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Review

An overview on how components of the melanocortin system respond to different high energy diets

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ABSTRACT

High energy diets are used to model the obesity epidemic. Moreover, from a variety of genetic studies, it has become clear that the melanocortin system plays an important role in the regulation of energy metabolism. Since most dietary interventions are not standardized, fat/sugar-induced effects on the melanocortin system vary distinctly among different studies. How components of the melanocortin system are affected by high energy diets remains unclear. Therefore, in this review, we first present an overview of the effects of high energy diets on different elements of the melanocortin system in both mice and rats. The effects of a high energy diet are most consistent for agouti related protein levels which were either not affected or decreased after consumption of a high energy diet, whereas for proopiomelanocortin and the melanocortin receptor expression (and binding) it was difficult to define an overall response to a high energy diet. Because of the complexity of the melanocortin system, it is important to measure more than one element of the system. Only a few studies measured both melanocortin peptide and receptor expression and show that a high fat diet consumed for a longer period of time starting at an early age increases melanocortin signaling, whereas in adulthood a very high fat diet decreases melanocortin signaling. Finally, we review our own data on diet-induced changes in peptide expression and melanocortin binding and show that short term exposure to a free-choice high-fat high-sugar diet also decreases melanocortin signaling which supports hyperphagia observed in this model.

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1. Introduction

The prevalence of obesity has dramatically increased over the last few decades which cannot solely be explained by a shift in genetics, but rather by changes in life style. Contemporary Western diets are frequently high in fats and sugars and are increasingly consumed in addition to sweetened liquid drinks, such as sodas. In fact, the consumption of sugar-sweetened soft drinks by children has been shown to be more than doubled between 1965 and 1996 (Cavadini et al., 2000). The Western Style diet, may, therefore, contribute to the increasing obesity epidemic. It is, therefore, important to understand the regulation of the intake of food containing high amounts of fat and sugar.

Multiple players are involved in the regulation of food intake. One key player is leptin, an adipose tissue-derived hormone that is

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released into the circulation proportional to increased energy stores in fat and acts via its receptors (OB-Rb) on several regulatory centers including the arcuate nucleus of the hypothalamus (Zhang et al., 1994). During a positive energy balance, concomitant with increased plasma leptin, a percentage of pro-opiomelanocortin (POMC) neurons become activated (Schwartz et al., 1997; Williams et al., 2010). The precursor POMC may be cleaved into α-melanocyte-stimulating hormone (α-MSH), β-MSH and γ-MSH, and acts as endogenous agonists for the main brain melanocortin receptors 3 and 4 (melanocortin$_3$ receptor and melanocortin$_4$ receptor respectively). Agouti-related protein (AgRP), also expressed in the arcuate nucleus neurons and activated during negative energy balance, functions as an inverse agonist. So the agonist and inverse agonist acting at the same receptor suggest a tight regulation of the melanocortin system in energy balance (Adan et al., 2006).

The underlying mechanisms by which overconsumption of energy dense foods and liquids result in overt hyperphagia, obesity and metabolic disorders still remain unclear. Several animal models have been developed to study diet-induced obesity aiming to unravel its physiological and molecular consequences. However, the dietary interventions are far from standardized and the experimental designs vary considerably. Moreover the resulting animal phenotypes and melanocortinergic expression patterns do not always correspond among the diet-induced obesity models. For instance, the energy content between 'high fat' diets vary considerably with fat contents ranging from 20 to 80%. Also the fat macronutrient can be derived from different sources as extensively reviewed (Buettner et al., 2007).

The response of the melanocortin system to a high fat diet may be dependent on type of diet, duration and composition. However, it has not been clarified in what way the type of (high fat) diet affects the responsiveness of the melanocortin system. Therefore, this review is aimed to provide an overview on the influence of high energy diets on the hypothalamic melanocortin system.

2. POMC and AgRP gene activation upon high fat diets

When consuming a diet that increases caloric intake and fat mass, the melanocortin system, in order to counter the obesity, is expected to increase its activity and thus decrease food intake and increase energy expenditure. Therefore, one would expect POMC mRNA to be increased and/or the AgRP expression to be decreased. Indeed, several studies in which rats or mice were subjected to a high fat diet ranging from 1 day to 7 weeks reported a decrease of AgRP expression, albeit no changes in POMC expression (details from different studies are depicted in Table 1) (Densmore et al., 2006; Wang et al., 2002; Ziotopoulou et al., 2000; Archer et al., 2004; Archer et al., 2007). Increased leptin levels have been proposed as a possible underlying reason for decreased AgRP levels, but do not explain the lack of POMC activation. Also, it is not clear why the response of AgRP seems to occur earlier than POMC and whether this is an important compensation for the attempted resistance to diet-induced obesity. In addition, many studies were not able to detect a difference in AgRP expression levels between the diets (Archer et al., 2005a; Clegg et al., 2003; Guan et al., 1998; Xu et al., 2010; Heijboer et al., 2005; Kinzig et al., 2005). The reason for this lack of difference is not explained by differences in species, fat content, sugar or a multiple palatable component. It could be that leptin resistance is causal to this effect, however not many studies have measured responses to leptin injections in the same animals as the expression levels were determined.

High fat diet feeding results in a non-consistent POMC gene activation pattern. Considering all studies with all time points included (Table 1), the expression was either increased (Huang et al., 2004; Ziotopoulou et al., 2000; Torri et al., 2002; Shiraev et al., 2009; Kinzig et al., 2005), decreased (Gout et al., 2008; Lin et al., 2000; Huang et al., 2003a; Kinzig et al., 2005; la Fleur et al., 2010a) but mostly unaffected (Wang et al., 2002; Densmore et al., 2006; Guan et al., 1998; Heijboer et al., 2005; Clegg et al., 2003; Archer et al., 2004, 2005a,b, 2007; Fam et al., 2007; Dziedzic et al., 2007). Because POMC is the precursor of melanocyte-stimulating hormone, a potent inhibitor of food intake, the increase of POMC may resist the effect of high-fat diet to promote increased food intake in an effort to maintain energy homeostasis and to counteract obesity. Yet, the downregulation of the POMC gene upon an obesogenic diet seems paradoxical, and might be a counterintuitive response. It is not clear what the origin is of this response, but apparently it seems specific for POMC as AgRP has not been shown to deviate from its 'expected' behavior upon caloric excesses.

The diets that showed the paradoxical POMC change lasted at least 8 weeks (Gout et al., 2008; Lin et al., 2000; Huang et al., 2003a; Kinzig et al., 2005). Although this could suggest that timing is an important part of this paradoxical finding, we observed that this paradoxical POMC response occurred already at one week in rats that were subjected to a free-choice high-fat high-sugar diet (la Fleur et al., 2010a, Fig. 1). Moreover, we showed that also neuropeptide Y expression exhibited a counterintuitive response; i.e. it was elevated after one week on a free-choice high-fat high-sugar diet (la Fleur et al., 2010a). Since we did not observe this response in rats on a free-choice sugar diet, we proposed that the choice component, and not the sugar, accounted for these paradoxical results. The other studies did not have a choice component, so this conclusion cannot be extrapolated to those studies. Still the choice component can still account for the fact that this paradoxical result was already visible at one week.

Besides our own study (la Fleur et al., 2010a), also Kinzig et al. (2005), showed this counterintuitive increase of neuropeptide Y when feeding rats a high fat diet for 8 weeks. The fat content of this diet was 80%, at the expense of the carbohydrates which were minimized to 5%, pointing to an unbalanced diet. It is debatable whether the paradoxical outcome is really imputable to the high fat content.

3. Effect of different diets on the melanocortin$_4$ receptor

Overconsumption of excess calories is expected to enhance signaling through melanocortin system, which, when activated, signals satiety and restores body weight towards normal levels. Deletion of the melanocortin$_4$ receptor results in hyperphagia and obesity (Huszar et al., 1997), and thus changes in the expression level of the melanocortin$_4$ receptor or melanocortin binding (as an indirect way to study melanocortin receptor availability) due to consuming a high energy diet could alter energy metabolism.

Expression of melanocortin$_4$ receptor mRNA after exposure to a diet does not provide a clear consistent view. One study found a downregulation of the melanocortin$_4$ receptor gene in the paraventricular nucleus after feeding mice a high fat diet for as little as 48 h. Also after 2 and 18 weeks this downregulation remained present (Densmore et al., 2006). On the contrary, an increase in paraventricular nucleus melanocortin$_4$ receptor gene expression was found after as little as 24 h of feeding high fat diet (Archer et al., 2005b) and the same pattern was visible in the ventromedial hypothalamus and amygdala or whole hypothalamus after 22 or 16 weeks high fat feeding, respectively (Huang et al., 2003a; Gout et al., 2008) (Table 1). In addition, some other feeding studies were not able to find any effect on the expression of melanocortin$_4$ receptor (Archer et al., 2004; Clegg et al., 2003; Shiraev et al., 2009; Xu et al., 2010). Although the fat percentage or the sugar amount within the diets used in these studies does not explain the different outcome, one interesting finding is worth to mention: rats were subjected for 8 weeks to two exact similar diets, except that 1 diet contains an additional 20% fat content (80% compared to 60%), but lower sucrose content (0% compared to 7%). This extra 20% fat increase has been shown to be sufficient to trigger a response to increase the melanocortin$_4$ receptor gene expression levels (Kinzig et al., 2005). This change in melanocortin$_4$