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Research Report

A positive change in energy balance modulates TrkB expression in the hypothalamus and nodose ganglia of rats

Nadine Zeeni[a,b], *Catherine Chaumontet*[a,b], *Emmanuel Moyse*[c], *Gilles Fromentin*[a,b], *Catherine Tardivel*[c], *Daniel Tome*[a,b], *André Jean*[c], *Nicolas Darcel*[a,b,*]

[a]*INRA, CNRH-IdF, UMR914 Nutrition Physiology and Ingestive Behavior, AgroParisTech, 16 rue Claude Bernard, F-75005 Paris, France*
[b]*AgroParisTech, CNRH-IdF, UMR914 Nutrition Physiology and Ingestive Behavior, F-75005 Paris, France*
[c]*Laboratoire de Physiologie Neurovégétative, Université Paul Cézanne Aix-Marseille III, CNRS (UMR 6231), INRA (UMR 1147), Marseille, France*

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) and its TrkB receptor play critical roles in the synaptic activity and plasticity of mature neurons and enhance adult neurogenesis. Furthermore, treatment with BDNF has been found to attenuate weight gain or even cause weight loss and appetite suppression in rats. The aim of this study was to look at the effect of nutrient intake on BDNF concentrations and cellular proliferation in the brain. Adult male Wistar rats were given one of three diets for 6 weeks: high-carbohydrate, high-fat or high-fat pair-fed diets. Rats were sacrificed at the end of the feeding period and BDNF concentrations in the dorsal vagal complex (DVC), hypothalamus and plasma were measured by ELISA on protein extracts of these samples. Cellular proliferation in the DVC was quantified by Ki-67 immunohistochemistry. Neither BDNF levels nor proliferation were modified by the diet. Secondly, using rats that received the same diets, real-time PCR was performed in the DVC, hypothalamus and nodose ganglia in order to compare TrkB receptor levels. The results showed significantly lower TrkB levels in the hypothalamus and nodose ganglia of fasted rats receiving the high-fat diet when compared to the other groups. These two complementary methodological approaches suggest that there is a relationship between long-term dietary intake and BDNF. More precisely, TrkB expression is more responsive to energy states than to diet composition. An increment in energy stores thus triggers decreased BDNF anorexigenic signaling at the receptor level in the hypothalamus and nodose ganglia, but not in the DVC.

1. Introduction

The peripheral and central neural pathways controlling food intake are probably highly flexible and it is now acknowledged that dietary conditions can affect the neural networks controlling food intake. These properties of neural circuits may be responsible for changes to energy intake and, as a consequence, may result in the onset of overweight and obesity. Neuronal plasticity mechanisms, consisting particularly in desensitization of the gut brain axis to anorexic signals are likely to be at the origin of this phenomenon. Neuronal plasticity is the ability of the nervous system to adapt its

* *Corresponding author*. INRA, CNRH-IdF, UMR914 Nutrition Physiology and Ingestive Behavior, AgroParisTech, 16 rue Claude Bernard, F-75005 Paris, France. Fax: +33 1 44 08 18 58.
E-mail address: Nicolas.darcel@agroparistech.fr (N. Darcel).

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structural organization to new situations that result from developmental or environmental changes as well as other factors (e.g. injuries) that may affect conditions in the nervous system and the whole (living) organism. For instance, if a subject (rat or mouse) is subjected to a high-fat diet, the neural pathways responsible for controlling meal size become much less efficient, causing an increase in meal size and elevated body weight (Savastano and Covasa, 2005; Paulino et al., 2008). Neurotrophins play an important role in the proliferation, differentiation and survival of neurons in the peripheral and central nervous systems during development (reviewed by Barde (1990)). In addition, some neurotrophins, and particularly BDNF, play critical roles in the synaptic activity and plasticity of mature neurons (Hennigan et al., 2007). Brain-derived neurotrophic factor (BDNF) is one of the trophic nerve growth factors. In the brain, BDNF exerts a trophic action on retinal, cholinergic and dopaminergic neurons, while in the peripheral nervous system it acts on both motor and sensory neurons (reviewed by Lebrun et al. (2006)).

There is evidence that BDNF and its high-affinity receptor TrkB contribute to the control of food intake and body weight. The central administration of BDNF has been found to attenuate weight gain or even cause weight loss and appetite suppression in rats (Lapchak and Hefti, 1992; Pelleymounter et al., 1995). Also, BDNF serum levels have been correlated to eating disorders. During a study in human subjects, serum BDNF levels were found to be significantly lower in female patients with anorexia or bulimia nervosa than in age-matched, normal female control subjects. In addition, a significant and positive correlation between serum BDNF levels and body mass index was detected in all of the subjects (Nakazato et al., 2003). Similarly, BDNF plasma levels were seen to be strongly correlated with the symptoms checklist 90 Revised (SLC-90R) questionnaire in a total of 78 anorexia nervosa patients (Mercader et al., 2008). In animal studies, BDNF has also been shown to act as an anorexigenic factor in the dorsal vagal complex (DVC). Indeed, in a study by Bariohay et al. (2005), BDNF infusion in the DVC of adult rats induced anorexia and weight loss. Furthermore, the BDNF protein content decreased significantly in the DVC after food deprivation for 48 h but increased after re-feeding. This same study also suggested that BDNF could be a common downstream effector of leptin and CCK and involved in their synergistic action. Indeed, acute and repeated peripheral leptin injections, as well as peripheral CCK treatment, induced a rise in BDNF protein levels in the DVC (Bariohay et al., 2005).

Although these processes are of importance to the onset of obesity and changes in eating behavior, our understanding of their molecular and cellular bases remains very poor. The aim of the present study was therefore to look at the effects of long-term nutrient intake on BDNF-related parameters. Our hypothesis was that the levels of BDNF and its receptor in specific brain areas could be dependent on the type of dietary regimen. Two studies were thus carried out to investigate this hypothesis. The first explored the influence of a high-fat (HF) diet on BDNF levels in the brain and on cellular proliferation using the Ki67 marker (expressed during active phases of the cellular cycle), while the second considered the effects of this HF diet on the level of TrkB receptor expression in specific brain areas.

2. Results

2.1. *Body weight and food intake*

Rats were fed one of three diets for 6 weeks: a standard high-carbohydrate diet (HC), a high-fat diet ad libitum (HF) or a high-fat diet pair-fed (HF-pf). As expected, the HF group displayed higher body weights than the high-carbohydrate (HC) and the high-fat pair-fed (HF-pf) groups over the last 10 days of the dietary treatment (F (6, 68) = 4.8, $P < 0.001$). On the last day of the experiment, the average body weights of the rats were 494.2 ± 13.5 g in the HF group and 406.8 ± 5.5 g and 397.22 ± 10.4 g in the HC and HF-pf groups, respectively. Both body weight values and the cumulative energy intake of the animals are presented in Fig. 1. The HF group displayed a significantly higher energy intake (387.5 ± 8.1 kJ) than the HC (348.4 ± 8.3 kJ) and the HF-pf (329.4 ± 8.2 kJ) groups, (F (2, 67) = 13.14, $P < 0.001$). The energy intake of HC and HF-pf animals did not differ significantly from each other.

2.2. *BDNF levels, cellular proliferation and TrkB receptor expression in the brain*

During the first set of experiments, BDNF levels were measured in the dorsal vagal complex (DVC), hypothalamus and serum of rats after the 6-week dietary treatment. These parameters were not affected by diet: F (2, 13) = 0.04, $p = 0.85$; F (2,13) = 0.79, $p = 0.48$ and F (2,13) = 0.79, $p = 0.48$, respectively. Also, cellular proliferation as measured in terms of Ki-67 protein levels in the DVC, did not significantly differ between the dietary groups: F (2, 13) = 0.32, $p = 0.77$. During the second study, levels of TrkB receptor expression were measured in the hypothalamus, DVC and nodose ganglia of the rats. TrkB mRNA levels in the hypothalamus were affected by diet: F (2, 13) = 4.92, $p = 0.026$ (Fig. 2). Indeed, rats fed the HF diet had lower TrkB expression levels (0.84 ± 0.18) than rats fed the HC (1.58 ± 0.23) or HF-pf diets (1.57 ± 0.18), $t(13) = 2.52$, $p = 0.026$ and $t(13) = 2.80$, $p = 0.047$, respectively (Fig. 3). Similarly, in the nodose ganglia, TrkB mRNA levels were affected by diet: F (2,13) = 4.92, $p = 0.026$. The results showed a decrease in TrkB mRNA expression in rats receiving the high-fat diet (0.69 ± 0.047) compared to the two other dietary groups (1.29 ± 0.25 and 1.16 ± 0.18) (Fig. 3). However, TrkB levels were not significantly affected by diet in the DVC of the rats (F (2, 14) = 0.36, $p = 0.71$) (Fig. 3).

3. Discussion

The objective of this study was to verify whether the levels of BDNF and its receptor in specific brain areas could be dependent on the type of dietary regimen. The results did not demonstrate any diet-related variations in BDNF levels or in cellular proliferation (as measured in terms of Ki-67 protein). By contrast, they showed significantly lower levels of TrkB expression in the hypothalamus and nodose ganglia of fasted rats that had received the high-fat diet *versus* the control dietary groups. These findings thus provide new evidence for a variation in BDNF receptor dynamics consequent on a positive change in the energy balance.