUCTION

Altered ambient force environments influence body size, energy intake, energy expenditure and adiposity. Because regulation of body fat underlies survival capacity, an understanding of the systems/mechanisms involved and their responsiveness to altered ambient force environments may be critical to extended periods in space. One such system involves leptin, an adipocyte hormone. At 1G, leptin acts centrally to inhibit feeding and to stimulate sympathetic signals to thermogenic tissues. As the energy content of the animal (i.e., adiposity) increases, more leptin is secreted; this leptin signals the hypothalamus to reduce food intake and increase energy expenditure. Fasting results in a significant decrease in serum leptin. Thus, leptin serves as a sensory signal in a negative feedback system linking peripheral energy stores with hypothalamic control of energy intake, energy expenditure, and specific metabolic pathways in adipose and muscle. To evaluate the importance of the leptin pathway on effects of hypergravity on components of energy balance, we measured responses of genetically lean and obese Zucker rats to 2G (obese Zucker rats have a dysfunctional leptin receptor). We tested 4 hypotheses; namely, that 2G exposure: (1) alters body mass, food intake and body composition in both genotypes; (2) lowers circulating leptin, adiposity, and adipose LPL activity in lean but not in obese Zucker rats; (3) increases thermogenic capacity, as indexed by brown fat UCP1 levels, in lean but not in obese Zucker rats; and (4) results in a greater recovery of food intake, body mass, and growth rate in lean than in obese Zucker rats, while effects on body composition (% fat and % lean body mass) are more pronounced in the lean rats.

CURRENT STATUS OF RESEARCH

Methods

Six groups of individually housed male Zucker rats (22-24 wks of age) were exposed to either 1 or 2G for 8 weeks: lean 1G (n = 7), obese 1G (n = 8), lean 2G (n = 6), obese 2G (n = 11), lean 1G pair fed (PF) to their lean counterparts at 2G (n = 9), and obese 1G pair fed to their obese counterparts at 2G (n = 8). All except the PF rats had ad libitum access to rat chow and water; PF rats had access to water ad libitum and were given the same quantity of food that their 2G counterparts consumed during the previous week. This quantity was divided into seven equal daily meals for the week. All rats were housed in a 12 hr light:12 hr dark cycle at 25°C ± 2°C. Baseline data were obtained for 2 weeks at 1G prior to the 8 week experimental period. The 2G field was produced via a 3.5 meter diameter centrifuge. The cage mounting system allowed for one degree of freedom, so the resultant acceleration vector was always perpendicular to the cage floor. The centrifuge was stopped daily for ~20 minutes for animal husbandry; body mass, food and water intakes were measured once weekly. The 2G rats were decapitated within the first 4 hours after lights on and within 30 minutes of centrifugation cessation; the 1G rats were sacrificed at the same time. We measured body composition gravimetrically; serum leptin with an RIA; white adipose lipoprotein lipase (LPL) activity; and brown adipose uncoupling protein 1 (UCP1) via immunoblot. Data were analyzed by ANOVA and Fisher's Protected Least Significant Difference post hoc test; P values ≤ 0.05 were considered significant.

Results

Lean Zucker rats showed responses to 2G that were similar to those in other species studied in increased ambient force environments. These included an initial reduction in body mass, a resumption of normal growth rate at a reduced mass, an initial hypophagia and a return to normal mass-independent food intake with acclimation, a significant reduction of both absolute and percent body fat, and increased energy expenditure. In addition, after 8 weeks at 2G, serum leptin levels were dramatically lower, consistent with the marked loss of body fat (~50% in terms of grams; ~40% in terms of percent). Based on current views that decreased circulating leptin stimulates feeding, we would expect the 2G lean rats to have greater energy intake than the controls. In fact, this was the case after 4 weeks at 2G. In contrast, the obese Zucker rats exposed to 2G for 8 weeks showed no resumption of growth, a larger decrease in the absolute amount of fat mass than in the lean, no decrease in circulating leptin, and no recovery of food intake to 1G levels. These genotype differences were not due to changes in adipose LPL activity (which showed significant effects of 2G only in the epididymal fat depot of obese rats) or in brown fat UCP1 levels (which were unchanged by 2G in both genotypes).
CONCLUSION
Altered gravitation fields influence body size, energy intake, energy expenditure, and adiposity. While LPL and UCP1 were not consistently altered by 2G exposure, leptin, a key hormone involved in the regulation of adiposity, was. Differences elicited by 2G in lean vs. obese Zuckers indicate that although both genotypes responded to hypergravity, the lean rats acclimated to a greater extent than did the leptin-resistant obese rats, emphasizing the importance of a functional leptin regulatory pathway for this acclimation [supported by NASA grant NAG5-3949 and NIH grant DK-35747].

FUTURE PLANS
To identify hypothalamic genes potentially involved in the 2G effects on energy balance, we will use 2 approaches: (1) a candidate-gene approach focussing on specific neuropeptides whose expression we know to be regulated by leptin; and (2) microarray techniques to identify other hypothalamic genes as candidates. Transgenic mice and proteomic technologies will help delineate the role of these proteins in the animals' response to altered gravitational fields.

INDEX TERMS
obesity, centrifugation, energy balance, food intake, leptin, uncoupling protein, LPL, hypergravity