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Dietary Slowly Digestible Starch Triggers the Gut-Brain Axis in Obese Rats with Accompanied Reduced Food Intake

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Abstract

Scope: Slowly digestible starch (SDS), as a functional carbohydrate providing a slow and sustained glucose release, may be able to modulate food intake through activation of the gut-brain axis.

Methods and results: Diet-induced obese rats were used to test the effect on feeding behavior of high fat (HF) diets containing a SDS, fabricated to digest into the ileum, as compared to rapidly digestible starch (RDS). Ingestion of the HF-SDS diet over an 11-week period reduced daily food intake, through smaller meal size, to the same level as a lean body control group, while the group consuming the HF-RDS diet remained at a high food intake. Expression levels (mRNA) of the hypothalamic orexigenic neuropeptide Y (NPY) and Agouti-related peptide (AgRP) were significantly reduced, and the anorexigenic corticotropin-releasing hormone (CRH) was increased, in the HF-SDS fed group compared to the HF-RDS group, and to the level of the lean control group.

Conclusion: SDS with digestion into the ileum reduced daily food intake and paralleled suppressed expression of appetite-stimulating neuropeptide genes associated with the gut-brain axis. This novel finding suggests further exploration involving a clinical study and potentially development of SDS-based functional foods as an approach to obesity control.

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Author Contributions

B.R.H., L.Y.H, T.L.P., and R.J.P. designed the research; T.L.P. provided the animal facility; K.K. provided the facility for euthanizing the animals and hormone analyses. L.Y.H. and R.J.P. conducted the animal experiments and acquired the data; L.Y.H. and B.R.H. analyzed and interpreted the data; R.J.P. assisted in extracting the instrumental data; J.B.S. performed statistical analysis; L.Y.H. and B.R.H. drafted the manuscript; B.R.H., G.Z., critically edited and revised the manuscript. We also thank Jennifer McAdams for assisting the animal experiments. All authors read and approved the final manuscript.

Conflict of Interest

There is no commercial conflict of interest in this work.

Keywords

slowly digestible starch; gut-brain axis; obesity; food intake; meal size

Introduction

Obesity is a risk factor of hypertension, type 2 diabetes, cardiovascular disease [1], and various types of cancer [2]. Fundamentally, it is associated with positive energy balance resulting from high caloric intake and low energy expenditure. Of the two, increase in caloric intake rather than lower physical activity was noted to be the greater driver of the obesity epidemic in the United States over the last three decades [3]. Thus, there is a causative relationship between food intake and obesity. A potential way to control body weight is through activation of the gut-brain axis by functional food components to trigger hormones such as the ileal-activated glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) that affect appetitive response and food intake [4–6]. This occurs through activity of different regions of the central nervous system, particularly the hypothalamus, which plays a crucial role in regulation of food intake [7–9]. The arcuate nucleus within the hypothalamus is key in the control of appetite [10] involving orexigenic (appetite-stimulating) neuropeptides [neuropeptide Y (NPY), Agouti-related peptide (AgRP)] and anorexigenic (appetite-suppressing) neuropeptides [pro-opiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript (CART)] [11]. Other neuropeptides, including the orexigenic melanin-concentrating hormone (MCH) and anorexigenic corticotropin-releasing hormone (CRH) from other regions of the hypothalamus, are additionally involved in appetite regulation [12]. In particular, NPY and AgRP have been shown to play important roles in the regulation of food intake and maintenance of energy balance [13–15]. Thus, it seems reasonable that an anti-obesity strategy could be achieved through identification and use of hypothalamus-modulating functional dietary components.

Starch, in the form of glucose, is the major dietary source of energy. For nutritional purpose, it has been classified into rapidly digestible starch (RDS), slowly digestible starch (SDS), and resistant starch (RS) [16]. RDS, which is high in many processed starchy foods, is digested rapidly and leads to a postprandial glucose spike; whereas SDS is digested slowly in the small intestine with measured and sustained glucose release [17]. RS is undigested in the small intestine and is largely fermented in the colon. There is a responsiveness of the small intestine to these nutritional categories of starch. In pigs, SDS caused increased glucose transporter in the ileum [18] and in humans resulted in sustained release of the incretin hormone GLP-1 [19], which has a role in appetite control and body weight regulation [20]. Considering the existence of the GLP-1-mediated ileal brake and its role in the gut-brain axis [21, 22], and evidence that glucose is a stimulator of GLP-1 secretion from L-cells in the rat ileum [23] and suppresses food intake [24], we postulated that ileal location of starch digestion is important for the activation of this feedback control of appetite [22, 25]. Although not all SDS-containing foods digest as far as the ileum, some do so and may induce the secretion of the gut hormone GLP-1 [26]. Thus, we hypothesized that a SDS material that is characterized by digestion in the ileum may have the capability to modulate food intake through the gut-brain axis.

To study properly this potential physiological effect of SDS, it was necessary to use a material in which starch digestion rate and location of digestion in the small intestine was controlled, and one in which the digestion profile would be repeatable. We had previously developed a defined SDS material by entrapping starch in a natural alginate polysaccharide matrix in the form of microspheres that contain pores for α-amylase to enter and to digest the interior starch at controlled rates [27]. The microspheres were shown to digest slowly and, in a preliminary study, we further showed that the microspheres digested to some extent in the rat ileum (~3% of ingested microspheres at 2 h after gavage). Thus, we used the SDS microspheres to assess the effect of their long-term consumption on feeding behavior and the gut-brain axis using diet-induced obese rats.

Materials and Methods

Preparation of SDS microspheres

SDS microspheres (in the range of 200–600 μm) were made according to the method of Venkatachalam et al [27] by dropping a mixture of sodium alginate (0.5% w/v) and waxy cornstarch (10% w/v) through a 21 gauge dispensing needle (EFD Inc., East Providence, RI, USA) into a 2% w/v calcium chloride bath. The *in vitro* Englyst starch digestibility test [16] was conducted on the cooked microspheres and values were 62.8, 33.3, and 4.2% for RDS, SDS, and RS. As mentioned above, in a preliminary experiment, rats were gavaged with the 0.5% alginate-prepared microspheres and some starch was recovered in the ileum, which showed that they were digested throughout the length of the rat small intestine. For purpose of this study, the microspheres are referred to as “SDS”. SDS microspheres were cooked in boiling water for 10 min to gelatinize the starch and were freeze-dried prior to incorporation into a pelleted chow-type diet, as explained below. The RDS material for the study was fast digesting pregelatinized waxy cornstarch (Ultra-Sperse A, National Starch, Bridgewater, NJ, USA).

Animals and diets

Forty-five 8-wk old Sprague Dawley male rats (Harlan Laboratories, Indianapolis, IN, USA) were individually housed in stainless steel hanging wire cages maintained at a constant temperature (21°C) on a 12:12 h light/dark cycle (lights on at 6:00 a.m.) with *ad libitum* access to rodent chow (5001 Rodent Diet, Purina LabDiet, St. Louis, MO, USA) and water. After 1 wk of acclimation to the laboratory, rats were randomly assigned to a control low-fat (LF) diet group (14% fat calories purified control diet, Teklad TD.10026, Harlan Laboratories, Madison, WI, USA) (n=6) or a high fat (HF) diet group (45% fat calories diet, Harlan Laboratories) (n=39) for 14 wks to induce obesity. At the end of the diet-induced obesity (DIO) phase, the body fat percentage (%) was determined using a rat/mice body composition analyzer (Echo-MRI, Echo MRI LLC, Houston, TX, USA). The animals were screened using percent (%) body fat as the criteria to exclude the rats in the LF group that were more prone to being obese (higher % body fat), and the rats in the HF group that were less prone to being obese (lower % body fat), and also the most obese (highest % body fat) rats. The remaining HF-fed obese rats were randomly assigned to three experimental diet groups: HF (n=6), HF-containing RDS (HF-RDS; n=6), HF-containing SDS microspheres (HF-SDS; n=5), and then transferred to the food intake monitoring cages for the study

phase. Lean control rats continued to be fed on the LF diet (n=4). Diet compositions are found in Table 1. The experimental diets were formulated at Harlan Laboratories (Harlan Teklad, Madison, WI, USA). All husbandry procedures followed the guidelines of The NIH Guide for the Care and Use of Laboratory Animals (8th ed., The National Academy Press, Washington, D.C.), and were approved by the Purdue University Animal Care and Use Committee (approval no. 1111000321). Every effort was made to minimize suffering and the number of animals used.

Automated food intake monitoring

The BioDAQ Episodic Food Intake Monitor (Research Diets, Inc., New Brunswick, NJ, USA) was used for continuous data collection of meal patterns in undisturbed rats. The BioDAQ system weighs the food hopper every second and detects “not eating” as weight stable and “eating” as weight unstable. Meals that consisted of one or more bouts were separated by an inter-meal interval (IMI) set as 900 sec (15 min) and the minimal meal size was set as 0.2 g, which means that food intake was considered to be one meal when a feeding bout occurred within 15 min from the previous response and the total sum of the intake was equal to or greater than 0.2 g. Meal parameters including meal size (g/meal), number of meals, and amount of food consumed were extracted and assessed from the software (BioDAQ 2.3.07).

Satiety ratio was calculated as IMI (min) between the first and second meal/the first meal size (kcal) and expressed in min/kcal, thus a higher number indicates that the meals were more satiating. First and last meals consumed during the dark cycle were excluded from the calculation of satiety ratios.

Analysis of total starch retained in microspheres in feces

Another treatment group, HF-SDS+RS, was run, but feeding behavior results are not reported due to poor digestibility of the starch. Microspheres were visible in the feces of HF SDS+RS group, and were recovered and analyzed for residual starch content. Three fecal droppings from each of two rats were used for the analysis. They were mixed 1:10 with 1x PBS buffer, and microspheres were manually separated from the suspension. Recovered microspheres were washed in deionized water three times and dried at 40°C overnight. Microspheres were then pulverized and total starch content determined as described above.

Gene expression of hypothalamic neuropeptides

At week 12 of the study phase, animals were euthanized with ether and decapitated following a 12 h overnight fasting. Brains of all animals were harvested and collected on iced isopropanol before being stored at −80°C. The hypothalamus from each brain was excised and homogenized in Trizol reagent (Invitrogen, Carsbad, CA, USA) to extract total mRNA according to the manufacturer’s protocol. RT-qPCR was performed in duplicate using a StepOne Real-Time PCR Thermal Cycler (Applied Biosystems, Carlsbad, CA, USA) with SYBR Green PCR Master Mix (Applied Biosystems, Carlsbad, CA, USA) for 40 cycles in which GAPDH was served as a housekeeping gene. Gene expression changes were calculated using a protocol of $2^{-\Delta\Delta Ct}$ after normalization based on the housekeeping gene. The primers for PCR are listed in Supplemental Table 1.

Statistical analysis

Data are expressed as mean ± SEM and were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test for *post hoc* analyses or one-way repeated measures ANOVA followed by the paired *t*-test. A power of 0.83 was achieved for food intake difference assuming a mean difference of 5 kcal with a statistical significance of $p = 0.05$ and an animal size of 5. Hypothalamic neuropeptide data were analyzed using the *t*-test. Differences between groups were considered significant at $P < 0.05$. Statistical analyses were performed using SAS 9.3 program (SAS, Inc; Cary, NC, USA).

Results

Daily intake (dark cycle feeding time, kcal)

Rats fed on the different diets had notable differences in food intake over the 11-week study period (Fig. 1A). The HF-SDS group showed lower daily food intake than the HF-RDS group at wk 8 ($P = 0.013$), and the HF-RDS group had higher food intake compared to the lean group with significant differences at wks 2, 3, and 8 ($P = 0.018$, 0.025, and 0.010) (Fig. 1A, Table S1). Rats fed the HF-SDS diet had a significant decrease in food intake over the 11 wk study period (between wk 1 and 11, P = 0.042), and food intake of the HF-SDS group trended similar to the LF lean control group. The Average daily food intake over the entire treatment phase of the HF-SDS group was lower than the HF-RDS group ($P < 0.05$), and trended close to the LF lean control group (Fig. 1B). In addition, average daily food intake of the HF-RDS group was higher than the HF control group.

A second SDS-containing diet was tested in the study design with microspheres made using a higher alginate concentration for slower starch digestion than the HF-SDS diet (termed HF-SDS+RS). Rats consumed significantly more of the HF-SDS+RS diet than HF-SDS diet (Fig. 1S) and it was later found that about 25% of consumed starch was recovered in SDS +RS microspheres from the feces. Rats in this treatment group apparently consumed more of the diet because of there was a lower caloric load due to lost starch than in the HF-SDS diet. This result was instructive, however, as it showed that the physical property of the microspheres was not a negative factor for the rats to consume the microsphere-containing diets.

Rats on the HF-SDS diet had a substantially decreased meal size throughout the study compared to other treatment groups (Fig. 2A, Table S1). Compared to the HF-RDS group, the decrease in meal size of the HF-SDS group was significant at wks 1 ($P = 0.014$), 2 ($P=0.020$), 3 ($P=0.007$), 7 ($P=0.003$), and 8 ($P=0.028$). Compared to the LF control group, decrease in meal size of the HF-SDS group was significant at wks 1 ($P = 0.035$), 3 ($P = 0.015$), 7 ($P = 0.003$), and 8 ($P = 0.012$). The range of meal size reduction of the HF-SDS group compared to the HF-RDS group and the LF control group was 11.1 – 30.5% and 11.2 – 29.1%, respectively. Meal size was not different between the HF-RDS and the LF lean control groups at all time points.

In the HF-SDS group, rats initially had a higher meal number (about 8 versus 6 meals per day), presumably to maintain same caloric intake in light of the reduced meal size they consumed. However, over the course of the 11-week treatment phase, daily meal number of

the HF-SDS group decreased to 5.6 meals per day, a level similar to the other treatment groups, and significantly less than at the beginning of the study ($P = 0.01$) (Fig. 2B, Table S1). Compared to the HF-RDS group, meal number was significantly higher for the HF-SDS group at wks 1, 3, and 7 ($P = 0.006$, 0.019, and 0.030, respectively), and to the LF lean control group at wks 1, 2, 3, and 7 ($P = 0.003$, 0.005, 0.001, and 0.001, respectively); but no differences were observed compared to either group after wk 7 and until the end of the study.

Starting at wk 3, the HF SDS group showed a trending of higher satiety ratio compared to the other groups, though values were not statistically significant from the other treatment groups (Fig. S2).

Hypothalamic neuropeptides

For the appetite-stimulating orexigenic neuropeptides, rats fed the HF-SDS diet showed a substantial decrease in gene expression of NPY compared to the HF-RDS group ($P = 0.019$; Fig 3A) that was similar and not significantly different from the LF control group. Gene expression of AgRP was also lower for the HF-SDS group compared to the HF-RDS group ($P = 0.020$). Gene expression of MCH was reduced in the obese rats and there was a slight, though significant increase, in MCH expression in the HF-SDS compared to the HF-RDS group ($P < 0.05$). For the appetite-suppressing anorexigenic neuropeptides, there were no differences in POMC among the three groups, though the obese rats had lower gene expression of CART than the LF control ($P = 0.011$ and $P = 0.029$ for HF-RDS and HF-SDS groups). For CRH, there was a significant increase in expression in the HF-SDS and LF groups compared to the HF-RDS group ($P < 0.001$ and $P < 0.01$, respectively) (Fig. 3B).

Discussion

Food carbohydrates have gained a negative connotation in the view of many consumers and researchers. There is the concept of “carbohydrate quality” that divides foods into high and low glycemic index or glycemic response foods, however there is rather little known about the real nature of these materials and how they interact with the body. Here, we show for the first time that when starch is digested slowly and into the ileum that the gut-brain axis is activated and, at least in obese rats, reduce their food intake.

The lower food intake of the HF-SDS treatment group occurred through a marked reduction in meal size. Although rats on the SDS diet initially consumed more meals, they adjusted to a normal meal frequency over the course of the 11 wk feeding period. Concurrently, by wk 11 there was a significant decrease in orexigenic NPY and AgRP in the HF-SDS versus HF-RDS groups, and for NPY the effect was substantial and to the same level as the LF lean control. Thus, foods containing slow digesting glycemic carbohydrates that reach the ileum appear to activate the gut-brain axis through endoendocrine L-cells and their effect on hypothalamic neurons to modulate food intake.

Notably, meal size was reduced in the HF-SDS group compared to the HF-RDS group. Meal size has been related to satiation and meal number to satiety [28, 29]. Satiation, which refers to processes leading to meal termination, is a within-meal effect governed by neural and humoral signals generated in response to ingested food through nutrient sensing [30]. That

the ileal digestion property of the SDS used in this study is linked to changes in hypothalamic neuropeptides implies activation of the gut-brain axis, possibly through GLP-1 [31, 32] and its related positive effect on satiation [33]. The reduction in NPY gene expression in DIO rats fed on the HF-SDS diet appears to have reduced appetite by signaling the animal to stop eating earlier in the same meal (higher satiation) than when consuming the HF-RDS diet. NPY is a potent appetite-stimulating peptide [7], and it is known to be overproduced during obesity [34]. Additionally, gene expression of the anorexigenic neuropeptide CRH, which is present in the paraventricular nucleus of hypothalamus, was significantly increased by HF-SDS diet. CRH is a potent neuropeptide to suppress food intake and reduce body weight [35, 36], and its increased expression in the HF-SDS group is consistent with HF-SDS reduction of food intake. Furthermore, the NPY neuron directly provides input into CRH cell bodies [37] to exert its anorexigenic function, and it is therefore logical that down regulation of NPY may lead to an increase in expression of CRH which suppresses food intake [38]. Both the decrease of NPY and AgRP and increase of CRH could contribute to the increased satiation response of rats consuming the HF-SDS diet.

Despite the observed lower daily food intake of the HF-SDS diet group, no significant reduction of the body weight of the rats was found (Fig. S3). We think this could have been due to a combination of factors, but mainly that reduction in daily food intake of the HF-SDS group only occurred in the latter part of the treatment phase, and that the DIO rats stayed on a high-fat diet instead of being placed on a normal lower fat diet. Change in treatment design DIO rats are placed on a low-fat diet during the treatment phase is needed.

It is noteworthy that only a small amount of the starch from the microspheres was measured in the ileum (~3% of ingested, as mentioned above), suggesting that it is sensitive to the stimulatory effect of starch digestion. All cooked starches digest more extensively in the proximal than in the distal small intestine, and even for SDS relatively little or no starch typically reaches the ileum. One might speculate that ileal-located starch digestion fits diets of early man, which presumably included starchy foods eaten in relatively dense food matrices; where a small portion of starch would digest into the ileum to trigger the gut-brain axis, thus naturally controlling appetite.

In conclusion, our study is the first to demonstrate that SDS that digests into the ileum of the small intestine alters feeding behavior of diet-induced obese rats by reducing meal size and over time modulating meal frequency through triggering of the gut-brain axis. Gene expression of appetite-stimulating orexigenic neuropeptides was reduced and a hypothalamic appetite-suppressing neuropeptide was increased. Weight reduction was not seen in the treatment phase and a future study on weight reduction of obese animals needs to be done using a longer treatment period and with changing obese rats from a high-fat to normal diet. Overall, a dietary approach using slow digesting carbohydrates to control food intake may have practical preventive or treatment implications for the obesity problem.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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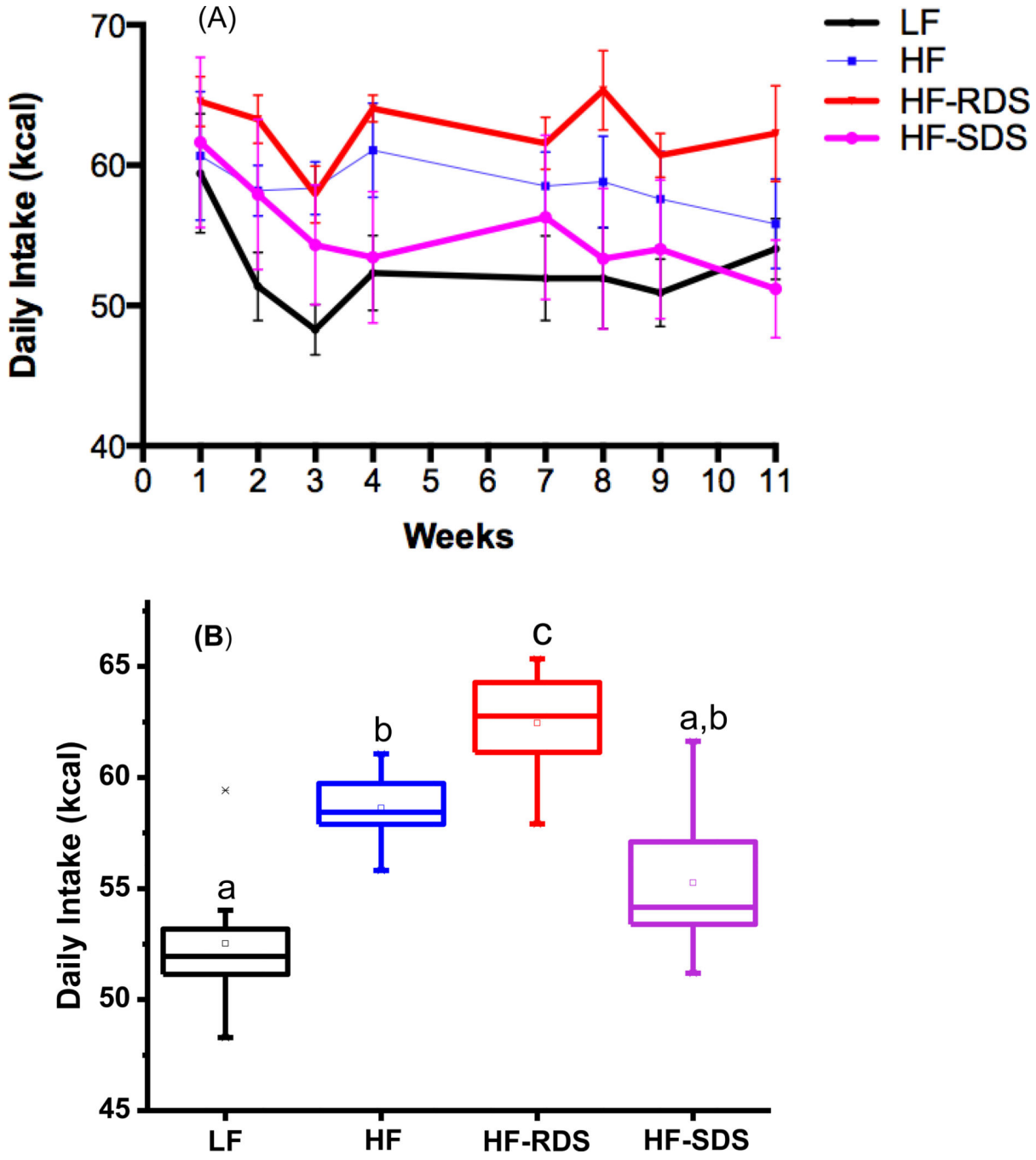

Figure 1.

Daily intake (kcal) measured during the study phase feeding period (dark cycle). (A) and the box-plot of the overall average of the 11 wk treatment (B). Different letters represent significance at $P < 0.05$.

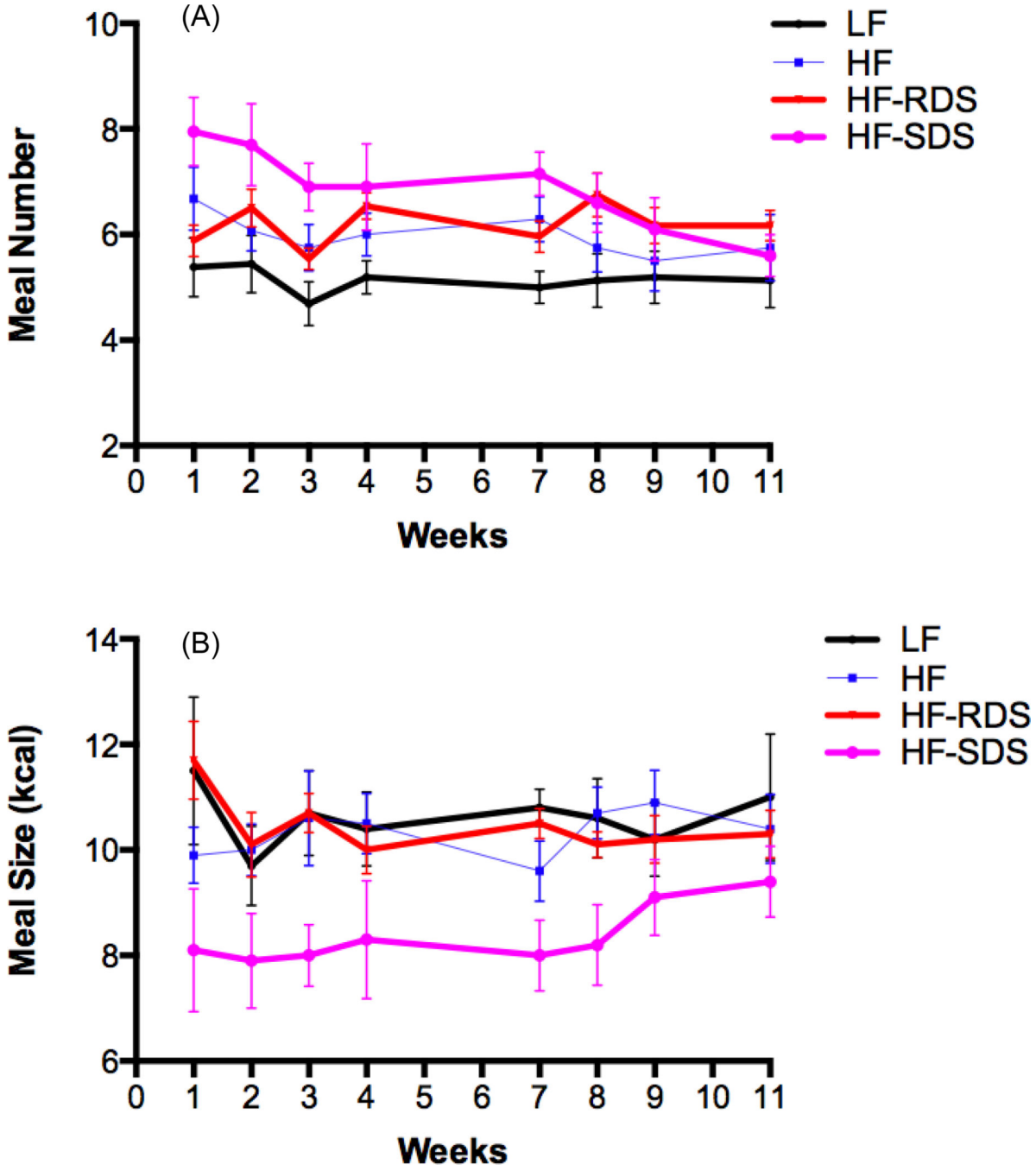

Figure 2.
The daily meal size (kcal) (A) and meal number (B) during the study phase feeding period (dark cycle).

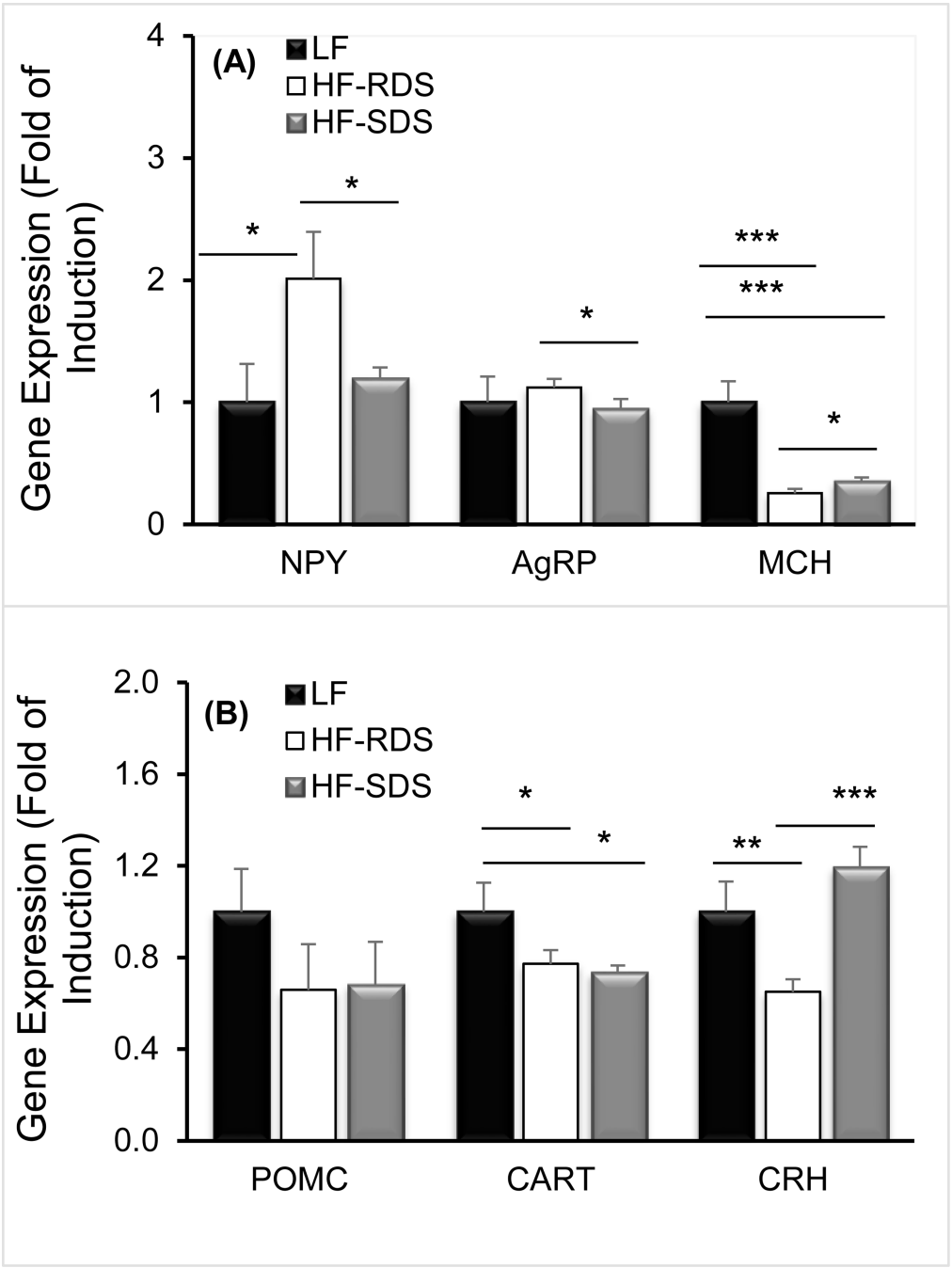

Figure 3.

Gene expression of the orexigenic neuropeptides Y (NPY), agouti-related peptide (AgRP), and melanin-concentrating hormone (MCH) (A), and anorexigenic neuropeptides proopiomelanocortin (POMC), cocaine-and amphetamine-regulated transcript (CART), and corticotropin-releasing hormone (CRH) (B)in the hypothalamus of rats fed the LF control, HF-RDS, and HF-SDS diets at the week of euthanasia (wk 12) following the study phase, * $p<0.05$, ** $p<0.01$, and *** $p<0.001$.

Table 1.

Composition of the experimental diets in g/kg and energy kcal (%).

Nutrients (g/kg)	LF[1]	HF[2]	HF-RDS	HF-SDS
Protein				
Casein	210	245	245	245
Kcal (%)	20.1	19.4	19.3	19.3
Carbohydrate				
Corn starch	449	85		
Pregelatinized starch[3]			283	83
Maltodextrin	100	115	115	115
Starch-microspheres[4]				200
Sucrose	90	200		
Kcal (%)	65.9	34.6	35.0	35.0
Fat				
Lard	28	195	195	195
Soybean Oil	28	30	30	30
Kcal (%)	14.1	45.9	45.7	45.7

*[1]LF: low-fat

[2]HF: high-fat

[3]Source of rapidly digestible starch (RDS), waxy cornstarch

[4]Waxy cornstarch. DS: rapidly digestible starch

[4]SDS: slowly digestible starch.