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Preference for high-fat diet is developed by young Swiss CD1 mice after short-term feeding and is prevented by NMDA receptor antagonists

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ABSTRACT

Obesity is a worldwide epidemic that is increasing at an alarming rate. One of its causes is the increased availability and consumption of diets rich in fat. In the present study, we investigated the effects of short-term consumption of a high fat diet (HFD) on dietary preferences in Swiss CD1 mice and its relation in time to specific metabolic effects. Mice that were weaned 21 days postpartum and fed a chow diet for one week were afterward subjected to a diet preference test for 5 days, exposed to both a regular diet (RD) and HFD. We found that mice did not show any preferences. In a second experiment, two groups of mice that were weaned 21 days postpartum and subjected to a chow diet for one week were fed either RD or HFD for 18 days, and a diet preference test was performed for 5 days. After this short-term consumption of HFD, mice preferred HFD, while mice subjected to RD did not show any preference. Importantly, no differences in blood glucose levels were found between the groups prior to and after the experiments. The results support our hypothesis that the preference for HFD is not a spontaneous behavior in CD1 mice, but it can be observed after short-term consumption; additionally, this preference develops before metabolic effects appear. Finally, this preference for HFD could not be observed when the mice were i.p. injected daily with low doses of the NMDA receptor antagonists, ketamine, ifenprodil or MK-801 during the HFD feeding period. These data suggest that acquisition of dietary preference for HFD is a NMDA receptor-dependent learning process.

1. Introduction

The prevalence of obesity has been growing at an exponential rate in Western societies (Foreyt & Goodrick, 1995; Pena & Bacallao, 2001). Many have speculated that this is due to the deep impact of modern lifestyle on health status, including an increasingly sedentary lifestyle, artificial alterations to the light–dark cycle, and increased consumption of foods rich in fat (Hill & Peters, 1998; Pena & Bacallao, 2001) and sugar (Kavey, 2010). Studies in humans have shown that genetic factors may also play a role, but they cannot fully explain this rapid increase in obesity (Hill & Peters, 1998).

Feeding behavior is complex and involves several brain regions as well as peripheral tissues; it is driven by food seeking and stopped by satiety signals. Feeding comprises homeostatic and hedonic components (Gao & Horvath, 2007; Shin, Zheng, & Berthoud, 2009; Zheng & Berthoud, 2008). Considering that ingestion of diets rich in fat leads to obesity in the long term, reward mechanisms are involved in the maintenance of high-fat feeding. Recent findings suggest that addictive-like states may emerge in adult mice that are fed high fat diet (HFD) (Teegarden & Bale, 2007) or in rats bingeing on HFD (Wojnicki, Roberts, & Corwin, 2006), which affects the accumbens dopamine system in a similar way to that of drugs of abuse (Avena, Rada, & Hoebel, 2009; Johnson & Kenny, 2010). We suspect that dietary preference for HFD, i.e., the choice to eat fat, is developed even before addictive-like behavior emerges. Fat preference is a spontaneous behavior in some mouse and rat strains (Castonguay, Hartman, Fitzpatrick, & Stern, 1982; Smith, Andrews, & West, 2000). With experience, however, animals refine their preferences as they associate the flavors of specific foods with

Abbreviations: HFD, high-fat diet; RD, regular diet; NMDA, N-methyl-D-Aspartate; PBS, phosphate buffer saline.

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the foods' post-ingestive consequences (Sclafani, 2001; Sclafani, 2004). Other animal studies indicate that fat preference can also be influenced by maternal food intake during pregnancy (Bellinger, Lilley, & Langley-Evans, 2004), giving rise to the notion that fat preference could be programmed during fetal life. More recently, it has been reported that C57Bl/6:129 mice, exposed to HFD at 3 weeks of age for one week and further fed a chow diet up to 3 months of age, showed an increased preference for HFD in the long-term (Teegarden, Scott, & Bale, 2009), thus indicating that exposure to HFD during early postnatal life may lead to a dietary preference for fat. This finding suggests that fat preference can be developed after early postnatal consumption, putting the organism at risk for maladaptive eating habits. Nevertheless, the study by Teegarden et al. (2009) was performed using C57Bl/6:129 mice, a mouse strain that demonstrates a marked spontaneous preference for HFD (Smith et al., 2000; Teegarden & Bale, 2007). In fact, the C57Bl/6 strain strongly prefers fat, consuming 72% of their calories from HFD, whereas BALB/c mice do not show any macronutrient preference (South & Huang, 2006). Compared to Swiss CD1 mice (ICR), C57Bl/6 mice have also shown a high consumption of calories in the form of ethanol (McMillen & Williams, 1998), which may also be related to the genetic traits of C57Bl/6 mice (Ng, O'Dowd, & George, 1994). Thus, the question of whether fat preference could be postnatally developed or unveiled by experience in animals that do not show a marked inherited and/or prenatally programmed fat preference still remains unexplored. Obese persons have a higher preference for foods rich in fat compared to lean persons (Mela & Sacchetti, 1991; Nakamura, Skimai, Kikuchi, & Tanaka, 2001); however, it is unclear whether this preference is a consequence or a cause of consuming HFD and developing obesity (Nakamura et al., 2001). How the preference develops and its relation in time to metabolic effects has yet to be studied in either human or animal models. It is also important to determine whether acquisition of dietary preferences is a NMDA receptor-dependent learning process since, as recently suggested by some authors (Dela Cruz et al., 2012; Popik, Kos, Zhang, & Bisaga, 2011), NMDA receptors are critically involved in the acquisition of appetitive instrumental learning.

The general aim of this investigation is to study the effects of short-term consumption of HFD on dietary preferences in young Swiss CD1 mice. The specific aims were to determine the following in young mice: (i) whether there is a spontaneous preference for HFD; (ii) whether previous high-fat feeding alters the preference for HFD; (iii) whether preference is developed before diet consumption had altered homeostatic variables, such as blood glucose levels and body weight; and (iv) whether preference for HFD is prevented by administering low doses of N-methyl-D-Aspartate (NMDA) receptor antagonists, such as ketamine, MK-801, or ifenprodil.

2. Materials and methods

This investigation was performed following protocols approved by the Committee for the Ethical Use of Experimental Animals at INTA, University of Chile and was in accordance to the NIH Guide for the Care and Use of Laboratory Animals (National Research Council., 1985).

2.1. Animals

Experiments were performed in young Swiss CD1 male mice from our inbred colony, individually housed with free access to water and either a regular diet (RD) or HFD, under controlled laboratory conditions (a 12-h light/dark cycle with lights on at 07:00 a.m.); after weaning at 21 days of age, animals were maintained on a chow diet (Champion, Santiago, Chile) for one week. RD (10 kcal% in fat; cat N° D1450B) and HFD (60 kcal% in fat; cat N° D1492) were both purchased from Research Diets (New Brunswick, NJ 08901, USA). Proximal analyses did not show any significant differences in the macronutrient composition between RD and the chow diet. At 29 days of age, animals were subjected to a preference test for 5 days (experiment 1) or fed either RD or HFD for 18 days (experiment 2).

2.1.1. Experiment 1

Mice were weaned 21 days postpartum and then fed chow diet for one week. Then, 28 day-old male mice ($n = 12$) were subjected to a preference test for 5 days, being exposed to both RD and HFD as described below (Section 2.2). Body weight and diet consumption were recorded every day.

2.1.2. Experiment 2

Two groups of mice ($n = 9$, each group) were weaned 21 days postpartum and then fed a chow diet for one week. Afterwards, they were either subjected to RD or HFD for 18 days. Mice were then subjected to a preference test (RD and HFD) for 5 days. Body weight and consumption were recorded daily during the entire experiment, while blood glucose was measured from the tail vein on the first and last days of the experiment, at days 28 and 46, using a glucometer ACCU-CHEK Sensor Comfort (Roche, Switzerland). Four additional groups of 29 days-old male mice ($n = 5$, each group) were i.p. injected daily with either 1 mg/kg ketamine, 1 mg/kg ifenprodil, or 0.1 mg/kg MK-801 dissolved in phosphate buffer saline (PBS) or PBS alone (control) while fed HFD during 14 days; then, animals fed chow diet for one week after NMDA receptor antagonists treatment ceased, and then, dietary preference was tested as described below.

2.2. Preference test

Two food receptacles (feeders) containing either RD or HFD were placed at opposite corners of the cage; the locations of the food containers were switched every day to avoid a side bias. Animals were fed individually using feeders made of a small glass placed in a bowl to collect spillage. Food consumed was weighed and replaced daily, and the mice were weighed daily. HFD preference was defined as the percentage of kilocalories consumed from HFD over the total energy intake when mice were given a choice between RD and HFD; this value was expressed as time-course curves. Thus, a 50% energy intake is expected by chance from any source in which mice prefer neither HFD nor RD.

2.3. Statistical analyses

All data were reported as the means ± SEM. Both RD and HFD intakes were expressed as kilocalories consumed per animal per day. The effects of age and diets on body weight and blood glucose were analyzed by comparing the scores obtained prior (28 days-old) and after RD or HFD feeding during 18 days (46 days-old) using two-way ANOVA, followed by the Bonferroni multiple comparisons test (Prism 3.0, GraphPad Software, Inc., San Diego, CA, USA). Intragroup analysis of time-course curves for changes in food intake and HFD preference over time in mice previously subjected to RD or HFD was performed by using repeated measures ANOVA followed by the Bonferroni multiple comparisons test (Prism 3.0 software package, GraphPad Software, Inc., San Diego, CA, USA). To determine whether the HFD preferences in each day of the 5-day preference tests were statistically similar or different to the expected 50% HFD preference, the HFD preference scores were compared as two-tailed measures against the expected 50% HFD preference using the Instat 3.0 software package (GraphPad Software, Inc., San Diego, CA, USA). Both groups tested for dietary pref-

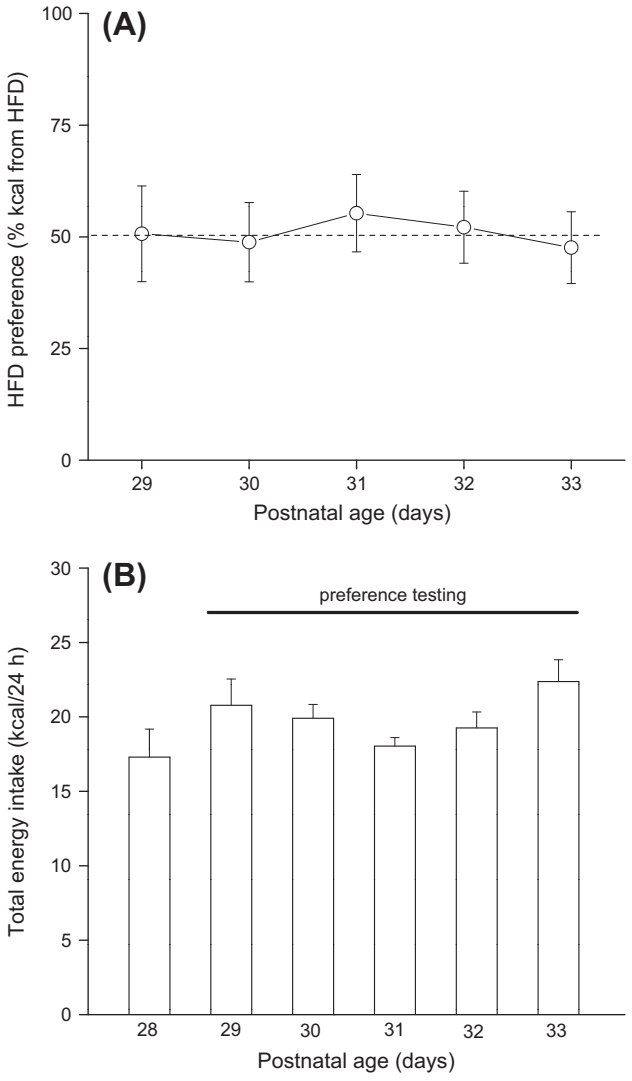

Fig. 1. Absence of dietary preference in recently weaned (naive) CD1 mice: (A) % HFD preference (% kcal ingested from HFD); (B) energy intake (in kcal/24 h). Data are the means ± SEM, $N = 12$ mice in each group. Neither a preference for HFD (A) nor changes in total intake compared to the intake on day 28 (the day before preference testing) (B) were detected during the 5-day period of testing (repeated measures ANOVA for HFD preference: P ANOVA = 0.9779, $F = 0.1141$; repeated measures ANOVA for total energy intake: P ANOVA = 0.1186; $F = 1.832$).

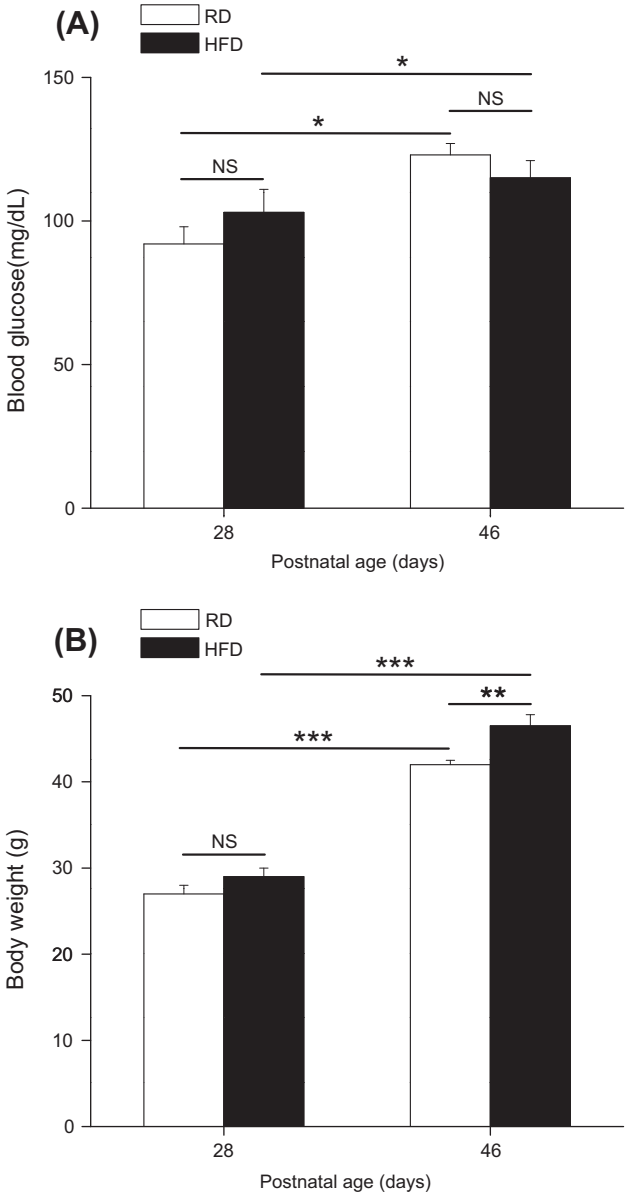

Fig. 2. Body weight and fasting blood glucose levels before and after a 18-day period of either RD or HFD feeding of young mice: (A) blood glucose (mg/dL); (B) body weight (mg). Data are the means ± SEM, $N = 9$ mice in each group. Two-way ANOVA detected a slight but significant increase in body weight (P ANOVA = 0.0025; $F = 10.72$; $^{**}p < 0.01$, Bonferroni multiple comparisons test) but not in blood glucose levels (P ANOVA = 0.8093; $F = 0.0592$), between mice fed HFD compared to mice fed RD. Blood glucose levels (P ANOVA = 0.0014; $F = 12.16$; $^{*}p < 0.05$, Bonferroni multiple comparisons test) and body weight (P ANOVA < 0.00001; $F = 268.1$; $^{***}p < 0.001$, Bonferroni multiple comparisons test) increased during the experiment in both RD and HFD animals.

erence were also compared by two-way ANOVA. Statistical significance was considered at $P < 0.05$.

3. Results

3.1. Experiment 1

At the end of the 5 days of preference testing, much variability was observed in the preference for HFD; there was no single trend in preference, that is, energy intake was supplied indistinctly from any of the diet sources. Overall, there was no preference for HFD during the 5-day period of testing (Fig. 1A). In addition, the total energy intake remained stable during the preference test (Fig. 1B).

3.2. Experiment 2

No significant differences in blood glucose or body weight were found upon weaning at the beginning of the experiment (Fig. 2A and B). A slight but significant increase in body weight ($p < 0.01$, two-way ANOVA followed by Bonferroni *post hoc* test), but not in blood glucose, was observed in mice subjected to 18 days of HFD compared to that of mice subjected to a similar period of RD (Fig. 2B). Body weight and blood glucose increased during the experiment in both RD and HFD animals (Figs. 2A and B, $p < 0.0001$, two-way ANOVA followed by Bonferroni *post hoc* test).

In the preference test, the mice that had previously eaten RD for 18 days showed no significant preference for either RD or HFD, except for the first two days of testing, in which mice consumed significantly more RD than HFD (Fig. 3A). Those mice that consumed HFD before the preference test initially had any preference, but after two days of testing, mice showed a preference for HFD (Fig. 3A), i.e., they received significantly more than 50% of energy

intake from HFD (at 49, 50 and 51 days of age). Both groups exhibited significantly different results after comparison by two-way ANOVA ($p < 0.0001$). The total intake of the RD and HFD animals increased significantly on the first two days of preference testing but afterwards returned to the range of scores obtained prior to preference testing (Fig. 3B). In order to address whether acquisition of HFD preference is a NMDA receptor-dependent process, four additional groups of 28-days-old male mice ($n = 5$, each group) were i.p. injected daily with either 1 mg/kg ketamine, 1 mg/kg ifenprodil, or 0.1 mg/kg MK-801 dissolved in phosphate buffer saline (PBS) or with PBS alone (control group) while fed HFD during 14 days; then, animals fed chow diet for one week before dietary preference was tested (Fig. 3C). Results show that any of the NMDA receptor antagonists used in this study was able to prevent preference for HFD. No differences in body weight between groups were detected during treatment suggesting that no taste aversion to food was induced by NMDA receptor antagonists at doses used herein, while higher doses of these chemicals have been shown to produce conditioned taste aversion after one or several pairings with flavor (Aguado, del Valle, & Pérez, 1997; Jackson & Sanger, 1989; Traverso, Ruiz, & De la Casa, 2012).

4. Discussion

Previous studies have shown that adult C57Bl/6 mice, a strain widely used in the field of obesity research, have a strong spontaneous preference for HFD over a diet rich in carbohydrates and RD (South & Huang, 2006; Teegarden & Bale, 2007). It was important for us to investigate whether HFD preference can be developed over time by Swiss CD1 (ICR) mice, a strain also known to develop diet-induced obesity and insulin resistance (Barrera, Gatica, & Morgan, 2012). In our first experiment, newly weaned mice fed chow diet for one week and thereafter subjected to a free choice of HFD or RD for the five following days. Although these mice showed much variability in their initial preference for HFD, no preference for HFD was observed overall. This result suggests that CD1 mice did not show inherited HFD preference, unlike to previous observations on C57Bl/6, A/J, and BALB/c mouse strains (South & Huang, 2006). In our second experiment, we investigated whether HFD preference can be detected after exposure to HFD by feeding two groups of newly weaned mice with either HFD or RD for 18 days. After this, we conducted a preference test, which revealed that mice previously fed RD did not show any dietary prefence at all (RD vs. HFD); overall, there was no preference for RD in those animals, except in the first day of preference testing, which may be indicative of neophobia. It is well known that mice eat a lower amount of novel foods, a neophobic response that is attenuated gradually over several hours following presentation of the novel food stimulus (Hughes, 2007). In fact, those mice that exhibited a fat preference after short-term exposure to HFD did show stable preference levels after two days of preference testing. It seems apparent that the preference for HFD in mice that consumed HFD beforehand was not biased by neophobia to RD and thus constitutes a true preference. Indeed, the symmetric design of the present study suggests that neophobia to diet switching did not constitute a confounding factor on preference testing because mice that consumed RD beforehand did not show an enduring neophobic reaction to HFD. Our results suggest that these mice developed a preference for HFD after a relatively short exposure to HFD, a result that is in agreement with the recent observation that two-week exposure to HFD paired with a light box in the conditioned place preference test produces conditioned preference for HFD in mice (Higuchi et al., 2010). Other studies have also shown that long-term consumption of HFD causes addiction-like symptoms (Johnson & Kenny, 2010; Pickering, Alsio, Hulting, & Schioth,

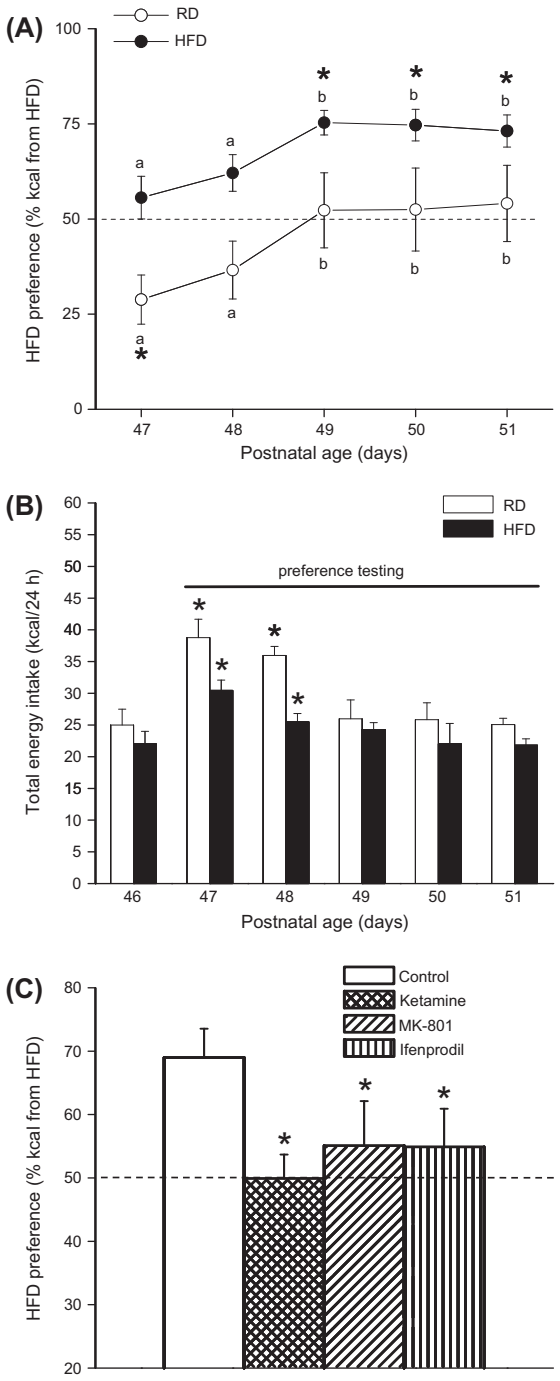

Fig. 3. HFD preference is expressed in young mice after a 18-day period of HFD feeding and is prevented by NMDA receptor antagonists: Data are the means ± SEM, $N = 9$ mice in each group. (A) % HFD preference (% kcal ingested from HFD): Intragroup statistics were assessed with repeated measures ANOVA (for RD mice, P ANOVA < 0.0001; $F = 8.686$; for HFD mice, P ANOVA < 0.0001; $F = 20.832$); different letters indicate significantly different HFD preference scores with a probability level of less than 0.01, according to the Bonferroni multiple comparisons test. Comparisons of HFD preference scores against the expected 50% HFD preference were assessed by using two-tailed t-test measures; asterisks indicate $P < 0.05$. (B) Total intake (in kcal/day): Intragroup statistics were assessed with repeated measures ANOVA (for RD mice, P ANOVA < 0.0001; $F = 6.914$; for HFD mice, P ANOVA < 0.0140; $F = 3.209$); asterisks indicate significant changes in total energy intake during preference testing compared to the intake on day 46 (the day before to preference testing) ($^*p < 0.05$, according to the Bonferroni multiple comparisons test). Both curves were also significantly different compared by two-way ANOVA ($p < 0.0001$, $F = 26.29$). (C) Preference for HFD (% kcal ingested from HFD) determined in control and NMDA receptor antagonists-treated groups either with ketamine, MK-801 or ifenprodil. Every treatment was compared to control group by repeated measurements ANOVA followed by Bonferroni *post hoc* test ($^*p < 0.05$). In addition, experimental groups were not different from 50% as assessed in (A).

2009; Teegarden & Bale, 2007). The fact that there were no significant differences in energy intake or blood glucose between mice subjected to RD or HFD in the short-term suggests that the preference developed before metabolic differences in blood glucose levels appeared. The fact that the blood glucose levels were not altered by feeding young animals with HFD for 18 days is a reasonable measurement that shows that gross metabolic alterations did not occur as a consequence of the treatment. The feeding time period is not enough to detect alterations to glycemia in this mouse strain. So, even though the treatment can affect body weight in a marginal but significant way, it still does not reflect an altered glucose homeostasis. That means that no signs of diet-induced insulin resistance were detected. In fact, differences in body weight between Swiss CD1 mice fed either RD or HFD are not detected before 8 weeks of exposure to the diet (Barrera et al., 2012). A goal of our findings was to detect a change in feeding behavior, that is, the appearance of a preference for a high-fat diet.

There are many ideas about how preference develops. Some studies have shown that preference is indeed an inherited trait in rats by demonstrating that a separate orosensory system may exist for lipids (Tsuruta, Kawada, Fukuwatari, & Fushiki, 1999). Other studies have suggested that preference is an inherited trait in mice by suggesting that chemicals in the brain, such as galanin, regulate fat preference and intake (Adams, Clapham, Wynick, & Speakman, 2008). Other studies, however, have suggested that preference can also be learned; they suggest that long-term exposure to HFD alters the reward pathway in the brain, much like drugs of abuse (Johnson & Kenny, 2010; Kalra & Kalra, 2004; Patel et al., 2006; Teegarden & Bale, 2007). Nevertheless, the reward pathway is involved in motivation but not in learning (Cagniard, Balsam, Brunner, & Zhuang, 2006). We considered the hypothesis that acquisition of dietary preferences well could be part of a learning process because it shows a behavioral change that depends on previous experience. Since many learning processes are known to depend on NMDA receptor activation, and therefore be sensitive to NMDA receptor antagonists, we choose injecting a subanesthetic dose of ketamine (1 mg/kg ketamine i.p.), or low doses of the NMDA receptor antagonists MK-801 (0.1 mg/kg i.p.) and ifenprodil (1 mg/kg i.p.), daily during the whole HFD feeding period. In fact, those animals treated with the NMDA receptor antagonists were unable to exhibit any dietary preference, similarly to those mice that never fed HFD. This observation suggests that acquisition of preference for HFD most likely is a NMDA receptor-dependent process as it is known for other learning processes. As it is known, glutamate is the dominant excitatory transmitter in hypothalamic neuroendocrine regulation (Meister, 2000), and injection of glutamate into the lateral hypothalamus rapidly elicits an intense feeding response in satiated rats (Stanley, Willett, Donias, Ha, & Spears, 1993) whereas injection of an NMDA antagonist suppresses feeding elicited by NMDA (Stanley, Willett, Donias, Dee, & Duva, 1996). That glutamate stimulates feeding after injection into the lateral hypothalamus may be explained by an excitatory role of glutamate on hypocretin/orexin neurons, since the majority of these neurons are glutamatergic (Meister, 2007). NMDA receptors are critically involved in the acquisition of appetitive instrumental learning, since the NMDA receptor antagonists are known to reduce fat conditioned flavor preferences (Dela Cruz et al., 2012) and binge eating of HFD (Popik et al., 2011) in rats. However, concentration levels of the NMDA receptor antagonists used in our study were below than those used to detect conditioned taste aversion by others (Aguado et al., 1997; Jackson & Sanger, 1989; Traverso et al., 2012).

In conclusion, the present study showed that fat feeding preference is not a spontaneous behavior in CD-1 mice but instead can be exhibited after short-term exposure to HFD, even before metabolic effects appear. Functional and molecular brain mapping studies will be required for understanding the neurobiological mechanisms underlying the development of preference for dietary fat. Preference for HFD has been previously associated with the expression levels of some neurotransmitters and mediators in the brain, such as opioids (Gosnell & Krahn, 1993), Agouti related peptide (Hagan, Rushing, Benoit, Woods, & Seeley, 2001), endocannabinoids (South, Deng, & Huang, 2007) and galanin (Adams et al., 2008), all of which add neurobiological support for such a preference, irrespective the inherited, programmed, or learned origin. Though extensive work from past decades in rats and humans, reviewed by Birch and collaborators (Birch, 1999), has focused on the role of genetics, taste and food familiarity in developing dietary preferences in childhood and adolescence, it is unclear whether other potential mechanisms might play a role in the appearance of food preferences. However, it is largely believed that the early exposure of children to macronutrients may play a role in determining food preferences in adulthood (Birch, 1999; Harris, 2008; Smithers, Golley, Brazionis, & Lynch, 2011). Despite the fact that the present findings do not account for the consequences in feeding behavior in the long-term or whether fat preference might be further extinguished, these results help to enlighten the relevance of feeding choices in early life, most conservatively including the time of weaning through adolescence in human beings.

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