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Perinatal high-fat diet increases hippocampal vulnerability to the adverse effects of subsequent high-fat feeding

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Summary Epidemiological observations report an increase in fat consumption associated with low intake of n-3 relative to n-6 polyunsaturated fatty acids (PUFAs) in women of childbearing age. However, the impact of these maternal feeding habits on cognitive function in the offspring is unknown. This study aims to investigate the impact of early exposure to a high-fat diet (HFD)

Abbreviations: AUC, area under the curve; C—C, control diet throughout life; C—HF, perinatal control diet and high-fat diet at weaning; DCX, doublecortin; DMA, dimethylacetal; DNMT, DNA methyltransferase; FAs, fatty acids; GD, gestational day; GFAP, glial fibrillary acid protein; HF—C, perinatal high-fat diet and control diet at weaning; HFD, high-fat diet; HF—HF, high-fat diet throughout life; PND, postnatal day; PP, post partum; PUFAs, polyunsaturated fatty acids; TLDA, TaqMan low-density array.

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with an unbalanced n-6/n-3 PUFAs ratio on hippocampal function in adult rats. Furthermore, we explored the effects of perinatal HFD combined with exposure to HFD after weaning. Dams were fed a control diet (C, 12% of energy from lipids, n-6/n-3 PUFAs ratio: 5) or HFD (HF, 39% of energy from lipids, n-6/n-3 PUFAs ratio: 39) throughout gestation and lactation. At weaning, offspring were placed either on control (C—C, HF—C) or high-fat (HF—HF) diets. In adulthood, hippocampus-dependent memory was assessed using the water-maze task and potential hippocampal alterations were determined by studying PUFA levels, gene expression, neurogenesis and astrocyte morphology. Perinatal HFD induced long-lasting metabolic alterations and some changes in gene expression in the hippocampus, but had no effect on memory. In contrast, spatial memory was impaired in animals exposed to HFD during the perinatal period and maintained on this diet. HF—HF rats also exhibited low n-3 and high n-6 PUFA levels, decreased neurogenesis and downregulated expression of several plasticity-related genes in the hippocampus. To determine the contribution of the perinatal diet to the memory deficits reported in HF—HF animals, an additional experiment was conducted in which rats were only exposed to HFD starting at weaning (C—HF). Interestingly, memory performance in this group was similar to controls. Overall, our results suggest that perinatal exposure to HFD with an unbalanced n-6/n-3 ratio sensitizes the offspring to the adverse effects of subsequent high-fat intake on hippocampal function.

1. Introduction

According to the hypothesis of the fetal origin of adult health, the early nutritional environment has long-term effects on later vulnerability to certain diseases (Barker et al., 1993). In western countries, the majority of the population, including childbearing women and children, consumes an excess of fat and high levels of n-6 polyunsaturated fatty acids (PUFAs) relative to n-3 PUFAs, resulting in an unbalanced n-6/n-3 PUFAs ratio (Cordain et al., 2005; Simopoulos, 2011). This ratio can reach 50 in some developing countries (India urban) instead of 5 as recommended (Simopoulos, 2011). While it has been proposed that the quantity and quality of fatty acids supplied by the maternal diet could influence child neurodevelopment (Bernard et al., 2013), the experimental evidence is limited. Animal models suggest that maternal consumption of a high-fat diet (HFD) could affect hippocampal function (Niculescu and Lupu, 2009; Tozuka et al., 2009) and spatial memory in offspring (Bilbo and Tsang, 2010; Page et al., 2014; Tozuka et al., 2010). However, the behavioral results are not consistent, and maternal HFD is variably linked with transient deleterious effects on memory (Page et al., 2014; Tozuka et al., 2010), no effect (White et al., 2009) or even memory improvement in the offspring (Bilbo and Tsang, 2010). Additionally, in all previous studies, the dams were kept on HFD for long periods, until they reached overweight status. Thus, the effects of maternal HFD per se, independent of maternal obesity, on the offspring's cognitive status remains unknown. Previous studies also used lard as the main source of fat for the HFD, and the type of PUFAs used was not taken into consideration. This question is particularly important given that several studies underline the importance of the nature of the fat (in particular the n-6/n-3 PUFAs ratio) in the long-term consequences of HFD on brain (Simopoulos, 2011). Furthermore, over the past few decades, in western countries, the consumption of fat from animal sources has decreased while there is an increasing consumption of fat from vegetal oils (Blasbalg et al., 2011). The consequences of these nutritional habits during development on brain function in adulthood remains to be explored. In the present study, we aimed to determine the impact of perinatal (during gestation and lactation) exposure to HFD with an unbalanced n-6/n-3 PUFAs ratio on hippocampal function in adult rats. We exposed dams during pregnancy and lactation to a diet containing 39% of energy from lipids (vegetable oils) and with an n-6/n-3 PUFA ratio of 39. A group of animals was also exposed to maternal HFD but kept on the same diet after weaning. We investigated whether HFD affected hippocampus-dependent spatial memory. To characterize the impact of HFD on the hippocampus, we conducted large-scale gene expression profiling using a TaqMan low-density array (TLDA, 95 genes tested). We also examined neurogenesis as an important index of hippocampal function in adult animals (Cameron and Glover, 2015). Previous studies demonstrate that HFD modulates astrocytes function (Camargo et al., 2012) and their morphology (Cano et al., 2015). Recent data also indicate that n-3 PUFAs 3 diets restore age-related impairments of the spatial memory and astrocytes morphology in the hippocampus (Labrousse et al., 2012), we thus explored the impact of HFD on the number and the length of astrocytes processes. Moreover, since cognitive impairments could be due to emotional disturbances, we controlled for stress responses and depressive-like behavior in adult rats. Finally, to determine the contribution of the perinatal diet to the effects reported in animals exposed to HFD from conception until adulthood, an additional follow-up experiment was conducted in which rats were only exposed to HFD starting at weaning.

2. Methods

2.1. Animals and diets

Animals were maintained in a 12 h/12 h light:dark cycle at 22 ± 2 °C with free access to food and water. Experiments were carried out in accordance with French (Directive 87/148, Ministère de l'Agriculture et de la Pêche) and