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BRAIN RESEARCH

Research Report

Activation of hindbrain neurons in response to gastrointestinal lipid is attenuated by high fat, high energy diets in mice prone to diet-induced obesity

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ABSTRACT

Food intake is controlled by peripheral signals from the gastrointestinal tract and adipocytes, which are integrated within the central nervous system. There is evidence that signals from the GI tract are modulated by long term changes in diet, possibly leading to hyperphagia and increased body weight. We tested the hypothesis that diet-induced obese-prone (DIO-P) and obese-resistant (DIO-R) mice strains differ in the long term adaptive response of the gut–brain pathway to a high fat diet. Immunochemical detection of Fos protein was used as a measure of neuronal activation in the nucleus of the solitary tract (NTS) in response to intragastric administration of lipid in DIO-P (C57Bl6) and DIO-R (129sv) mouse strains maintained on chow or high fat, high energy diets (45% or 60% kcal from fat). Intragastric lipid administration activated neurons in the NTS in both DIO-P and DIO-R mice; the number of activated neurons was significantly greater in DIO-P than in DIO-R mice ($P<0.001$). However, lipid-induced activation of NTS neurons in DIO-P mice was attenuated by ≈30% after maintenance on either 45% or 60% HF diet, for 4 or 8 weeks, compared to chow fed controls ($P<0.05$). In contrast, in DIO-R mice, maintenance on a HF diet (45% or 60%) had no effect on lipid-induced activation of NTS neurons. These results demonstrate that DIO-P and DIO-R mice strains differ in the adaptation of the pathway to long term ingestion of high fat diets, which may contribute to decrease satiation and increased food intake.

1. Introduction

The gut–brain axis plays an important role in nutrient detection and in control of short term food intake (Schwartz, 2000). For example, lipid in the gastrointestinal tract is detected via release of CCK and activation of CCK_1 receptors on vagal afferent nerve terminals in close apposition to endocrine cells (Raybould, 1999). The CCK_1R dependent pathway, together with activation of vagal afferents in response to other gut peptides that can decrease food intake, seems to be important primarily in short-term control of food intake. However, evidence is accumulating to suggest that alteration in the function of this pathway maybe involved in long term control of food intake and body weight. Maintenance of rats on a high fat (HF) diet causes decreased hindbrain sensitivity to lipid (oleate) and to CCK (Covasa and Ritter, 1998; Covasa and Ritter, 1999); this occurs after ingesting the HF diet for only 2 weeks and even in the absence of obesity, when fed an isocaloric HF diet (Covasa and Ritter, 2000; Paulino et al., 2008). It has been suggested that the decrease in vagal afferent

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sensitivity in response to lipid may, in part, be responsible for increased food intake when rodents, or humans, ingest high fat diets (Savastano and Covasa, 2005).

Different strains of mice have been classified as "obesity prone" or "obesity resistant" (West et al., 1992), dependent on their propensity for weight gain when placed on high fat, high energy diets. However, it is not clear what factors are responsible for these phenotypic differences. Mice maintained on an HF diet can be grouped into two main categories according to their ability to gain weight; mouse strains such as AKR/J, C57BL/6J, DBA/2J, and A/J have been shown to rapidly gain weight on HF diet and have been termed diet-induced obesity prone (DIO-P); in contrast, strains 129sv, SWR/J, I/STN and SJL/J have been termed diet-induced obesity resistant (DIO-R) due to their relative resistance to weight gain when on HF diets (West et al., 1992). Whether there is any difference in the response of the gut–brain axis to lipid in different mice strains, either DIO-P or DIO-R, or adaptation to HF diets, has not been investigated.

We tested the hypothesis that adaptation of the lipid-induced activation of the vagal afferent pathway to long term maintenance on a HF diet differ in DIO-P and DIO-R mice strains. We determined the effect of intragastric gavage of lipid on activation of neurons in the NTS, the region where vagal afferents terminate, in two mouse strains; one classified as DIO-P (C57BL/6) and one classified as DIO-R (129sv) (Almind and Kahn, 2004; West et al., 1992). We investigated the effect of long term consumption (4 and 8 weeks) of two diets with increased levels of fat (45% and 60% kcal/fat) which cause obesity in mice (Van Heek et al., 1997).

2. Results

2.1. *Effect of high fat diets on body weight and adiposity*

There was no significant difference in body weight gain in DIO-P and DIO-R mice maintained on chow for either 4 or 8 weeks (NS, $n=5$–14 in each group) (Fig. 1 A). Maintenance on a diet containing 45% kcal from fat (45% HF) caused a tendency for increased body weight gain in both strains after either 4 or 8 weeks on the diet, but this did not reach statistical significance (Fig. 1 A; NS, $n=3$–6 in each group). However, maintenance on a 60% HF diet resulted in a significant increase in body weight gain at both 4 and 8 weeks in DIO-P, but not DIO-R mice (Fig. 1A). Thus, DIO-P mice gained significantly more weight on the 60% HF diet after 4 weeks and 8 weeks compared to DIO-R mice (4 weeks, $P<0.05$, 8 weeks 60% $P<0.01$, $n=4$–14 in each group).

Examination of the epididymal fat pad data revealed differences between diets and phenotype; data is expressed as a % of final body weight (Fig. 1B). DIO-R mice maintained on either the 45% HF or 60% HF diet for 4 or 8 weeks had significantly larger epididymal fat pad mass compared to mice maintained on the chow diet; however, there was no significant difference between either the diet or time on the diets. Maintenance of DIO-P mice on either 45% or 60% HF diets for 4 or 8 weeks caused a significant increase in epididymal fat pad mass ($P<0.05$ versus chow). There was no significant difference between either diet or time point in DIO-P mice.

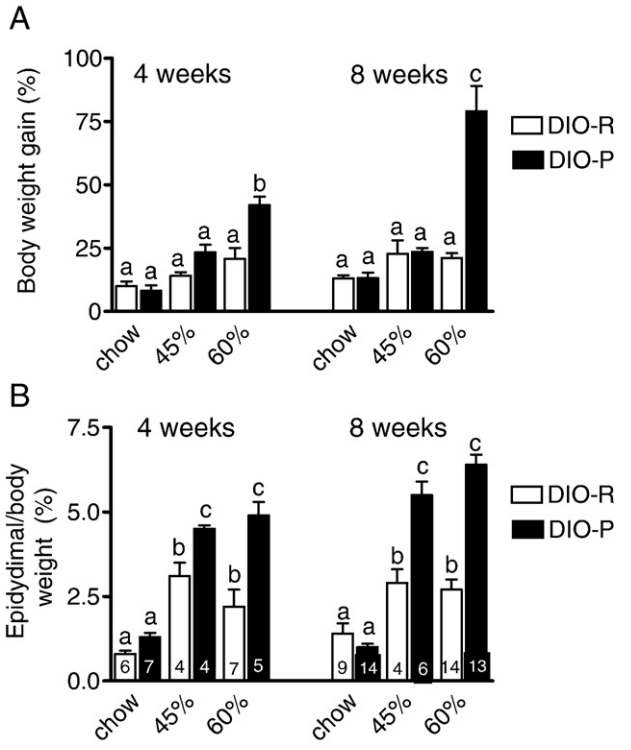

Fig. 1 – Effect of maintenance on chow (C) or high fat diets (45% or 60% calories from fat) on body weight gain and adiposity in two strains of mice, C57Bl/6J (DIO-P) or 129sv (DIO-R). (A) Body weight gain (expressed as % of initial body weight) in DIO-P mice and DIO-R mice maintained on chow, 45% HF or 60% HF diets for 4 weeks or 8 weeks. Maintenance on 60% HF diet for 4 or 8 weeks significantly increased body weight in DIO-P but not DIO-R mice, compared to chow-fed mice (4 weeks, $P<0.05$, $n=8$ weeks, $P<0.001$; $n=5$–14 in each group). (B) Adiposity (weight of epididymal fat pad expressed as % of final body weight) following four or eight weeks of maintenance on either the 45% HF or 60% HF diet in DIO-R and DIO-P mice, compared to chow-fed controls (45% $P<0.05$ and 60% $P<0.01$, $n=5$–14). Maintenance on the 45% HF or the 60% HF diet for 8 weeks caused significantly greater adiposity in DIO-P mice compared to DIO-R mice ($P<0.001$, $n=4$–8). Columns with different letters are significantly different from each other.

However, there was a significant increase in fat pad weight in DIO-P compared to DIO-R mice at both time points and on both diets (chow versus 45% or 60% HF diets; $P<0.05$).

2.2. *Effect of high fat diets on intestinal lipid-induced activation NTS neurons*

Intragastric gavage with lipid (0.2 ml of 20% lipid; 40 mg) activated neurons in the NTS of mice as determined by expression of Fos protein; in both strains of mice, activation was highest in the mid-NTS as previously described (Whited et al., 2006) (Fig. 2). There was a significantly greater number of Fos-positive neurons in mid-NTS in response to lipid gavage in DIO-P mice compared to DIO-R mice ($P<0.001$, $n=8$–9 in each group). There was no significant difference between strains in