Journal of Neurochemistry

JOURNAL OF NEUROCHEMISTRY | 2018 | 145 | 358–361 doi: 10.1111/jnc.14334

EDITORIAL HIGHLIGHT

Maternal obesity reprograms offspring's executive brain centers in a sex-specific manner?

An Editorial for 'Perinatal high fat diet and early life methyl donor supplementation alter one carbon metabolism and DNA methylation in the brain' on page 362.

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Unhealthy dietary patterns in childhood have long been linked to increased risk of obesity, metabolic disorders, and poor mental health in adolescence, but recent studies suggest that child's health may be programmed already in its mother's uterus. The so called 'early-life reprogramming' concept considers maternal diet as an important predictor of offspring's permanent and sustained phenotypic consequences, such as increased risk of disease (Navarro *et al.* 2017). With the rapidly growing prevalence of obesity worldwide, over-nutrition and excess weight gain in pregnant women raise a genuine concern about the next generations' metabolic health. Currently, 20–60% of women gain more weight than recommended during pregnancy (Lindsay *et al.* 2018; Nunnery *et al.* 2018), resulting in increased risk of obesity and type-2 diabetes among their children (Alfaradhi and Ozanne 2011; Alfaradhi *et al.* 2016). More recently, this concept of transgenerational amplification of disease was extended to the neurological field. The central nervous system (CNS) undergoes an astonishingly rapid development during the perinatal stage when its vulnerability to environmental changes is high. Exposure of the developing fetus to an unfavorable environment may predispose the unborn child to reduced brain plasticity (Moody *et al.* 2017) and complex neurological disorders such as depression (O'Neil *et al.* 2014), autism, and attention deficit hyperactivity disorder (Andersen *et al.* 2017). Collectively, these findings demonstrate the importance of maternal diet in offspring development and also point to the potential of dietary manipulation in the perinatal period as a strategy for improving health outcomes in children.

Reprogramming a child's health by altering mother's dietary habits is further supported by epigenetic studies investigating the impact of diet on DNA methylation status. Methylation, the addition of a methyl group (H_3C) to DNA, typically on carbon 5 of the pyrimidine ring of cytosine, is an epigenetic modification that can be heritable and capable of affecting gene expression without affecting the underlying DNA sequence. In recent years, it has been recognized that epigenetic marks such as DNA methylation provide a strong mechanistic link between environment, nutrition, and disease (Anderson *et al.* 2012). Nutrition status, particularly micronutrient intake, regulates DNA methylation profile by affecting the availability of so-called methyl donors produced during the cyclical process of one-carbon metabolism. This metabolic pathway is dependent on availability of essential nutrients from the diet (e.g., folate, vitamin B12, choline, and betaine) and plays a crucial role in a variety of cellular process such as synthesis of nucleotides, production of methionine, and universal methyl donors, precursors of phospholipids, hormones, and neurotransmitters. Since several key enzymes in one-carbon metabolism are dependent on diet-derived

Received February 22, 2018; accepted March 1, 2018.

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Abbreviations used: CNS, central nervous system; HFD, high-fat diet; MDS, methyl-donor supplementation; PFC, prefrontal cortex; SAH, S-adenosyl-homocysteine; SAM, S-adenosyl-methionine; T2D, Type 2 Diabetes.

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micronutrient cofactors (Selhub 2002; Friso *et al.* 2017), deficiency or imbalance in these micronutrients can cause adverse effects on development, physiological health, cognition, and disease risk, at least in part through altered DNA methylation. Evidence from animal studies confirms that maternal over-nutrition or high-fat diet (HFD) feeding lowers circulating folate and micronutrient levels in offspring, leading to global alterations in DNA methylation status in the brain (Liu *et al.* 2015; Sullivan *et al.* 2017). Interestingly, these changes could be normalized or reversed by maternal or early-life methyl-donor supplementation, suggesting that prevention during early development may become an important strategy against epigenetically inherited traits.

The recent work of Reyes lab sheds new light on the adverse effects of maternal over-nutrition on physiological health of offspring and prevention by MDS. Using a maternal obesity model (dams fed 60%-fat diet), the authors have previously shown that the prefrontal cortex (PFC) – the brain's executive center, is vulnerable to alterations upon HFD feeding *in utero* (Vucetic *et al.* 2010, 2012; Carlin *et al.* 2013). The biochemical changes within the PFC of offspring from obese dams were associated with increased weight gain, altered motivation, and increased preference for sucrose in pups, suggesting that maternal obesity can reprogram offspring frontal lobe to an obesity-prone phenotype. McKee *et al.* (2017) and Carlin *et al.* (2013) further demonstrated that some of the PFC abnormalities in offspring can be normalized by pre- and postnatal dietary MDS. These findings confirmed that micronutrient availability alters the dynamic regulation of epigenetic changes in offspring brain. However, it was unclear whether early-life MDS restores the prefrontal function in offspring via direct effects on brain one-carbon metabolism and thereby affecting brain DNA methylation. In the recent study by McKee *et al.* (2018), the authors investigated whether early-life dietary MDS diet is sufficient to normalize the adverse effects of perinatal obesity on brain DNA methylation status as early as 6 weeks of age in male and female pups. Using a global methylation approach, McKee *et al.* (2018) demonstrated that perinatal HFD increased body weight and induced a robust DNA hypomethylation in the PFC of male offspring as early as 3 weeks of age. Early-life MDS was sufficient to restore the methylation status in male pups by 6 weeks of age, and this was associated with normalized levels of several folate intermediates and overall higher levels of methionine in the PFC. Interestingly, maternal HFD feeding did not affect global DNA methylation profile in the brains of female offspring at this age.

The interesting sexual dimorphism observed in response to maternal obesity is reminiscent of sex differences in other aspects of diet-induced obesity in rodents (Pettersson *et al.* 2012). It is not clear that such dimorphism should be expected to translate to humans; indeed, dietary effects on phenotype differ across mouse strains (Shockley *et al.* 2009). McKee *et al.* (2018) employed an interesting hybrid breeding (C57BL/6J dams × DBA/2J sires), and this could prove consequential. Parent-of-origin effects have been reported for insulin resistance, and inheritance patterns are consistent with epigenetic mechanisms (Hines *et al.* 2011). McKee *et al.* (2018) demonstrated via LC/MS that levels of methionine were boosted remarkably in the PFC of male offspring by MDS, while female methionine levels remained unchanged. Furthermore, postnatal MDS increased the levels of several folate intermediates in female offspring independently of maternal diet, and this response was somewhat blunted in male pups from HFD-fed dams. Collectively, McKee *et al.* (2018) demonstrate that male offspring may be more susceptible to early alterations in PFC one-carbon metabolism and DNA hypomethylation upon maternal obesity (see Fig. 1). Notably, female pups had increased levels of cofactors involved in DNA methylation (SAM/SAH) in response to perinatal HFD,

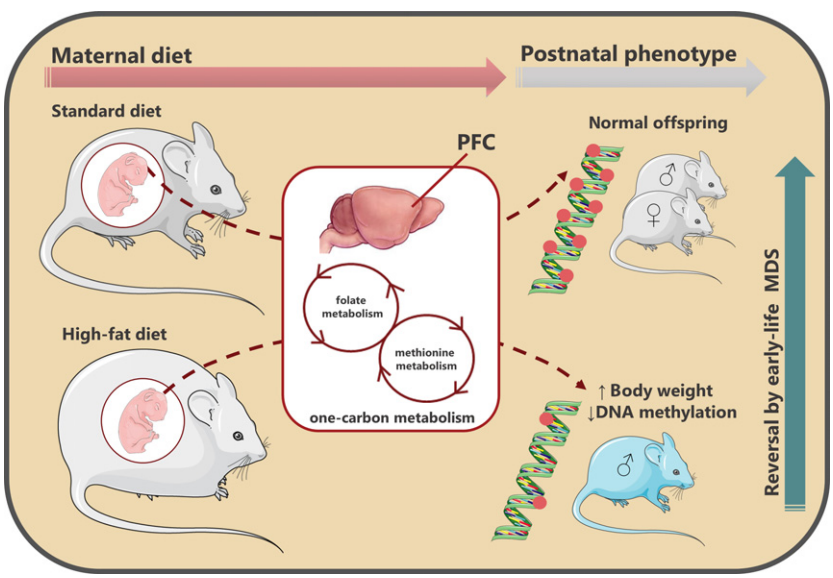

Fig. 1 Maternal high-fat diet feeding reprograms offspring prefrontal cortex (PFC) through alterations in brain one-carbon metabolism in a sex-specific manner. Increased weight gain and DNA hypomethylation profile induced by maternal over-nutrition can be normalized by early life (postnatal) methyl donor supplementation (MDS) in offspring.

suggesting a compensatory mechanism to maintain normal DNA methylation at this age. However, since maternal HFD feeding promoted weight gain in female offspring without affecting the PFC methylation status, it is likely that perinatal overfeeding affected other brain regions in these mice. For example, folate deprivation was previously shown to affect neurogenesis in murine hippocampus (Yang *et al.* 2016). More importantly for metabolism, a recent study demonstrated that maternal and postnatal HFD consumption reprograms energy balance and hypothalamic melanocortin signaling in non-human primate offspring (Sullivan *et al.* 2017). Thus, in combination with findings from McKee *et al.* (2018), further studies concerned with epigenetic propagation of metabolic disease and modulation by MDS may gain informative insights from investigating hypothalamic DNA methylation status in offspring. Furthermore, since the balance of fuel sources in maternal diet is known to affect offspring's glucose homeostasis in a sex- and stage-specific manner (Zambrano *et al.* 2006), the low-carbohydrate/high-fat concentrations in the maternal diet employed by McKee *et al.* (2018) may have an effect on the sex-dependent postnatal brain DNA methylation that are more complicated than simply maternal *over*-nutrition. Finally, a systemic identification of a cell population within the PFC, as well as gene-specific changes in DNA methylation, could further extend the work of McKee *et al.* (2018) on effects of perinatal HFD on brain one-carbon metabolism.

Altogether, the study by McKee *et al.* (2018) supports the notion that maternal diet and early-life MDS alter brain DNA methylation profile, and it demonstrates for the first time that these changes are associated with a dynamic and sex-dependent shift in brain one-carbon metabolism. Although the functional significance of altered one-carbon metabolism intermediates may prove difficult to interpret, the data point to an important impact of offspring sex on frontal-lobe DNA-methylation status, which ultimately may affect both the onset of phenotypic traits as well as responsiveness to early-life MDS intervention. Given the negative health outcomes of maternal overfeeding for childhood development, early-life dietary intervention may provide a means to correct undesirable sequelae that might otherwise contribute to lifelong mental and metabolic issues. And given the differences in maturity at birth between rodents and humans, it remains to be seen if postnatal intervention will be adequate in our own species.

Acknowledgments and conflict of interest disclosure

Steven W. Barger is an editor for Journal of Neurochemistry. Kaja Plucinska has no conflict of interest to disclose.

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