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Environmental stimulation rescues maternal high fructose intake-impaired learning and memory in female offspring: Its correlation with redistribution of histone deacetylase 4

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ABSTRACT

Impairment of learning and memory has been documented in the later life of offspring to maternal consumption with high energy diet. Environmental stimulation enhances the ability of learning and memory. However, potential effects of environmental stimulation on the programming-associated deficit of learning and memory have not been addressed. Here, we examined the effects of enriched-housing on hippocampal learning and memory in adult female offspring rats from mother fed with 60% high fructose diet (HFD) during pregnancy and lactation. Impairment of spatial learning and memory performance in HFD group was observed in offspring at 3-month-old. Hippocampal brain-derived neurotrophic factor (BDNF) was decreased in the offspring. Moreover, the HFD group showed an up-regulation of histone deacetylase 4 (HDAC4) in the nuclear fractions of hippocampal neurons. Stimulation to the offspring for 4 weeks after winning with an enriched-housing environment effectively rescued the decrease in cognitive function and hippocampal BDNF level; alongside a reversal of the increased distribution of nuclear HDAC4. Together these results suggest that later life environmental stimulation effectively rescues the impairment of hippocampal learning and memory in female offspring to maternal HFD intake through redistributing nuclear HDAC4 to increase BDNF expression.

1. Introduction

Maternal food intake, during fetal and early postnatal development, determines disease manifests in later life of the offspring (Lillycrop, 2011; Yokomizo et al., 2014), including cardiovascular diseases (Barker, Osmond, Golding, Kuh, & Wadsworth, 1989), hypertension (MohanKumar et al., 2007), obesity (Swanson, Entringer, Buss, & Wadhwa, 2009), metabolic disorders (Li, Sloboda, & Vickers, 2011; Vickers, 2014) and neurological diseases (Krakowiak et al., 2012; Sandman, Davis, Buss, & Glynn, 2011). Growing evidence indicates that the decline in cognitive performance in offspring correlates to maternal nutrition intake (Hoeijmakers, Lucassen, & Korosi, 2014; Page, Jones, & Anday, 2014; Tozuka et al., 2010; Wu et al., 2013). Heavy consuming dietary fructose, a common sweetener in desserts and beverage, resulting in cognition decline in adulthood has been reported in both clinical and animal studies (Agrawal & Gomez-Pinilla, 2012; Ross, Bartness, Mielke, & Parent, 2009; Stephan, Wells, Brayne, Albanese, & Siervo, 2010; Stranahan et al., 2008). These data identify the hippocampus as a brain area vulnerable to high dietary fructose ingestion. However, whether the detrimental effect of heavy fructose consuming during gestation and lactation be transferred to offspring and impairs the hippocampal learning and memory in later life of offspring is still unknown.

Histone acetylation of brain-derive neurotrophic factor (BDNF) promoter in hippocampus plays a critical role in BDNF expression and capability of learning and memory (Bousiges et al., 2013; Bredy et al., 2007; Intlekofer et al., 2013; Korzus, Rosenfeld, & Mayford, 2004; Levenson et al., 2004; Sharma, Taliyan, & Ramagiri, 2015). Epigenetic regulation has been proposed in the developmental programming of the health and diseases to

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maternal food intake (Lillycrop, 2011; Lillycrop & Burdge, 2015; Lupu, Tint, & Niculescu, 2012; Wadhwa, Buss, Entringer, & Swanson, 2009). Previous studies suggest that epigenetic modulation is involved in maternal diet-associated changes in hippocampal structure and function of offspring (Lucassen et al., 2013). As one of the major regulators in epigenetic mechanisms, histone deacetylase (HDAC) is a family of enzymes that remove acetyl groups ($O = C–CH_3$) from a ε-N-acetyl lysine amino acid on a histone, allowing the histones to wrap the DNA more tightly, preventing gene transcription. Treatment with HDAC inhibitors, such as trichostatin A or sodium butyrate, enhances hippocampal cognitive functions (Levenson et al., 2004). Currently, there are at least five classes of HDACs identified (Dokmanovic, Clarke, & Marks, 2007). Class IIa HDAC includes HDAC4, HDAC5, HDAC7 and HDAC9 (Lombardi, Cole, Dowling, & Christianson, 2011); among them HDAC4, 5 and 7 have been identified in the brain (Sando et al., 2012). HDAC7 is abundant in embryonic stage in forebrain while HDAC4 and 5 express throughout the later life (Sando et al., 2012). Class IIa HDAC has been reported to suppress BDNF expression in the cortical neurons (Koppel & Timmusk, 2013), and HDAC4 and 5 have been documented to regulate the cognitive functions (Fitzsimons, 2015; Kim et al., 2012; Sando et al., 2012; Wang et al., 2011). However, whether the increase in HDAC4 or HDAC5 is involved in epigenetic regulation of hippocampal BDNF transcription and its association to deficit of cognitive functions in offspring to maternal HFD has yet to be identified.

Environmental stimulation modulates neuronal circuitry for sensory, motor and cognitive functions. Results of animal studies suggest that these beneficial effects on hippocampal functions are correlated to enhancement of neuronal structure, including neurogenesis, synapse formation, and dendritic branching (Karelina et al., 2012; van Praag, Christie, Sejnowski, & Gage, 1999; Volkmar & Greenough, 1972). These beneficial effects following environment stimulation correlate positively to the enhancement of hippocampal learning and memory (Lee, Hsu, Ma, Lee, & Chao, 2003; Rampon et al., 2000; Tang, Wang, Feng, Kyin, & Tsien, 2001). Recently, environmental stimulation has been demonstrated to facilitate hippocampal learning and memory by the increase in BDNF (Novkovic, Mittmann, & Manahan-Vaughan, 2015). Moreover, environmental enrichment associated with increased histone acetylation has been proposed (Fischer, Sananbenesi, Wang, Dobbin, & Tsai, 2007). Whether the HDAC-associated developmental programming is rewritable by environmental stimulation in later life, however, is still unknown.

While growing evidence showing the influence of maternal high energy diet during gestation and lactation on the cognitive function in male offspring (Giriko et al., 2013; Page et al., 2014; Tozuka et al., 2010), less attention has been focus on the female offspring. Therefore, in the present study we examined whether maternal HFD during pregnancy and lactation would affect hippocampal learning and memory in adult female offspring, and the involvement of class IIa HDAC and hippocampal BDNF in the behavioral changes. Moreover, we also investigate whether environmental stimulation could ameliorate these molecular changes and function impairment evoked by maternal HFD during progeny and lactation.

2. Materials and methods

2.1. Animals

Virgin female and male Sprague-Dawley (SD) rats at 7-week old were purchased from the BioLASCO Taiwan Co., Ltd., Taipei, Taiwan. Animals were allowed to acclimatize in a temperature – (22 ± 1 °C), humidity – (55 ± 5%) and light – (12:12 light-dark cycle, light on from 07:00) controlled room in an AAALAC certified animal facility for at least 14 days before the experiments. All experiments were carried out in accordance to the guidelines for animal experimentation endorsed by our institutional animal care and use committee. Male SD rats were housed with individual females until mating was confirmed by observation of vaginal plug. Pregnant female rats received regular chow (ND; 5001, 3.35 kcal/g; Purina, USA) or high fructose diet (HFD; TD. 89247, 60% fructose; 3.6 kcal/g; Harlan Laboratories, USA) during the whole period of pregnancy and lactation. Both food and water were provided *ad libitum*. After weaning, all female offspring received regular chow.

2.2. Enriched housing

At the age of 8 weeks old, female offspring (body weight: 210–240 g) were randomly assigned to the following groups: ND in standard cage (ND, $n = 43$), ND in environmental enriched cage (ND+EN, $n = 37$), HFD ($n = 40$), and HFD+EN ($n = 36$) for 4 weeks. In both ND and HFD groups, three rats were kept in a 10.5 × 19 × 18 inch standard cage; while for ND+EN and HFD+EN groups, three rats were kept in a standard cage equipped with plastic toys and nesting material. To maintain novelty, the plastic toys and nesting material were replaced with a clean cage every week. Food and water were provided *ad libitum* during the entire EN condition. Fig. 1 illustrates experimental design of the study.

2.3. Spatial learning task via Morris water maze

The Morris water maze (MWM) was performed in a custom-made circular pool with a diameter of 1.8 m and a wall height of 50 cm filled with clear tap water at a temperature of 25 ± 2 °C and depth of 25 cm. The escape platform made of transparent Plexiglas (10 cm × 10 cm × 24 cm) was submerged 1 cm below the surface of the water (Huang et al., 2002). The circular pool was divided into four quadrants, and during all trials of spatial navigation, the location of the hidden platform was kept constant in a specific quadrant. Animals were given a single-session training (09:00–12:00) per day for 4 days. Each session included four swim trials (120 s per trial) with each trial started from a different quadrant. The 4-day training was followed by a probe test 1 day after the last training session. During the probe test, animals were placed in the pool in the longest distance from the previous platform position, and the rats were allowed to swim for 120 s without platform present. The entire process was recorded by a charge-coupled device camera and the time in target (sec), time in target quadrant (sec), target cross (times), target quadrant cross (times) and moving counts were analyzed by EthoVision video tracking system (Noldus Information Technology, Wageningen, Netherlands) (Wu et al., 2007).

2.4. Fasting plasma glucose assay, HOMA-IR score, and oral glucose tolerance test

Major metabolic traits were evaluated for confirmation of metabolic syndrome. The levels of fasting blood glucose (FBG) and the Homeostasis Model Assessment – insulin resistance (HOMA-IR) score were monitored in the offspring at the age of 3 months to mothers received ND or HFD. The offspring was fasting for at least 15 h for the tests. Blood samples were collected from a punch at the tip of the tail and glucose levels were analyzed using the glucose oxidase method (Roche, Basel, Switzerland). The collected blood samples were centrifuged at 1000g for 15 min to separate the plasma for insulin detection. The HOMA-IR score was calculated by free software (provided by University of Oxford, UK) with the following formula: fasting serum insulin (μU/L) × fasting plasma glucose (mmol/L)/22.5. HOMA-IR score values 2.6 were considered as a cut-off point for IR (Ascaso et al., 2003).

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