REVIEW

This paper is dedicated to the 70th anniversary of the founding
of Physiologia Bohemoslovaca (currently Physiological Research)

Parental Overnutrition by Carbohydrates in Developmental Origins of Metabolic Syndrome

Ondřej ŠEDA[1]

[1]Institute of Biology and Medical Genetics, the First Faculty of Medicine, Charles University and the General University Hospital, Prague, Czech Republic

Summary

Metabolic syndrome is a prevalent disease resulting from an interplay of genomic component and the exposome. Parental diet has been shown to affect offspring metabolic health via multiple epigenetic mechanisms. Excess carbohydrate intake is one of the driving forces of the obesity and metabolic syndrome pandemics. This review summarizes the evidence for the effects of maternal carbohydrate (fructose, sucrose, glucose) overnutrition on the modulation of metabolic syndrome components in the offspring. Despite substantial discrepancies in experimental design, common effects of maternal carbohydrate overnutrition include increased body weight and hepatic lipid content of the "programmed" offspring. However, the administration of sucrose to several rat models leads to apparently favorable metabolic outcomes. Moreover, there is evidence for the role of genomic background in modulating the metabolic programming effect in the form of nutri-epigenomic interaction. Comprehensive, robust studies are needed to resolve the temporal, sex-specific, genetic, epigenetic and nutritional aspects of parental overnutrition in the intergenerational and transgenerational pathogenesis of metabolic syndrome.

Corresponding author

Ondřej Šeda, Institute of Biology and Medical Genetics, First Faculty of Medicine, Charles University, Albertov 4, 12800 Prague 2, Czech Republic. E-mail: oseda@lf1.cuni.cz

Metabolic syndrome

Many epidemiological and clinical studies show consistent correlations between anthropometric parameters (obesity, visceral storage of body fat), metabolic markers (increased triacylglycerol concentration, hyperinsulinemia, glucose intolerance, low HDL cholesterol levels), and hemodynamic dysregulations (Kesaniemi *et al.* 1992). Finding that non-obese hypertensive individuals show more marked insulin resistance compared to non-obese normotensive subjects led Reaven (1988) to the introduction of the term "metabolic syndrome X." According to its original definition, the main components of metabolic syndrome (MetS) were: glucose intolerance, resistance to insulin-stimulated glucose uptake, hyperinsulinemia, hypertriglyceridemia, and hypertension. Over time, other conditions have been proposed as part of the metabolic syndrome including obesity, microalbuminuria (Palaniappan *et al.* 2003), hyperuricemia (Yanai *et al.* 2021), coagulation disorders (Meigs 2000) or increase in serum gamma-glutamyl transferase (Godsland *et al.* 2005). So far, a number of definitions of metabolic syndrome have been proposed by different professional organizations. Among the most commonly used are the National Cholesterol Education Program's definitions Adult Treatment Panel III report (Grundy *et al.* 2004), WHO definition (Alberti and Zimmet 1998), and the worldwide consensus definition of International Diabetes Federation (Alberti *et al.* 2006). The latter definition introduces geoethnically specific criteria for assessing individual thresholds for the components of metabolic syndrome. Despite some differences between

these definitions, resulting from the emphasis on either insulin resistance or obesity, there exists a considerable overlap between those diagnosed with metabolic syndrome by any of the criteria.

In this context, the debate whether metabolic syndrome per se constitutes a separate nosological unit and if its diagnosis somehow contributes to therapeutic decision-making compared to the consideration of individual findings has been long underway (Kahn *et al.* 2005). There is a considerable effort to transform the binary MetS into a continuous indicator using different MetS scores that should allow finer resolution for assessing MetS-conveyed risks, particularly that of type 2 diabetes and cardiovascular disease (DeBoer and Gurka, 2017). The prevalence of MetS is on the rise worldwide, affecting over 25 % of the general population in westernized countries but also reaching "double-digit" percentages in developing regions, including sub-Saharan Africa (Jaspers Faijer-Westerink *et al.* 2020), Asia, or South America (Saklayen, 2018). In terms of its pathogenesis, metabolic syndrome is a cluster of multifactorial traits as each of its components has both substantial heritable component, which interacts with forces of the exposome, i.e., the totality of environmental exposures (Vermeulen *et al.* 2020). The dynamic nature of the gene-environmental architecture of MetS and its features was described both in humans and experimental model systems (Hamet *et al.* 2005, Seda *et al.* 2005).

Complexity (dimensionality) reduction approaches in metabolic syndrome

The detailed dissection of the intertwined network of genes and environmental factors (i.e., the ecogenomic architecture) of most complex conditions, including MetS, is complicated in general human populations for apparent reasons. Therefore, several approaches aimed at reducing the inherent complexity are being employed to elucidate the underlying mechanisms. For instance, genetically heterogeneous, complex metabolic and cardiovascular traits may need to be subdivided into clinically and genetically distinct subsets (Zak *et al.* 2014) to analyze their genomic architecture successfully. Another level of reduction involves the use of genetically designed experimental models. The use of mice and rats as experimental models has several advantages over many other possible complexity reduction approaches because of the physiological, anatomical, and genomic similarities between rodents and

humans and the wealth of scientific data already available in these species (Aitman *et al.* 2016). Inbred animal strains are often used, representing genetically identical animals within one strain and gender, overcoming thus the genetic heterogeneity present in human cohorts (Sedova *et al.* 2000). Targeted manipulation of the rodent genome allows assessing the importance of particular genomic regions or gene variants in the pathogenesis of metabolic syndrome (Shamansurova *et al.* 2016, Sedova *et al.* 2021, Seda *et al.* 2002). Additional advantages include selective mating, relatively short generation time, and the possibility of standardization and specific manipulation of environmental conditions (e.g., diet, temperature, day/light regimen). Although the experimental findings are not directly transferable to the human situation and need to be validated (Seda *et al.* 2017), significant insights have been obtained through integrative and comparative genomics (Aitman *et al.* 2016). While rodent models represent the most common choice of experimental models for developmental origins of health and disease (DOHAD), other animal models systems are used to address specific questions based on physiological similarities of development (e.g., the sheep and non-human primates as models for developmental origins of polycystic ovary syndrome, Dumesic *et al.* 2020).

Developmental origins of adult disease and metabolic syndrome.

The "Thrifty Phenotype Hypothesis" (Hales and Barker 1992) perceives MetS in adults with a history of fetal malnutrition due to the predictive-adaptive strategies adopted by the fetus to maximize its chances of postnatal survival. Several other factors were identified as potential epigenetic modulators of cardiovascular disease, including maternal stress, maternal and early offspring nutrition, maternal smoking and alcohol abuse, litter size in rodent studies, etc. Despite considerable evidence for the developmental plasticity involvement in adult disease (Fleming *et al.* 2018), our understanding of the mechanisms underlying this process is still incomplete; an authoritative account of the current knowledge on DOHAD in metabolic disease was recently published (Hoffman *et al.* 2021). While the original DOHAD studies focused on malnutrition and placental-induced intrauterine growth restriction leading to catch-up growth and development of MetS features in adulthood in the affected offspring, maternal overnutrition seems to pose

detrimental effects in this regard as well, suggesting a "U-shaped" pattern of risk. It was recently shown in a meta-analysis of 79 studies that pre-conception maternal obesity increases the odds of child obesity by 264 % (Heslehurst *et al.* 2019). Maternal obesity is associated with a substantially higher risk of gestational diabetes mellitus, which in turn is associated with childhood increased adiposity (Lowe *et al.* 2019), impaired glucose tolerance, and high blood pressure (Tam *et al.* 2017). Furthermore, at least some of the effects of maternal obesity on offspring's metabolic dysfunction seem to be sex-specific (Dearden *et al.* 2018, Nicholas *et al.* 2020), concurring with the described sex-specific genome-environmental architecture of MetS and its components (Seda *et al.* 2008, Ohkuma *et al.* 2020).

Epigenetic and genetic aspects of developmental origins of adult disease

The current understanding of the mechanisms, how the imbalanced prenatal environment triggers lasting changes in the exposed offspring involves modulation of gene expression by epigenetic cues (DNA methylation, histone acetylation, chromatin remodeling, small RNAs, particularly microRNAs and tRNA-derived fragments), and a detailed account on the molecular level and the current understanding of their trans- and inter-generational inheritance is beyond the scope of this review (for details, see the recent accounts of the topic (Hoffman *et al.* 2021, Galan *et al.* 2020)). Interestingly, there is a tighter interaction between epigenomic and genomic components in the pathogenetic process as some of the outcomes of epigenomic modulations depend on the genomic constitution (Pausova *et al.* 2003, Buresova *et al.* 2006, Skolnikova *et al.* 2020b). If proven true, the thrifty gene x thrifty phenotype (nature x nurture) dichotomy may eventually dissolve as these seemingly incompatible concepts can be integrated within a unifying gene-by-environmental network (Li *et al.* 2019). Utilizing many inbred, genetically distinct experimental rat strains may allow modeling, in a limited yet supervised fashion, the genetic diversity within the DOHAD. At the same time, this approach allows studying the epigenome modifications within genetically identical animals, i.e., in standardized genomic and environmental setup. In humans, the recent attempts to gauge the effect of genetic factors in DOHAD, e.g., using the Mendelian randomization approach (Moen *et al.* 2020), have been complicated by the inherent complexity mentioned earlier and by the methodological issues (D'Urso *et al.* 2021).

Microbiome importance in developmental origins of adult disease

Maternal microbiota contribute significantly to the initial microbial colonization of the neonate, with both short- and long-term impact (Calatayud *et al.* 2019). While there is ample evidence for nutritional modulation of microbiota (reviewed by Moszak et al. 2020), a detailed assessment of associations between maternal and offspring microbiome in connection to specific dietary regimens during pregnancy is missing. Most DOHAD studies do not involve metagenomic analyses assessing the microbial diversity aspects of early-life perturbations. The associations between the early gut microbiome and DOHAD were recently comprehensively reviewed (Sarkar *et al.* 2021).

Paternal overnutrition

While the potential effects of paternal environmental exposures and lifestyle in terms of programming the metabolic dysfunction of offspring have received less attention so far, an increasing body of evidence led to the establishment of the Paternal Origins of Health and Disease paradigm (Soubry, 2018). Sharp and Lawlor (2019) recently identified 47 studies showing a link between paternal adiposity (including BMI and high-fat diet-induced obesity) and obesity- or type 2 diabetes-related offspring outcomes, including birth weight, body fat, BMI, and obesity-related gene expression. However, the authors concluded that despite the accumulating data, more targeted research is needed to provide more robust causal evidence. Bodden et al. (2020) recently summarized the existing literature on diet-induced modification of sperm epigenome and its programming effect on offspring's metabolism, including the possible responsible mechanisms. These include diet-induced alterations in seminal plasma, qualitative and quantitative changes in sperm microRNAs, transfer RNA-derived small RNAs, long non-coding RNAs, oxidative-stress-induced sperm DNA damage or reduced sperm mitochondrial function. All the so far performed studies of paternal overnutrition involved high-fat or mixed high-fat, high-sucrose diets, i.e., none involved diets enriched by carbohydrates only. So, the following section is focused only on maternal carbohydrate overnutrition.

Maternal carbohydrate overnutrition

The recent rise of increased carbohydrate intake

is often related to the utilization of sucrose and high fructose corn syrup (HFCS) as sweeteners in soft drinks and processed foods (Sloboda *et al.* 2014). According to the available data, the use of HFCS increased over last several decades by over 1000 % in spite of its clear connection to the pathogenesis of MetS and related metabolic complications (Hannou *et al.* 2018). Moreover, it was shown recently that feeding fructose drives an increase in the surface area of the gut that is associated with enhanced absorption of dietary nutrients and weight gain (Taylor *et al.* 2021). As evident from Tables 1-3, the studies on maternal carbohydrate overnutrition differ in many aspects making their comparison complicated. First, they include several distinct approaches in terms of overnutrition timing: from the most prolonged periods encompassing month prior conception till weaning of offspring to selected critical windows (Kunes *et al.* 2015) only, most commonly gestation or lactation. Second, both

Table 1. Maternal fructose overnutrition studies.

Organism	Strain	Maternal fructose overnutrition	Overnutrition timing	Offspring age	MetS-related offspring effect	Affected generation	Reference
Mouse	C57BL/6	Liquid 20 % w/v	Gestation → Weaning	P210	M,F: BW ↑, Liv TG ↑, AST ↑, TG ↑, TC ↑, Glu ↑, SBP ↑	F1	(Koo *et al.* 2021)
				P240	activation of renin-angiotensin-aldosterone system	F1-F4	(Seong *et al.* 2019)
Rat	SD	Liquid 10 % w/v	Gestation	P0	TG ↓, Liv TG ↑	F1	(Rodriguez *et al.* 2013)
				P90	M: Lep ↑, Adiponectin ↑, FPI ↑; F: FPI ↓		(Rodriguez *et al.* 2015)
				P261	M: HDL-C ↑; F: TC ↓		(Rodrigo *et al.* 2018)
		Liquid 20 % w/v	12 weeks pre-conception → weaning	P21	FPG ↑, FINS ↑, HOMA-IR ↑, TG ↑, NEFA ↑, LivTG ↑		(Yuruk and Nergiz-Unal, 2017)
					Body fat ↑, Leptin ↓		(Kisioglu and Nergiz-Unal, 2020)
		Solid (50 % w/w)	2 weeks pre-conception → birth	P0, P22	M/F: Glu ↑ at P0		(Jen *et al.* 1991)
			Gestation → Weaning	P87	M,F: BW ↑, Adiposity ↑, TG ↑, TC ↑, FPG ↑, FINS ↑, Lep ↑, Adiponectin ↓		(Tobar-Bernal *et al.* 2021)
		Solid (60 % w/w)		P84	M: SBP ↑		(Tain *et al.* 2015), (Tain *et al.* 2018)
	Wistar	Liquid, 20 cal% fructose	Gestation → P10	P10	M: BW ↑, Glu ↓, Ins ↓ F: BW ↑, Ins ↓, Lep ↑		(Vickers *et al.* 2011)
		Crystalline, 20 cal% fructose			M: ALP ↑; M,F: TP ↓; M,F: LivTG ↑		(Clayton *et al.* 2015)

SD: Sprague Dawley rat, P: postnatal day, M: male, F: female, BW: bodyweight, LivTG: Liver triacyglycerols, AST: Aspartate aminotransferase, TG: triacylglycerols, TC: total cholesterol, Glu: glycemia, SBP: systolic blood pressure, Lep: leptin, FPI: fasting plasma insulin, HDL-C: high-density lipoprotein cholesterol, FPG: fasting plasma glucose, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, NEFA: non-esterified free acids, Ins: insulin, ALP: alkaline phosphatase, TP: total protein, F1-F4: filial generation 1-4.

Table 2. Maternal sucrose overnutrition studies.

Organism	Strain	Maternal sucrose overnutrition	Overnutrition timing	Offspring age	MetS-related offspring effect	Gene-ration	Reference
Rat	BHE	Solid diet with 65% sucrose	Gestation	P142	M: TG ↓, Ins ↓	F1	(Berdanier, 1975)
			Lactation		M: TG ↓,BW gain ↓		
			Gestation→Weaning		M: TG ↓, Liv lip ↑, Ins ↓		
	SD	Solid diet with 50% sucrose	2 weeks pre-conception → birth	P0, P22	M/F: Glu ↑ at P0		(Jen et al. 1991)
	PD	Solid, 70 cal%	Gestation→Weaning	P0, P21, P140	M(P0): Glu ↓; M(P21): BW ↑, Adiponectin ↑; M (P140): Adiposity ↑, LDL-C ↑, Adiponectin ↑		(Sedova et al. 2007)
	SHR, SHR.PD^{Zbtb16}			P180	M: BAT ↑, LDL-C ↓		(Skolnikova et al. 2020a)
					M$_{SHR}$: BAT ↑, FPG ↓, HDL-C ↑ M$_{SHR.PD}$: BAT ↑, FINS↑, HDL-C ↑	F2	(Skolnikova et al. 2020c)
	Wistar	Liquid 10 % w/v	Gestation→Weaning	P21, P84	Hepatic Srebp1c expression ↑	F1	(Kaur et al. 2018)
			4 weeks pre-conception → birth	P60-P90	M,F: no effect		(Kendig et al. 2015)
			4 weeks pre-conception → weaning	P21, P84	F(P21):Adiposity↑; Glu↓; M(P21): Adiposity ↑; Glu ↓, TG ↓; M(P84): Adiposity ↓; FFA ↑; F(P84): Adiposity ↓		(Toop et al. 2017)
			4 weeks pre-conception → birth		M(P21): Glu ↓, TG ↓, HDL-C ↑; F(P21): Glu ↓, HDLC ↑ M(P84): Adiposity ↓; FFA ↑; F(P84): Adiposity ↓		
			4 weeks pre-conception + lactation		M(P21): TG ↑, HDL-C ↓; F(P21): Glu ↓; M(P84): FFA ↑; F(P84): Adiposity ↓		
	N.A.	Liquid 10 % w/v	N.A.	N.A.	BW ↑		(Ozkan et al. 2019)
		20 % w/v			BW ↑, Glu ↑, Ins ↑		
		30 % w/v			BW ↑, Glu ↑, Ins ↑		
	SD	Liquid 20 % w/v	12 weeks pre-conception → weaning	P21	TG ↑, NEFA ↑, Liv TG ↑		(Yuruk and Nergiz-Unal, 2017)
					Body fat ↑		(Kisioglu and Nergiz-Unal, 2020)

Table 2. Maternal sucrose overnutrition studies. (Continued)

Organism	Strain	Maternal sucrose overnutrition	Overnutrition timing	Offspring age	MetS-related offspring effect	Gene-ration	Reference
	SD	Liquid 20 % w/v	Gestation	P14, P180	BW ↑		(Bocarsly *et al.* 2012)
				P30, P60	BW ↑, brain weight ↓		(Kuang *et al.* 2014)
				P150	M: BW↑, FPG ↑		(Gu *et al.* 2017)
				P150	M: Ang II-mediated oressir response and vessel tone ↑		(Wu *et al.* 2014)
				P180	M: GT ↓, LI area↑		(Zhang *et al.* 2018)
				P540	M: BW ↑, FINS↑, HOMA-IR ↑, oxidative stress ↑		(He *et al.* 2017)
				P660	SBP↑, DBP↑, MAP↑		(Wu *et al.* 2016)

BHE: Bureau of Home Economics rat strain, SD: Sprague Dawley rat, PD: polydactylous rat strain, SHR: spontaneously hypertensive strain, P: postnatal day, N.A.: not available, M: male, F: female, TG: triacylglycerols, Ins: insulin, BW: bodyweight, Liv lip: Liver lipids, Glu: glycemia, LDL-C: low-density lipoprotein cholesterol, BAT: brown adipose tissue, FPG: fasting plasma glucose, HDL-C: high-density lipoprotein cholesterol, FPI: fasting plasma insulin, FFA: free fatty acids, NEFA: non-esterified free acids, Liv TG: liver triacylglycerols, AngII: angiotensin II, GT: glucose tolerance, LI: Langerhans islets, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial blood pressure. TP: total protein, F1-F2: filial generation 1-2.

ways of administering excess carbohydrates, i.e., in liquid and solid form, have been used in the annotated metabolic programming studies (Tables 1-3). There is currently no consensus on the optimal approach regarding its translational relevance to human conditions, as recently discussed by Eng and Estall (2021). Even though studies directly comparing the liquid and solid administration of fructose or sucrose in the same model under the same protocol are not available, it seems that the effects concerning the manifestation of MetS attributes in programmed offspring are similar. Third, different rodent strains are used, though Sprague-Dawley and Wistar rat strains seem to be the most common models for maternal carbohydrate overnutrition. As mentioned above, the genomic background upon which the nutri-epigenomic stimuli are acting can modify the ultimate programming effect. In almost all studies, only the intergenerational effects targeting directly F1 generation are studied. In a set of experiments, it has been shown that sucrose feeding of rat dams of two inbred strains affects two subsequent generations of male offspring (F1, F2) with similar outcomes, including the increase of brown fat adipose tissue depots and similar shifts in lipid profile (Skolnikova *et al.* 2020c, Skolnikova *et al.* 2020a). In the only truly transgenerational inheritance study, Seong *et al.* (2019) showed that administration of 20% fructose in drinking water induced multigenerational (down to F4) activation of the renin-angiotensin-aldosterone system as well as sodium transporters, leading to increased oxidative stress factors and inflammatory cytokines (Seong *et al.* 2019). Only two studies assessed, within a complex study design, specific overnutrition by administration of 10% glucose in the drinking water during the gestation of SD rats only (Table 3). The three-month-old male progeny showed increased adiponectin and lower fasting plasma insulin (Rodriguez *et al.* 2015), and the offspring of both sexes had decreased liver cholesterol (Rodrigo *et al.* 2018).

Despite the described discrepancies in experimental design, several common effects are observable. For instance, in the offspring of fructose and sucrose-fed mothers, increase of body weight is often present, particularly if the exposition encompassed both gestation and complete lactation periods. A possible mechanism recently suggested based on results from

Table 3. Maternal glucose overnutrition studies.

Organism	Strain	Maternal glucose overnutrition	Overnutrition timing	Offspring age	MetS-related offspring effect	Affected generation	Reference
Rat	SD	Liquid 10 % w/v	Gestation	P90	M: Adiponectin ↑, F: FPI ↓	F1	(Rodriguez *et al.* 2015)
Rat	SD	Liquid 10 % w/v	Gestation	P261	M,F: Liv C ↓	F1	(Rodrigo *et al.* 2018)

SD: Sprague Dawley rat, P: postnatal day, M: male, F: female, FPI: fasting plasma insulin, Liv C: liver cholesterol, F1: filial generation 1.

EPOCH cohort involved early insulin hypersecretion as a major contributing process in the development of childhood obesity in children exposed to maternal overnutrition (Perng *et al.* 2021). This is corroborated by increased offspring insulinemia found in the same experiments (Table 1). Increased hepatic triacylglycerol content of the programmed offspring is the second most common finding in the fructose maternal overfeeding studies. It was shown that the fetal liver and hepatic mitochondrial function are particularly susceptible to dysregulated maternal fuel metabolism and increased hepatic lipid stores, disrupted mitochondria, and elevated oxidative stress ensue, eventually leading to non-alcoholic fatty liver disease, which is in turn tightly interconnected with MetS (Baker and Friedman, 2018). The administration of sucrose in the form of a solid diet or 10% solution to rat dams of several different rat models led, surprisingly, to apparently favorable metabolic changes, including a decrease in glycemia, triacylglycerols or LDL-cholesterol or increase of HDL-cholesterol. Glucose overfeeding solely during gestation formed part of only two studies (Table 3). Consistent with the different metabolic effects of postnatal administration of glucose vs. fructose (Softic *et al.* 2017), the offspring showed dissimilarities concerning the effects on circulating and tissue stores of lipids.

In conclusion, maternal carbohydrate overnutrition leads, in numerous rodent models and different overnutrition timing schemes, to substantial alterations of the metabolic profile of the offspring and often results in the manifestation of MetS or its individual components. Nevertheless, the effect of the metabolic programming by carbohydrates is clearly dependent on multiple factors, including the genomic background it acts upon, and in specific combinations, it may result even in metabolically favorable outcomes. Whether these observations represent the proposed predictive-adaptive responses due to mismatch of pre- and postnatal environments (Gluckman *et al.* 2019), or strain-specific, nutri-epigenomic interactions remains to be elucidated by conducting rigorous, full-factorial studies.

Conflict of Interest
There is no conflict of interest.

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