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Research Report

Differential feeding behavior and neuronal responses to CCK in obesity-prone and -resistant rats

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ARTICLE INFO

Article history:
Accepted 18 October 2009
Available online 24 October 2009

Keywords:
Obesity
Vagal afferents
Food intake
Fos expression

ABSTRACT

Deficits in satiation signals are strongly suspected of accompanying obesity and contributing to its pathogenesis in both humans and rats. One such satiation signal is cholecystokinin (CCK), whose effects on food intake are diminished in animals adapted to a high fat diet. In this study, we tested the hypothesis that diet-induced obese prone (OP) rats exhibit altered feeding and vagal responses to systemic (IP) administration of CCK-8 compared to diet-induced obese resistant (OR) rats. We found that CCK (4.0 μg/kg) suppressed food intake significantly more in OP than OR rats. To determine whether enhanced suppression of feeding is accompanied by altered vagal sensory responsiveness, we examined dorsal hindbrain expression of Fos-like immunoreactivity (Fos-Li) following IP CCK injection in OP and OR rats. After 4.0 μg/kg CCK, there were significantly more Fos-positive nuclei in the NTS of OP compared to OR rats. Treatment with 8.0 μg/kg CCK resulted in no significant difference in food intake or in Fos-Li between OP and OR rats. Also, we found that OP rats were hyperphagic on a regular chow diet and gained more weight compared to OR rats. Finally OP rats had decreased relative fat pad mass compared to OR rats. Collectively, these results show that OP rats exhibit a different behavioral and vagal neuronal responses to CCK than OR rats.

1. Introduction

Consumption of a high fat (HF) diet is correlated with passive overconsumption and the onset of obesity in both rats and humans (Woods et al., 2003). In specific subsets of human populations, some individuals are resistant to the onset of obesity caused by a HF diet while others are prone to becoming obese (see Blundell et al., 2005, for review). One of the contributing factors to overconsumption on a HF diet and subsequent obesity is the resistance or loss of sensitivity to satiation signals that serve to terminate a meal (Covasa and Ritter, 1998; Moran et al., 1998; Speechly and Buffenstein, 2000; Warwick and Weingarten, 1995). Diet-induced obesity prone (OP) and resistant (OR) rodents are used to delineate the contributing factors to obesity induced by changes in diet. Prior work in OP models has shown that hyperphagia, in the form of increased meal size, as well as increased energy efficiency, accompany the persistent obesity produced by long-term, high fat feeding (Dourmashkin et al., 2006; Farley et al., 2003; Ricci and Levin, 2003; Wang et al., 1998).

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doi:10.1016/j.brainres.2009.10.045

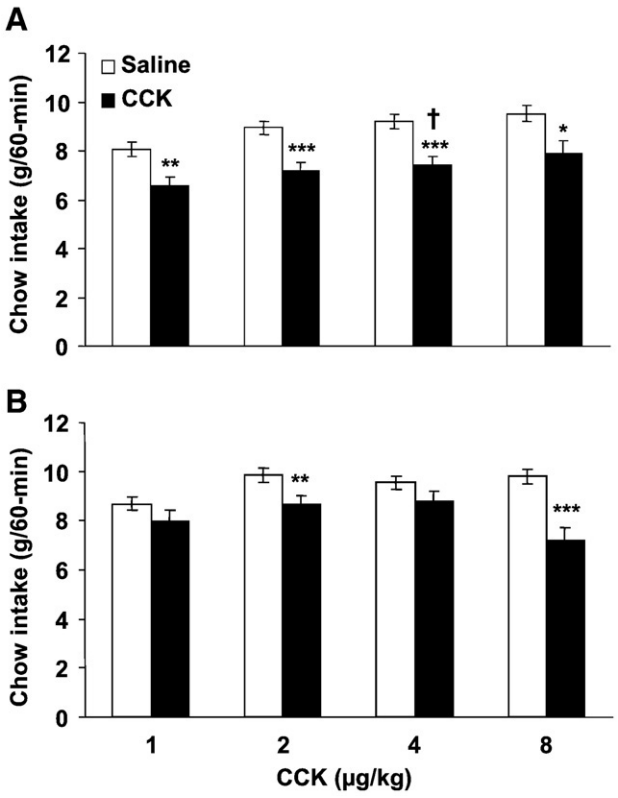

Fig. 1 – Sixty minutes of chow intake (g ± SEM) following injection (IP) of CCK-8 at doses of 1.0, 2.0, 4.0, and 8.0 µg/kg. (A) OP rats significantly decreased food intake at all doses of CCK tested, (B) OR rats significantly decreased intake from saline after 2.0 and 8.0 µg/kg CCK. Suppression of intake was significantly different between strains at 4.0 µg/kg CCK. * denotes statistical difference from saline, *P < 0.05, **P < 0.01, ***P < 0.001. † denotes statistical difference from OR rats when expressed as percentage suppression from saline, P < 0.05.

Mechanisms underlying this persistent change in the metabolic and motivational regulation of food intake are not fully understood. However, in addition to deficits in responses of hypothalamic systems to dietary obesity (Bouret et al., 2008; Clegg et al., 2005; Irani et al., 2009; Levin et al., 2004), there is circumstantial evidence that these rats have altered peripheral sensitivity to food stimuli (Donovan et al., 2009; Leibowitz et al., 1998). Although little investigation has been performed to examine potential peripheral satiation signal deficits in general and in OP models, in particular, accumulating evidence has shown decreased sensitivity to satiation signals on HF diets. Specifically, we and others have shown that rats or mice on a HF diet are less sensitive to satiation induced by fats or CCK compared to low fat (LF) fed animals (Covasa and Ritter, 1998; Donovan et al., 2009; Gaysinskaya et al., 2007; Paulino et al., 2008; Savastano and Covasa, 2005).

Furthermore, several obese rodent models such as Zucker (Maggio et al., 1988) and Otsuka Long Evans Tokushima Fatty (OLETF) (Covasa and Ritter, 2001; Schwartz et al., 1999) rats are less sensitive to reduction of food intake by CCK or intraintestinal fats, suggesting that obesity may be associated with a reduced responsiveness to exogenous CCK or other regulatory systems controlled by CCK. Because changes in CCK responsiveness seem to develop independent of adiposity (Covasa and Ritter, 1998; Covasa et al., 2001; Savastano and Covasa, 2005) and begin before the onset of obesity (McLaughlin and Baile, 1979) and OP rats increase meal size, but not meal frequency, when placed on a HF diet (Farley et al., 2003), we hypothesize that alteration in sensitivity to CCK may be partly responsible for hyperphagia and obesity in this animal model. To our knowledge, only one study examined responses to exogenous CCK in OP rats. In this study, Chandler et al. showed that after administration of a subthreshold dose of CCK, OP rats suppressed food intake significantly more than OR rats. However, only one dose of CCK was tested in this study (0.3 µg/kg), and all rats were maintained on a HF diet (Chandler et al., 2004), which has been previously shown to induce diminished sensitivity to CCK (Covasa and Ritter, 1998; Nefti et al., 2009). Since OP rats gain more weight even on a chow diet compared to OR rats (Ricci and Levin, 2003), it is not known whether this is due to an altered sensitivity to peripheral satiation signals, such as CCK. Therefore, in order to examine the differential feeding responses following acute administration of CCK between OP and OR rats, the present study assessed food intake in response to CCK (1.0, 2.0, 4.0, and 8.0 µg/kg) when rats were maintained on a standard rat chow diet.

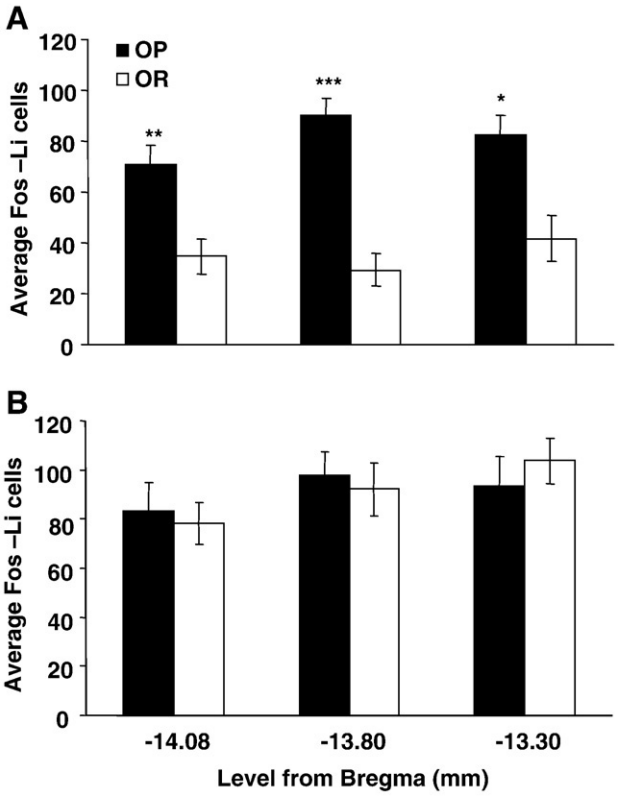

Fig. 2 – Fos-Li counts (± SEM) in the NTS in OP and OR rats after treatment with (A) 4.0 and (B) 8.0 µg/kg CCK-8. OP rats had significantly increased levels of Fos-Li compared to OR rats in the NTS at all brain levels after treatment with 4.0 µg/kg. There were no differences in Fos immunopositive nuclei between OP and OR rats following the 8.0 µg/kg CCK-8. * denotes significant difference from OR. *P < 0.05, **P < 0.001, ***P < 0.0001.