

Nutritional Research and Fetal Programming: Parental Nutrition Influences the Structure and Function of the Organs

Investigación Nutricional y Programación Fetal: La Nutrición Parental Influye en la Estructura y Función de los Órganos

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SUMMARY: Rodents are animals extensively used in biomedical and nutrition research, a necessary step before the research in humans. The composition and type of administration of the experimental diets are relevant and should be thought, considering each type of animal used in the research. It is particularly important to consider, among others, the metabolic differences between species and food needs in macro- and micronutrients to avoid possible bias. The American Institute of Nutrition (AIN) made recommendations for rodents, adapted to the period of growth (AIN-93G), which are pivotal in fetal programming studies. The experiments can be compared among different studies and better translated into humans, considering these limitations in the nutrition of parents and offspring. The review addresses different compositions of experimental food for rodents during development with the ability to induce fetal programming in the offspring and chronic diseases in adulthood due to the nutrition of the mother and father. The 'developmental origins of health and disease' (DOHaD) concept due to maternal nutrition is commented considering the protein restriction, vitamin D restriction, obesity, and intake of fructose or fish-oil. The 'paternal origins of health and disease transmission' (POHaD), because of the nutritional state of the father, were also analyzed in the review, primarily considering the obesity of the father. The review proposes some diet compositions to experimental research considering varied nutritional situations, hoping to assist young researchers or researchers not familiar with experimental diet manipulations in the elaboration of the projects.

KEY WORDS: Protein restriction; High-fat diet; High-fructose diet; Vitamin D restriction; Fish oil-rich diet.

INTRODUCTION

Although there are limitations of generalizing from an animal model to the condition of humans, animals can be useful to get information from a homogeneous group at the same stage of the disease, and free from other puzzling factors (Nevzorova *et al.*, 2020). Life conditions (embryology, anatomy, and physiology) between humans and other mammals might be relatively analogous, indicating the animals as potential models for experimentation (Lorberbaum *et al.*, 2020). An additional advantage of animal models, including nutritional research, is comparing appropriate controls, separating the effect of food intake from other metabolic effects by pair feeding, and the precise manipulation of the diet (Vianna *et al.*, 2016). Likewise, the short life span and genetic and environmental influences in animals can be controlled (Armitage *et al.*, 2004).

The review was thought as a basis for basic scientists focusing on models for epigenetic changes due to dietary manipulations to the mother or father and the consequent programming of diseases in the adulthood offspring (Gusmão-Correia *et al.*, 2012).

Dietary manipulations and rodent experiments. The diets offered to rodents should follow the American Institute of Nutrition (AIN-93G for growth, pregnancy, and lactation; AIN-93M for adult maintenance) to be nutritionally adequate (Reeves *et al.*, 1993).

The age ratio between animals and humans should be well determined for setting up models more analogous in age to humans to translate the findings to humans (Heindel,

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2019). We know that, after the sexual maturity (around two months old to mice) and puberty in humans, an amount of ten days in mice is linked to one year in humans. Thus, mature mice feeding an experimental diet for ten weeks might be generalized to eight years of experimentation in 30-year-old humans (Dutta & Sengupta, 2016).

The sex of animals should also be considered since fats tend to accumulate in the visceral depots in males but the subcutaneous depots of females. Sex hormones also induce an increase in the fat pads by modulating the distribution of estrogen receptors in the adipocytes (Ornellas *et al.*, 2013; Borges *et al.*, 2020). Hence, experimental manipulations might include alterations in the nutritional status of the pregnant and lactating female and the father.

MATERNAL DIETARY MANIPULATIONS

Epidemiological reports and experimental studies confirmed that the intrauterine environment has a meaningful and long-term influence on the developing fetus and the promotion of disease in later life (Barker, 1995).

The fetal programming is based on the maternal feeding status during pregnancy and lactation, and the resultant fetal and neonatal nutrition impact, which may cause developmental adaptations and the permanent change in the physiology and metabolism in the offspring (Barker, 1997). The fetal programming would be associated with epigenetic changes during early life (cytosine methylation of DNA, histone posttranslational modifications, and micro-RNAs), without changes in the DNA sequence (Waterland & Jirtle, 2004; Aagaard-Tillery *et al.*, 2008).

David Barker introduced the concept that maternal malnourishment and altered infant nutrition can permanently influence offspring metabolism and predispose progeny to the cardiovascular and metabolic diseases (Hales & Barker, 1992). There is an association between parents' nutrition and progeny health (Ravelli *et al.*, 1998; Brookheart & Duncan, 2016). Also, the metabolic programming of offspring because of maternal obesity increases the risk of developing major health complications (Ornellas *et al.*, 2015).

The 'Developmental Origins of Health and Disease' (DOHaD) concept helps us better understand the current situation. Epidemiological and experimental evidence indicates a connection between the early-life environment and the metabolic health in adulthood (Plagemann *et al.*, 2012). The 'thrifty phenotype' hypothesis proposed in the early 90s was essential for the DOHaD concept by catching the attention of the scientific community to the link between fetal and infant growth, and later life impaired glucose

tolerance in adulthood (Hales & Barker). The adverse nutritional environment in early life creates a situation in which the organism metabolically programmed to cope with low food availability fails to adapt to the energy-rich environment. Contrarily, precocious overnutrition is linked with increasing adipogenesis, eating behavior modification, and appetite control (Gluckman & Hanson, 2008).

Maternal nutritional restrictions

Protein. Table I provides examples of experimental diets, considering the background of the AIN-93G formulation. Control and protein restriction diets should be isocaloric, with differences only in protein content. The lipid supplied should guarantee the essential fatty acid amount. Just complex carbohydrates might be added in the form of starch to compensate for the difference in the energy mix, which would not bring any bias to the study. Also, it is necessary to maintain the same protein: lipid: carbohydrate ratio in the studies with a maternal protein restriction diet (Pinheiro *et al.*, 2008; Frantz *et al.*, 2011).

Maternal protein restriction in rodents might have consequences in offspring adulthood, as an increased susceptibility to obesity (Ozanne *et al.*, 2004; Zambrano *et al.*, 2006), hepatic peroxisome proliferator-activated receptors modifications (Lillycrop *et al.*, 2005), adipocytes with enhanced expression of 11-hydroxysteroid dehydrogenase type 1, increasing cortisol exposure, and adipocyte proliferation (Reynolds *et al.*, 2001). Also, the maternal protein restriction might affect male and female offspring differently, including differences in the nephron number, and arterial hypertension development (Woods *et al.*, 2005), with impairment of glomerulogenesis (Almeida & Mandarim-de-Lacerda, 2005a), and cardiac remodeling (Almeida & Mandarim-de-Lacerda, 2005b).

Vitamin D. Low vitamin D status and obesity have concomitantly reached epidemic levels worldwide, and research linking these two public health issues has grown extensively over the last years (Prasad & Kochhar, 2016; Savastano *et al.*, 2017).

Vitamin D is attained through endogenous production or diet, mainly as vitamin D₃ (Holick, 2007). In the liver, vitamin D becomes biologically active as 25-hydroxyvitamin D (25 (OH) D), in a first hydroxylation step catalyzed by four enzymes (CYP2R1, CYP27A1, CYP2J6, and CYP3A11) (Schuster, 2011). The second hydroxylation step occurs in the kidney, catalyzed by CYP2B1, then producing 1,25-dihydroxy vitamin D (1,25 (OH)₂ D), the active form of cholecalciferol, which is a potent activator of the vitamin D receptor (Carlberg & Muñoz, 2020). The 24-hydroxylase,

CYP24A1, catabolizes both 25 (OH) D and 1,25 (OH) 2 D, then generating inactive metabolites (Dusso, 2014).

In obese mice with constant vitamin D3 intake, there is a transient increase of total 25 (OH) D and a decrease of plasmatic vitamin D3 because of the upregulation of 25-hydroxylase genes in the liver. The adipose tissue modulates vitamin D metabolism. Therefore, when free 25 (OH) D is diminished, probably Cyp2r1 is the reason (since it is responsible for the production and storage of 25 (OH) D in the adipose tissue) (Bonnet *et al.*, 2019).

Maternal vitamin D restriction leads to the developmental programming of several features of the metabolic syndrome in offspring adulthood (Morris *et al.*, 1995), impairing the pancreas development and mature offspring (insulin-signaling pathway) (Maia-Ceciliano *et al.*, 2016). Besides, maternal vitamin D restriction relates to the glomerular retard maturation by prolonging the period of nephrogenesis (Nascimento *et al.*, 2012), leading to the disarray of pancreatic islet cytoarchitecture with effects on insulin production in the adult mice (Borges *et al.*, 2016).

The vitamin D restricted diet should be produced, thus, without vitamin D in the vitamin mixture (Table I). However, in experimental studies, both the control diet and the vitamin D restricted diet should be isocaloric (the only difference should be for vitamin D content), avoiding other biases.

Maternal obesity

Saturated fatty acid intake. Diet-induced obesity has been a model of obesity often used in mice with translational purposes (Fraulob *et al.*, 2010). Fetal exposure to maternal obesity might initiate a vicious cycle, transmitting metabolic disease across generations and thus exacerbating the epidemic of obesity (Catalano, 2003), which is particularly relevant because women have frequently gone into pregnancy in overweight or obese (Fisher *et al.*, 2013).

Overnutrition mimics the pathophysiology of mammalian obesity because of the excess intake of fat in rodent, including insulin resistance and hyperglycemia (Bringhenti *et al.*, 2013), hepatic and pancreatic fat accumulation (Gregorio *et al.*, 2010, 2013), and higher expression of lipogenic and reduced expression of beta-oxidation genes (Volpato *et al.*, 2012).

The intake of a high-fat diet by mother leads to the development of adult offspring hypercholesterolemia, higher adiposity, insulin resistance, and arterial hypertension (Samuelsson *et al.*, 2008). Besides, mice continuously exposed to the high-fat diet through pregnancy, lactation, and post-weaning to adulthood were more likely to develop features comparable to the human metabolic syndrome than mice fed a high-fat diet only post-weaning (Bruce *et al.*, 2009).

Table I. Diet examples of fetal programming studies (to feed mothers during pregnancy and lactation, or fathers). Vitamins and mineral mixes were formulated according to the American Institute of Nutrition AIN-93G for rodents. The protein restriction diet has 5% energy from protein; the high-fat diet has 49% energy from lipid, and the high-fructose diet has 45% of energy from fructose.

Ingredients (g/kg)	Experimental diets for fetal programming studies					
	Control	Protein restriction	High-Fat	High-Fructose	Vitamin D restriction	Fish oil
Casein (>85 % protein)	200.0	50.0	230.0	200.0	200.0	200.0
L-cystine	3.0	1.5	3.0	3.0	3.0	3.0
Cornstarch	529.486	680.986	299.472	85.486	529.486	529.486
Sucrose	100.0	100.0	100.0	100.0	100.0	100.0
Fructose	-	-	-	444.0	-	-
Soybean oil	70.0	70.0	70.0	70.0	70.0	7.0
Fish oil	-	-	-	-	-	63.0
Lard	-	-	200.0	-	-	-
Fiber	50.0	50.0	50.0	50.0	50.0	50.0
Vitamin mixture	10.0	10.0	10.0	10.0	10.0*	10.0
Mineral mixture	35.0	35.0	35.0	35.0	35.0	35.0
Choline bitartrate	2.5	2.5	2.5	2.5	2.5	2.5
Antioxidant	0.014	0.014	0.028	0.014	0.014	0.014
Total (g)	1000.0	1000.0	1000.0	1000.0	1000.0	1000.0
Energy (kcal/g)	3.95	3.95	4.95	3.95	3.95	3.95
Carbohydrate (%Energy)	64.0	78.0	32.0	64.0	64.0	64.0
Fructose (%Energy)	-	-	-	45.0	-	-
Protein (%Energy)	19.0	5.0	19.0	19.0	19.0	19.0
Lipid (%Energy)	17.0	17.0	49.0	17.0	17.0	17.0

* whitout vitamin D.

In late pregnancy and early postnatal life, the hypothalamus plasticity is vital in programming appetite, metabolism, and determine a body mass set-point (Keesey & Hirvonen, 1997). The neonatal exposure to a hypercaloric diet leads to a higher body mass in adulthood (Choi, 2018). Then, the hypothalamus is directly involved with obesity (Velloso, 2012), and the adult offspring of dams fed a high-fat diet showed exaggerated feeding response to neuropeptide Y, eating twice as much as control animals (Kozak *et al.*, 2000; Spezani *et al.*, 2020).

Maternal obesity affects male and female offspring differently, with males being more adversely affected than females (Ornellas *et al.*, 2013). Maternal obesity affects the developing fetus with acute hyperglycemia, initiating a beta-cell compensation, which progresses to beta-cell exhaustion, death, and beta-cell dysfunction, often co-presents with insulin resistance and type 2 diabetes mellitus (Cerf, 2015; Mandarim-de-Lacerda, 2019).

Fish oil intake. Fish oil is a source of n-3 polyunsaturated fatty acids (n-3 PUFA [alpha linolenic acid (LNA, 18:3 n3), eicosapentaenoic acid (EPA, 20:5 n3), and docosahexaenoic acid (DHA, 22:6 n3)].

Fish oil has a potent well-characterized hypolipidemic action, decreasing adiposity and serum lipids in mice (Bargut *et al.*, 2015, 2016a) and humans (Couet *et al.*, 1997). N-3 fatty acids, LNA, EPA, and DHA, are essential fatty acids with several health benefits (Bremer *et al.*, 2014). They form the structural component of cell membranes, affecting its fluidity, development, cognitive, and visual functions (Noakes *et al.*, 2012). Besides, n-3 PUFA causes a hypolipidemic effect related to the transcriptional factors that are significant regulators of the hepatic metabolism of lipids (peroxisome proliferator-activated receptors, sterol regulatory element-binding protein, and liver X receptor) (Jump, 2008).

EPA and DHA have multiple well-established health benefits, as anti-obesity (Bargut *et al.*, 2016b), antihypertensive (Medeiros *et al.*, 2005), and anti-inflammatory effects in white adipose tissue, diminishing markers of activation of mitogen-activated protein kinase, local renin-angiotensin system, and infiltration of macrophages (Bargut *et al.*, 2015). The high intake of long-chain n-3 PUFAs during pregnancy might reduce adult disease risks in rat offspring (Joshi *et al.*, 2003).

In experimental studies, the control diet and fish oil-enriched diet should be isocaloric, and their difference should only exist in the proportion of soybean oil and fish oil content (Table I). The soybean oil added to the diet could be

manipulated to compensate for the addition of fish oil and maintain the total amount of lipids in the fish oil diet.

Maternal fructose intake. Fructose has become a significant ingredient of the modern human diet, while it was almost absent in the diet until a few years ago, because of the low cost of fructose (corn syrup), which results from the processing of corn (Marshall & Kooi, 1957; Livesey & Taylor, 2008).

Converting doses of macronutrients between different species should consider the caloric intake. An adult mouse should have a daily intake of approximately 12 kcal, and around 2400 kcal for an adult human (Jang *et al.*, 2018). Consequently, 0.5 g/kg of fructose in mice corresponds to approximately 0.5 % of daily calorie intake, which is equivalent to a person to 3 g of fructose (Marriott *et al.*, 2009).

Exposure to high levels of fructose during critical periods of development might lead to obesity through the direct effect of fructose on adipose tissue and the developing hypothalamus, disrupting endocrine signaling between adipose tissue and hypothalamus (Goran *et al.*, 2013). Maternal high-fructose intake results in hyperinsulinemia at weaning and increased leptinemia in rodent offspring adulthood (Vickers *et al.*, 2011). Besides, the consumption of a high-fructose diet by the mother or father leads to adverse effects on liver metabolism in adult offspring. When both mother and father are fed the fructose diet, the adverse effects on the offspring are more severe (Carapeto *et al.*, 2018).

It is noteworthy to remark that high dietary fructose intake in rodents enhances plasmatic uric acid level, and simultaneously hyperuricemia and insulin resistance develop (Nakagawa *et al.*, 2006), then arterial hypertension and improved sympathetic nervous system activity and kidney sodium reabsorption (Magliano *et al.*, 2015).

In Table I, fructose was added in powder, and the complex carbohydrates were reduced to provide isocaloric diets, avoiding bias in the study. In fructose-rich diets, to change only one variable, it is possible to add an amount of fructose and removed the equivalent amount of cornstarch (Maia-Ceciliano *et al.*, 2019; Ornellas *et al.*, 2020). Studies that administer fructose in drinking water should consider that, in this case, control of the amount of fructose ingested is lost, which can make reproducibility and interpretation of results difficult.

PATERNAL DIETARY MANIPULATIONS. Mammals might have a non-genetic, intergenerational communication of metabolic changes in obesity from father to offspring (Ng

et al., 2010; Ornellas *et al.*, 2018). Data from animal models are progressively providing evidence that the spermatozoon is not a passive component in the development of the embryo, as well as paternal experiences preconception might affect the developing embryo and fetal uterine growth (Ornellas *et al.*, 2015, 2018).

The epigenetic information contained in the male gamete and transmitted to the zygote through copulation makes possible the paternal origin of health and disease transmission or POHaD, allowing the fetal programming induced by the obese father (Soubry, 2018). The phenotypic transmission is related to epigenetics, the mechanism that does not change the DNA structural sequence, but is transmissible and causes a reversible change in the gene expressions (McPherson *et al.*, 2014).

Moreover, the origin and transmission of paternally mediated pathologies to offspring might be related to the aberrant repair of spermatozoon DNA damage (Aitken *et al.*, 2004). The first step in this process requires imperfect chromatin remodeling through spermiogenesis resulting in spermatozoa released into the seminiferous tubules in an imperfect state and adverse compaction of chromatin. The defective chromatin remodeling increases the spermatozoa susceptibility to DNA strand breaks, mediated by oxidative stress, enhancing spermatozoon apoptosis and oxidative DNA damage. The oocyte presents a limited capacity to repair the oxidized DNA damage brought into the zygote by the fertilizing spermatozoon. Therefore, incomplete or aberrant repair of paternal DNA damage might generate mutations that will affect every cell in the body because it precedes the S phase in the first mitotic division (Aitken, 2004).

Male obesity negatively impacts the sperm molecular composition and function, decreasing the spermatozoa motility, count, usual morphology, ability to capacitate and bind to an oocyte, also increasing sperm reactive oxidative species-associated DNA damage, and mitochondrial dysfunction (Palmer *et al.*, 2012). Both obese humans and rodents might have enhanced oxidative spermatozoon DNA damage. Male obesity is multifactorial, with changes in DNA methylation and a range of post translational modifications affecting chromatin-associated proteins. Besides, sperm short non-coding RNAs (miRNAs) are a distinct subspecies sensitive to environmental adjustments, and obesity alters the profile in sperm. Once transferred into the zygote, miRNAs might cause embryonic epigenetic changes, thus altering fetus development (Dupont *et al.*, 2019).

The connection between paternal health and offspring outcomes seemed to be sex-dependent and have initially been

reported in epidemiological studies. Indeed, murine models have reinforced the hypothesis that paternal obesity could exert transgenerational and sex-specific effects on offspring health (Ornellas *et al.*, 2018). Besides, there is an association between paternal obesity and pancreatic beta-cell dysfunction without altering growth or adiposity in female rat offspring (Ng *et al.*). However, both sexes offspring of obese fathers are hyperglycemic, glucose intolerant, with high levels of total cholesterol and triacylglycerols, although obesity is not present (Tarevnic *et al.*, 2018).

FINAL REMARKS. In biomedical and nutrition research, rodents are regularly used even in fetal programming studies, as a vital step to cross before to research in humans. Thus, it is logical that the composition and type of administration of the diets are relevant and should be specified for the type of animal used in the research, such as metabolic differences between species and food needs in macro- and micronutrients. The AIN recommendations for rodents are adapted to the period of growth or maintenance of the mature animal, which is particularly significant in fetal programming studies. This review was prepared to assist young researchers or researches not familiar with nutritional manipulations in the elaboration of their projects.

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RESUMEN: Los roedores son animales utilizados frecuentemente en la investigación biomédica y nutricional, un paso necesario antes de la investigación en humanos. La composición y el tipo de administración de las dietas experimentales son relevantes y se debe considerar cada tipo de animal utilizado en los estudios. Es particularmente importante considerar las diferencias metabólicas entre las especies y las necesidades alimentarias de macro y micronutrientes para evitar posibles sesgos. El Instituto Americano de Nutrición (AIN) estableció recomendaciones para los roedores, adaptadas al período de crecimiento (AIN-93G), que son fundamentales en los estudios de programación fetal. Los experimentos se pueden comparar entre diferentes estudios y aplicar en humanos, considerando estas limitaciones en la nutrición de padres e hijos. La revisión aborda diferentes composiciones de ali-

mentos para estudios experimentales en roedores durante su desarrollo, con la capacidad de inducir programación fetal en la descendencia y enfermedades crónicas en la adultez, considerando la nutrición de los padres. El concepto de 'orígenes del desarrollo de la salud y la enfermedad' (DOHaD) debido a la nutrición materna se comenta considerando la restricción de proteínas, la restricción de vitamina D, la obesidad y la ingesta de fructosa o aceite de pescado. Los 'orígenes paternos de la salud y transmisión de enfermedades' (POHaD), debido al estado nutricional del padre, también fueron analizados considerando principalmente la obesidad del padre. La revisión propone algunas composiciones dietéticas a la investigación experimental considerando situaciones nutricionales variadas, con la esperanza de ayudar a jóvenes investigadores o investigadores no familiarizados con las manipulaciones experimentales de la dieta en la elaboración de los proyectos.

PALABRAS CLAVE: Restricción de proteínas; Dieta alta en grasas; Dieta rica en fructosa; Restricción de vitamina D; Dieta rica en aceite de pescado.

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