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BRAIN RESEARCH

Research Report

Central interleukin-1 (IL1) signaling is required for pharmacological, but not physiological, effects of leptin on energy balance

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ABSTRACT

Hypothalamic IL1 is suggested to be a critical mediator of the central effects of the adipocyte hormone leptin on energy balance. We hypothesized that IL1 receptor signaling is required for exogenously administered leptin to cause anorexia and weight loss, but not for physiological effects of endogenous leptin signaling on energy balance. To test this hypothesis, we investigated whether chronic hypothalamic over-expression of an IL1 receptor antagonist (AdV-IL1ra) alters food intake and weight gain in normal rats. Our findings demonstrate that impaired IL1 signaling in the CNS did not cause excess weight gain over a period of 11 days (AdV-IL1ra +38.1±4.1 g vs. VEH +42.2±5.6g; $p=0.6$) and caused a slightly reduced daily food intake (AdV-IL1ra 29.0±1.1 g/day vs. VEH 33.0±1.6 g/day; $p<0.05$). Blocking central IL1 signaling also did not alter the re-feeding response to a prolonged fast, yet was entirely effective in preventing the anorexic effect of exogenously administered leptin (2 mg/kg ip, cumulative food intake at 18 h AdV-IL1ra 30.5±1.1 g vs. VEH 26.4±1.7 g, $p<0.05$) and prevented leptin-induced weight loss (AdV-IL1ra −0.1±1.3 g vs. VEH −2.7±1.9 g, $p<0.05$). Together these findings suggest that hypothalamic IL1 signaling is required for the pharmacological effects of leptin administration, but that impaired hypothalamic IL1 signaling does not alter the physiological regulation of energy balance.

1. Introduction

Following the identification of the adipocyte hormone leptin as a physiological regulator of energy balance, a large body of work has begun to define the critical neuronal pathways that mediate its behavioral and metabolic effects (Richard and Baraboi, 2004; Sahu, 2004; Spiegelman and Flier, 2001). Neuronal melanocortin signaling plays a key role since genetic or pharmacological disruption of melanocortin signaling blocks leptin action and invariably leads to obesity (Benoit et al., 2000; Butler et al., 2006). Several findings also implicate the pro-inflammatory cytokine IL1β as a mediator of leptin action

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Abbreviations: icv, intracerebroventricular; IL1ra, interleukin-1 receptor antagonist; AdV, adenoviral; IL1, interleukin-1; CNS, central nervous system; MTII, melanotan II; POMC, pro-opiomelanocortin; ARC, arcuate nucleus; CRH, corticotrophin releasing hormone; NT, neurotensin

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in the brain. First, leptin-induced anorexia is prevented by intracerebroventricular (icv) administration of an IL1 receptor antagonist (Luheshi et al., 1999; Wisse et al., 2006). In addition, our own studies, as well as those of others, have shown that exogenous leptin administration increases hypothalamic IL1β signaling (Hosoi et al., 2002; Wisse et al., 2004) supporting a potential role for IL1β in mediating the CNS effects of leptin. Unlike mutations that disrupt leptin or melanocortin signaling, however, targeted mutation of IL1 receptors does not cause obesity in mice (Glaccum et al., 1997) challenging the notion that this signaling pathway plays a physiological role in energy homeostasis.

Based on these observations, we hypothesized that IL1 receptor signaling is required for responses to pharmacological leptin administration, but not for physiological effects of endogenous leptin signaling. To test this hypothesis, we sought to determine whether hypothalamic IL1 signaling is necessary for energy balance under physiological conditions, in addition to its known role in the response to exogenous leptin administration (Luheshi et al., 1999; Wisse et al., 2006). Specifically, we investigated whether chronic hypothalamic over-expression of an IL1 receptor antagonist alters food intake and weight gain in normal rats. Our data demonstrate that impaired IL1 signaling in the CNS does not increase daily food intake or weight gain, nor does it alter the re-feeding response to a prolonged fast, yet is entirely effective in preventing the anorexic effect of exogenously administered leptin.

2. Results

2.1. *Effect of adenoviral-induced CNS over-expression of IL1ra on body weight and food intake*

Following adenoviral gene transfer surgery all rats were monitored without further intervention for a period of 11 days (Fig. 1 period 1). During this time, weight gain was not different between AdV-IL1ra injected animals and controls

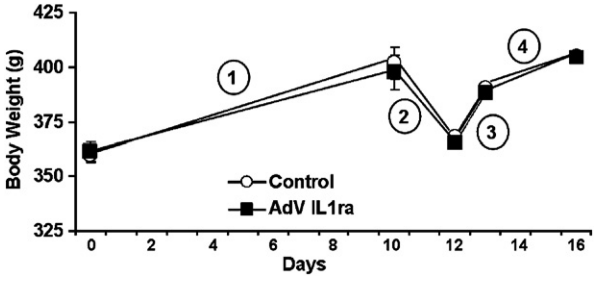

Fig. 1 – Effect of CNS adenoviral over-expression of IL1ra on body weight. Mean body weight in the AdV-IL1ra group (black square, *n*=15) and Control group (white circle, *n*=6) is shown over time. Period 1 demonstrates the weight gain in both groups during the 11 days following adenoviral injection surgery. Period 2 shows the weight loss induced by a 36 h fast. Period 3 demonstrates the weight regain following 1 day of re-feeding. Period 4 shows the weight gain following 4 days of re-feeding. Data presented are means±SEM. Statistical analysis by unpaired Student's *t*-test.

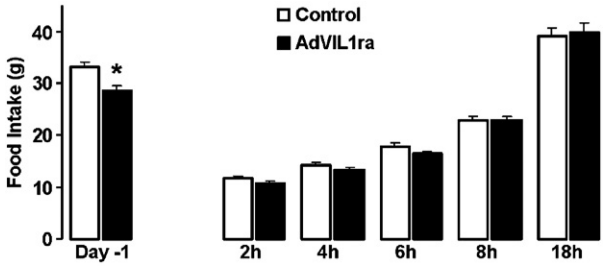

Fig. 2 – Effect of CNS adenoviral over-expression of IL1ra on food intake. Food intake (g) in two adenoviral injection groups, Control (white bars, *n*=6) and AdV-IL1ra (black bars, *n*=10), on the day prior to a 36 h fast (Day −1) and at five indicated time points following the initiation of re-feeding. Data presented are means±SEM. **p*<0.05 by unpaired Student's *t*-test.

(38.1±4.1 g vs. 42.2±5.6 g; respectively, $p=0.6$). Cumulative food intake during this time period was slightly lower in AdV-IL1ra injected rats than in control animals (mean 29.0±1.1 g/day vs. 33.0±1.6 g/day; respectively, $p=0.05$). Though IL1ra is a secreted protein, following gene transfer of the adenoviral-IL1ra vector into the third ventricle, diffusion of the protein from the third ventricle into key hypothalamic nuclei may be necessary for effects on energy balance. Both weight gain (34±5 g) and daily food intake (28.5±1.6 g) were no different in animals having received AdV-IL1ra in the third ventricle (3rdV AdV-IL1ra) in comparison to the combined AdV-IL1ra data presented above. Thus chronic adenoviral-mediated CNS over-expression of IL1ra does not cause weight gain and, if anything, causes a modest reduction in food intake.

2.2. *Effect of adenoviral-induced CNS over-expression of IL1ra on food intake and body weight recovery following a prolonged fast*

Since re-feeding following a prolonged fast is, perhaps, the only physiological paradigm in which plasma leptin concentration increases rapidly (Kolaczynski et al., 1996; Wisse et al., 1999), we evaluated whether adenoviral-mediated CNS over-expression of IL1ra alters the feeding response following a fast. Weight loss at the end of the 36 h fast was not different between the two groups (AdV-IL1ra rats −32.3±1.1 g vs. −34.1±2.2 g in Control rats, $p=0.4$, Fig. 1 period 2). Evaluation of food intake during the day prior to the fast was consistent with the mean daily food intake described above (AdV-IL1ra 28.6±0.8 g and Control 33.0±1.1 g; $p=0.01$). During re-feeding, food intake in the AdV-IL1ra group was not different from that in Control rats at any of the four time points evaluated (Fig. 2). Weight regain 24 h following the end of the fast (AdV-IL1ra 23±1.2 g and Control 23±1.7 g, $p=0.9$, Fig. 1 period 3) and body weight 96 h after the fast (AdV-IL1ra 404±8.0 g and Control 405±8.5 g, $p=0.9$, Fig. 1 period 4) were also equivalent between the two groups. In response to fasting and re-feeding, food intake (2 h 10.3±0.4 g; 4 h 13.5±0.6 g; 6 h 16.6±0.8 g; 8 h 22.5±0.8 g; 18 h 40.4±3.5 g) and body weight changes (fasting −32±1.5 g, first day of re-feeding 23±1.6 g, 4 days post fast 42±6 g) were no different in 3rdV AdV-IL1ra relative to the AdV-IL1ra group as a whole. Thus, chronic adenoviral-mediated CNS over-