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Editorial

The Effect of Proteins in Maternal Diet on Fetal and Early Post-Natal Development of Food Intake Regulation in Hypothalamus (A Short Conversation)

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Altered fetal development of food intake regulatory system in hypothalamus can contribute to the etiology of obesity in later life. Both protein content and protein source in maternal diet during gestation and lactation affect hypothalamic development of food intake regulatory system in fetus and neonate.

Components of the central neural network for regulating food intake are present before birth in rodents and higher-order mammals [1-4]. The neuronal circuitry is not fully developed until 16 days after birth in rodents which is quite different from human and sheep [1,5,6]. In the rat, Neuropeptide Y (NPY) neurons first appear in the arcuate and dorsolateral hypothalamus at 14.5 days gestation [4,7,8] and thereafter, NPY mRNA expression rapidly increases between 2 and 15–16 days after birth and it returns to adult levels at approximately 30 days of age [1]. NPY receptors are present and functional at early life as evidenced by the observation that microinjection of NPY directly into the Paraventricular Nucleus (PVN) at 2 days after birth stimulates milk and water intake [9]. Moreover, vagal sensory information from the gastrointestinal tract relating to fullness may be an important factor in regulating food intake in the first week after birth since during this period is a relative dominance of NPY and alpha-melanocyte stimulating hormone (α-MSH) innervation of the PVN by efferents derived from the brain stem, rather than the arcuate nucleus [1]. However, NPY/Agouti-related peptide (AgRP) projections from the arcuate nucleus to the dorsomedial hypothalamic nucleus (DMN) are not complete until some 10–11 days after birth, and projections to the PVN do not fully develop until 15–16 days [1]. Peripheral leptin treatment at *day 10* after birth reduces NPY mRNA expression in the rostral arcuate nucleus. However, it has little impact on food intake, which is in compliance with the lack of NPY projections within the hypothalamus during the early postnatal period [10]. Pro-opiomelanocortin (POMC), AgRP, and Melanocortin-4 receptor (MC4R) mRNA are also all present in the hypothalamus in early postnatal period.

In rats, the perinatal period is a critical window for the programming of postnatal appetite [11]. Plagemann and colleagues reported that increased nutritional intake due to small litters induced hyperphagia and obesity combined with hyperleptinemia, hyperglycemia, hyperinsulinemia, and insulin resistance in rats that causes various alterations in hypothalamic structures, neuropeptide levels, neuronal activity and hormonal responsiveness [12-14]. It was associated with increased in NPY and galanin expression and decreased responsiveness to leptin, insulin and neuropeptides within neurons of the arcuate nucleus (ARC) and PVN [15-17]. Daily insulin treatment between 8 and 11 days after birth also results in a greater body weight gain, chronic hyperinsulinemia, impaired glucose tolerance, hypertension and also morphological alterations in hypothalamic structures that persist in adult life [18-20]. It supports the notion that perinatal hyperinsulinaemia confers malformation of hypothalamic structures.

Low protein diet fed throughout gestation and lactation provoked hypoinsulinemia, normal leptin concentrations, an increase in NPY levels in the arcuate nucleus, PVN and lateral hypothalamic area, and unchanged NPY levels in the ventro-

medial nucleus (VMN) [21]. Food intake of the offspring was not measured. It is consistent with the observation that offspring born to dams fed the soy protein-based diet had higher food intake after weaning, higher hypothalamic mRNA expressions of AgRP at weaning and relatively higher plasma concentrations of insulin in fetal period (day 20 gestation) compared with those from dams fed a casein-based diet [22].

Additionally, a low protein diet fed throughout gestation and lactation impairs hypothalamic mechanistic target of rapamycin (mTOR) activation in adult rat offspring. mTOR is involved in the control of feeding behavior by integrating hormonal and nutrient signals in the hypothalamus; therefore, regulating energy homeostasis systematically. Disruption or impairment in mTOR signaling caused by perinatal protein restriction may be a possible mechanism in the developmental programming of metabolic disorders.

Guzman-Quevedo *et al*. [23] found that adult rats born to dams fed a low protein diet during gestation and lactation exhibit enhanced activation of hypothalamic mTOR in the fed state as well as impaired mTOR responses to fasting and re-feeding from one hypothalamic nucleus to another. Protein restricted adult rats exhibited a decrease in number of phosphorylated rpS6 and pmTOR immunostained cells in the ventromedial nucleus of hypothalamus (VMH) and ARC but increased numbers of pmTOR immunopositive cells in the PVN under ad libitum feeding conditions. In controls, however, the phosphorylation of rpS6 and mTOR in the VMH decreased with fasting, whereas in malnourished rat offspring, fasting decreased the phosphorylation of mTOR in the PVN of the hypothalamic nucleus. No differences in the number of POMC/pmTOR co-labelled cells were found between control and malnourished rats in the fed state and both groups exhibited a significant decrease in the activation of mTOR in POMC expressing neurons in response to fasting, suggesting that early protein restriction may not alter the nutrient sensing function of mTOR in POMC neurons [23].

In conclusion, both protein content and protein source in maternal diet can alter the development of hypothalamic intake regulatory system and therefore influence the risk of obesity in later life. However, underlying mechanisms are still unclear and need further studies.

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