Journal of Developmental Origins of Health and Disease (2016), **7**(3), 222–230.

doi:10.1017/S2040174415007187
Themed Issue: Ibero-American DOHaD Society

REVIEW

The fetal programming of food preferences: current clinical and experimental evidence

R. Dalle Molle[1†], A. R. Bischoff[2†], A. K. Portella[3] and P. P. Silveira[1,2*]

[1]*Departamento de Pediatria, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil*
[2]*Programa de Residência Médica em Pediatria, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil*
[3]*Departamento de Pediatria da Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil*

Increased energy consumption is one of the major factors implicated in the epidemic of obesity. There is compelling evidence, both clinical and experimental, that fetal paucity of nutrients may have programming effects on feeding preferences and behaviors that can contribute to the development of diseases. Clinical studies in different age groups show that individuals born small for their gestational age (SGA) have preferences towards highly caloric foods such as carbohydrates and fats. Some studies have also shown altered eating behaviors in SGA children. Despite an apparent discrepancy in different age groups, all studies seem to converge to an increased intake of palatable foods in SGA individuals. Small nutrient imbalances across lifespan increase the risk of noncommunicable diseases in adult life. Homeostatic factors such as altered responses to leptin and insulin and alterations in neuropeptides associated with appetite and satiety are likely involved. Imbalances between homeostatic and hedonic signaling are another proposed mechanism, with the mesocorticolimbic dopaminergic pathway having differential reward and pleasure responses when facing palatable foods. Early exposure to undernutrition also programs hypothalamic–pituitary–adrenal axis, with SGA having higher levels of cortisol in different ages, leading to chronic hyperactivity of this neuroendocrine axis. This review summarizes the clinical and experimental evidence related to fetal programming of feeding preferences by SGA.

Received 18 June 2015; Revised 28 August 2015; Accepted 31 August 2015; First published online 28 September 2015

Key words: feeding behavior, fetal programming, food preferences, IUGR

Introduction

In one of his latest writings, David Barker said 'The more limited a baby's resources are, the more economical in resource allocation, or thrifty, it may have to be. But, this seems to predispose it to disease in later life, especially if it encounters stressors along the way. This predisposition could reflect reduced functional capacity or altered metabolic settings and hormonal responses. The fundamental biological reasons why thrift initiates disease are not known. A thrifty strategy is likely to affect more than one organ or system whose critical periods occur around the same time'.[1] We have spent the last few years exploring the idea that the thrifty strategy spreads out beyond the functioning of organs and systems and can, in fact, be recognized in behavioral characteristics. Avid for energy, thrifty phenotype individuals not only exercise less[2–4] and eat more food in general,[5,6] but have specific food preferences towards highly caloric, highly palatable foods.[7,8]

Increased energy consumption, especially due to high intake of palatable (sugar/fat) energy-dense food, is one of the main contributors to the escalating rates in overweight and obesity globally.[9,10] Although appetite and the homeostatic control of energy intake/expenditure is a major determinant of caloric intake, ingestive responses are significantly mediated by hedonic mechanisms (i.e. pleasure associated with the intake of a palatable food), food preferences and social behavior. The two systems interact with each other. The close proximity between the hypothalamic arcuate nucleus and the median eminence allows this structure to detect changes in peripheral signals, such as glucose and lipids. This information is processed within the hypothalamus,[11–15] but signals are also sent to regions such as the ventral tegmentar area (VTA),[16,17] nucleus accumbens (NAc)[18] and prefrontal cortex (PFC).[19] In return, the NAc, VTA and PFC project back to the hypothalamus[20–22] to regulate neurochemical signaling.

In this review, we synthesize current clinical and experimental evidence demonstrating that the fetal exposure to a paucity of nutritional resources affects the offspring's food preferences in different ages and that programming of these preferences may contribute to the development of metabolic disturbances later in life. We used PubMed (inception to April 2015) database for the search and combined two sets of keywords. Group 1 of keywords: 'low birth weight', 'intrauterine growth restriction', 'small for gestational age' and 'intrauterine growth retardation'. Group 2 of keywords: 'feeding preferences', 'food preferences', 'food intake', 'eating behavior', 'feeding behavior', 'overweight' and 'obesity'. After the search, titles and abstracts were reviewed. Full text articles of relevant abstracts were retrieved and studied in detail. Next, all references of the articles selected were carefully reviewed

*Address for Correspondence: P. P. Silveira, Departamento de Pediatria, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul. Ramiro Barcelos, 2350, Largo Eduardo Zaccaro Faraco, 90035-903 Porto Alegre, Brazil. (Email 00032386@ufrgs.br)
† These two authors contributed equally to the work.

to find any other possible study to be included. A last search using the name of authors of the articles that meet the inclusion criteria was performed to amplify the findings. No limit for data was established. We selected articles written in English, Portuguese or Spanish. We limited this review to articles involving alteration in food preferences toward specific types of foods or regarding peculiar feeding behaviors, not to appetite or hyperphagia. While both 'programming of appetite' and 'programming of food preferences' may be occurring in low birth weight individuals, they refer to very different phenomena. The programming of appetite has to deal with hyperphagia in general (increased caloric intake, mainly related to hypothalamic function). Programming of food preferences refers to food choices (energy dense, unhealthy food, palatable food, etc.) and its neural basis rely on mesocorticolimbic structures.

Clinical evidence

The first studies to show evidences for the fetal programming of food preferences were performed in adults. Barbieri *et al.* demonstrated a higher intake of carbohydrate in young women born with severe intrauterine growth restriction (IUGR). There was also a preference for carbohydrate over protein in the severely growth restricted group. The waist/hip ratio was also larger in IUGR in this sample.[23]

Studies regarding famine exposure have also shown an increased body mass index in adult life. Stein *et al.* conducted a study comparing adults whose mothers were exposed to the Dutch famine with their siblings (pregnancies not exposed to the famine) and controls whose mothers were not exposed to the famine. There was a positive association of famine exposure with higher energy intake, higher fat density on their diets, lower physical activity and higher predicted energy expenditure.[24] In addition, Lussana *et al.*[25] revealed that those exposed to the famine in early gestation were twice as likely to consume a high-fat diet at 58 years of age.

Perala *et al.* aimed at verifying if ponderal index (PI) at birth (weight [kg]/length [m^3]), birth weight and length, were associated with food and macronutrient intake in adult life. It was demonstrated that a small size at birth (considering birth weight and/or PI) was associated with a lower consumption of fruits, berries, rye and rye products in adults of 56–70 years old. There was also a positive correlation of small size at birth and increased consumption of fats, as well as a lower intake of carbohydrates, sucrose, fructose and fiber. There was a stronger correlation between PI at birth than between birth weight and macronutrient intake in adulthood. Birth length did not associate significantly with food intake.[26]

Kaseva *et al.* analyzed a sample of young adults aged 19–27 years born with very low birth weight (VLBW) ($\leqslant$1500 g) to evaluate if there were differences in food and nutrient intake that could explain an increased risk for noncommunicable diseases such as osteoporosis, impaired glucose regulation and cardiovascular diseases. VLBW showed markedly reduced consumption of vegetables, fruits, berries, milk products and low-fat dairy products when compared with controls. There was also a higher intake of polyunsaturated fatty acids and essential fatty acids. Vitamin D, calcium, zinc, iodide and magnesium intakes were lower among the VLBW. These dietary differences could partially explain the increased risk of chronic adult diseases. Within the VLBW group there were 35.8% born small for gestational age (SGA), and there were no significant differences in macro and micronutrient intake between VLBW-AGA (adequate for gestational age) and VLBW-SGA.[27]

Although the relationship between low birth weight/IUGR and food preferences in adulthood is seen in several studies as cited above, the direction of causality of it is unclear. One could argue that IUGR leads to metabolic changes, which secondarily influence eating behavior over time. To deal with this question, many studies were performed in children, before the likely metabolic disturbances take place. Silveira *et al.* investigated impulsive eating at three years of age, both in AGA and SGA children, demonstrating that girls with normal birth weight had a significantly higher ability than boys to delay response to an eating impulse. That relationship was not significant in the SGA sample. This suggests that IUGR girls do not have the same ability to delay their response to impulsive eating as compared to non-IUGR girls. Furthermore, the mean response delay score during the snack delay test at 36 months was inversely related to the amount of fat consumed and to body mass index (BMI) values at the age of 48 months in girls. Because this study was conducted at an early age, it suggests that the obesogenic changes in eating behavior associated with IUGR are unlikely to be secondary to metabolic effects.[28]

Migraine *et al.* evaluated two French cohorts regarding eating behavior at 2 years of age. Data were collected from preterm (<33 weeks gestational age) and term children at 24 months of age (corrected for the preterm, and civil age for the term). Initially they found that preterm children had a lower drive-to-eat and a tendency for lower-food-repertoire. These children also had specific food preferences, with a higher intake of milk products and potatoes, but less consumption of fruit, cereals and prepared dishes. However, once the data were adjusted for maternal age, BMI, educational level, breastfeeding, sex, birth weight and z score, the association of gestational age with an impaired eating behavior was no longer significant. The study identified that a birth weight z score less than −1 was associated with eating difficulties, regardless of gestational age. Therefore, IUGR appears to be a major risk factor for eating difficulties, even in term infants.[29]

Similarly to Migraine *et al.*, Oliveira *et al.* conducted a study involving three European cohorts to evaluate the impact of birth weight in eating behaviors of young children. In this study, children were classified in three groups (SGA, adequate for gestational age and large for gestational age) and the problematic eating behaviors were assessed at 4–6, 12–15, 24 and 48–54 months. It was demonstrated that SGA were more likely to have feeding difficulties and poor eating, particularly at 4–6 months. One possible bias is that parents of lower birth weight children may have differential parental food rules in

https://doi.org/10.1017/S2040174415007187 Published online by Cambridge University Press

Table 1. *List of the different studies comparing small to normal birth weight children in their food preferences and feeding behavior, at different ages*

References	Population studied	Main findings
Ayres *et al.*[32]	Preterm newborns (25–29 weeks gestational age)	IUGR programs the hedonic response to sweet food
Rotstein *et al.*[33] Reviewed by Laureano *et al.*[34]	Term newborns (>37 weeks gestational age)	SGA children are less likely to recognize the pleasurable sensation associated with sugar
Migraine *et al.*[29]	24 months	IUGR associated with eating difficulties, regardless of gestational age
Oliveira *et al.*[30]	4–54 months	SGA more likely to have feeding difficulties and poor eating
Silveira *et al.*[28]	3 years	IUGR girls are more impulsive towards sweet food
Escobar *et al.*[72]	4 years	Better mother–child interaction may protect IUGR children from emotional overeating
Reis *et al.*[71]	6 years	n-3 PUFAs may protect IUGR children from difficult feeding behaviors (food fussiness) later on in childhood
Crume *et al.*[31]	10 years	IUGR have higher percent energy intake of fat
Kaseva *et al.*[27]	19–27 years born ⩽1500 g	Reduced consumption of vegetables, fruits, berries, milk products and low-fat dairy products; higher intake of polyunsaturated fatty acids
Barbieri *et al.*[23]	22–26 years	IUGR women have higher carbohydrate intake
Lussana *et al.*[25]	58 year-old whose mothers were exposed to the Dutch famine	Exposure to famine in early gestation associated with high-fat diets in adulthood
Stein *et al.*[24]	58-year-old whose mothers were exposed to the Dutch famine	Famine exposure: higher energy intake and fat density
Perala *et al.*[26]	56–70 years	Small size at birth correlated with increased fat intake

IUGR, intrauterine growth restriction; SGA, small for gestational age.

order to stimulate growth and, therefore, can increase their perception of eating difficulties.[30]

Crume *et al.* also demonstrated a significantly higher percent energy intake of fat in IUGR children at 10 years of age compared to the unexposed. The IUGR children had higher waist circumference, higher subcutaneous adipose tissue, higher fasting insulin, lower glucose levels and lower adiponectin levels. These findings were independent of other perinatal exposures, current lifestyle and socioeconomic factors.[31]

The programming of the sensitivity to the hedonic signaling (i.e. pleasure) associated with the ingestion of palatable food is one of the mechanisms that could explain different individual's food choices. Ayres *et al.* evaluated the hedonic response after sucrose solution was given orally to 25 to 29-week gestational age babies in the first day of life and there was a negative correlation between the degree of fetal growth restriction and the hedonic response. In other words, the intensity of IUGR was highly and inversely related to the frequency of positive affective reactions to the sweet taste. IUGR may lead to a decreased sensitivity to the enjoyment of the sweet taste, which may be associated with an increased consumption in order to achieve a higher degree of pleasure.[32]

Recently, a similar study was conducted by Rotstein *et al.*,[33] evaluating the innate patterns of smell and taste recognition in SGA newborns, compared to AGA controls. In this study, the population was composed by term babies (>37 week gestational age) and the parameter used to define IUGR was birth weight <10th percentile for gestational age. Sucrose was rated with significantly higher 'like' reaction in both AGA and SGA, and water was rated as 'dislike' for AGA and 'neutral' for SGA. The authors concluded that there were no differences in the facial reaction to stimuli during immediate postnatal life in SGA. However, reviewing Rotstein data, it becomes clear that the response ratio of sucrose to water is ~ 1 in the SGA group, while almost doubles in AGA; this suggests that SGA children are less likely to recognize the pleasurable sensation associated with sugar,[34] confirming our previous findings.[32] Table 1 delineates the studies described here.

Future challenges

From the above-mentioned data, it is clear that specific feeding behaviors and food preferences in this population plays an important role in the increased risk of obesity and noncommunicable diseases. Adequate prenatal care with careful surveillance of mother's health and prevention of risk factors for IUGR (i.e. smoking, obesity, hypertension, diabetes) is key in order to avoid long-term consequences of fetal programming.[35] After birth, pediatric follow-up of infants with identifiable vulnerabilities is also a window for intervention prior to the development of metabolic consequences. Health workers should take into account the perinatal history to focus counseling on the positive impacts of breastfeeding and healthy foods, especially in this at-risk population.

Future research is needed to identify possible mechanisms involved and potential targets of interventions. Since IUGR is a dynamical process, the ideal study design would include repeated ultrasound fetal measurements to adequately define a failure to achieve full potential growth and exclude other causes of low birth weight (i.e. constitutional). Furthermore, little is known about the role of catch-up growth in the programming

https://doi.org/10.1017/S2040174415007187 Published online by Cambridge University Press

of feeding preferences. Larger birth cohorts, with appropriate IUGR definition and prospective long-term follow-up may further clarify the relation and causality of these findings.

Experimental evidence

Behavioral changes

It is well established in the literature that fetal growth-restricted rat pups nursed by control dams demonstrate significantly increased food intake with rapid catch-up growth. In adult life, these animals have increased body weight and percent body fat, as well as increased plasma leptin levels, insulin resistance and hypertriglyceridemia.[36,37] Studies with large animals found similar results. For instance, George *et al.*[38] investigated female offspring of lambs exposed to maternal nutrient restriction (50% of the recommendation) and observed that IUGR lambs had greater and more rapid food intake. This was accompanied by greater body weight gain and caloric efficiency. They also assessed insulin and glucose dynamics and found lower insulin sensitivity and higher insulin secretion in IUGR animals. In addition, Dellschaft *et al.*[39] observed leptin resistance and raised cortisol in IUGR sheep. Ovilo *et al.*[40] investigated IUGR in a swine model and observed greater body weight gain and fat mass in adult females. They also found increased cortisol levels in the female restricted newborns, which may reflect metabolic stress caused by nutrient insufficiency. These behavioral and metabolic results support the thrifty phenotype hypothesis - more efficient acquisition and storage of food energy[41,42] that possibly predisposes the offspring to developing metabolic diseases. However, to date few studies focused on the programming of food preferences in IUGR animals, which may contribute to overeating.

The first studies regarding fetal programming of food intake/preference emerged in the early 2000. Vickers *et al.*[43,44] used an animal model of maternal undernutrition throughout pregnancy (30% of *ad libitum* diet) to investigate eating and sedentary behavior and observed that increased food intake coincided with reduced physical activity and higher body fat, results that correspond to the 'couch-potato' phenotype. Afterwards, Bellinger *et al.*[45] offered three types of diet (high-fat, high-protein and high carbohydrate) to adult rats exposed to protein restriction prenatally and found that the prenatal undernourished rats preferred the high-fat diet, which promotes an elevation of energy intake in females, but not in males. The preference for fatty foods was observed when the rats were 12 weeks old (young adults), while new testing at 30 weeks of life revealed no differences. In another study they tested the difference between animals derived from three gestation periods of protein restriction: day 0–7 (LPEarly), day 8–14 (LPMid) or day 15–22 (LPLate). Using this protocol, it was found that prenatal protein restriction programmed feeding behavior in females, but not males, offspring. Interestingly, among females, all low-protein exposed groups consumed less fat than the control group.[46] Using almost the same maternal protein restriction protocol (LPEarly, LPMid, LPLate and LPAll – low protein throughout gestation) food intake was measured at 18 months of age with standard rat chow offer. The results show a greater food intake in LPMid males. Among females hypophagia was noted in groups LPAll and LPLate.[47] These results suggest that programming of feeding behavior is likely to be gender-specific, age-specific and dependent upon the timing of nutrient insult in fetal life.

Recent animal studies from our research group continued to verify the food preference and feeding behavior in an animal model of IUGR based on food restriction of 50% during pregnancy (starting on day 10 of gestation).[36,48] Alves *et al.*[49] observed that IUGR adult males, compared to controls, eat more sweet food when acutely exposed to it. In spite of no food intake differences in females, it was found that IUGR females needed fewer trials to reach criterion in the Attentional Set-Shifting Task (ASST), using a sweet food as reward. Also DalleMolle *et al.* (2015)[50] observed that IUGR adult rats have an increased preference for palatable food (a pellet rich in fat and added sugar) when compared to control rats. However, the increased preference was accompanied by diminished conditioned place preference for this type of food. Interestingly, two studies assessed animals' motivational behavior in adulthood by giving them a stimulus of food reward and observed that the rats submitted to the perinatal low protein protocol (IUGR) were more motivated by food reward,[51,52] and in one of these studies they found that IUGR animals had delays during learning of the task.[51] All these results suggest that IUGR animals are more driven towards food reward and are able to deal with the difficulty to find the food, even though they have learning and/or association difficulties. This type of behavioral programming seems to be an adaptation to deal with scarcity.

Vucetic *et al.*[53] also demonstrated that maternal malnutrition (through reduced protein diet) causes behavioral alterations in the offspring. IUGR animals had an exaggerated response to cocaine, hyperactivity when receiving a high fat diet after weaning and a decreased sucrose preference, suggesting an increased addiction risk as a result of suboptimal prenatal environment. According to this article discussion, there are two factors that can contribute to the development of addiction: the activation of the reward system by drugs of abuse, and the underactivation of reward circuitry in response to natural rewards (i.e. sucrose). Both factors were observed in this animal model. Social interaction was also tested, either by interpreting interactions between unfamiliar dyads (in male mice) or in a three chamber test (in female mice). In both conditions, IUGR animals spent significantly less time interacting with the co specific, indicating deficits in sociability.[54]

Exploring the mechanisms

The early programming of eating behavior is a very complex process since we know that food intake can be influenced by homeostatic, hedonic, and executive components. Also, there are many peripheral signals that can act in different brain regions modulating specific neurotransmitters systems.[7] Studies have been developed focusing on the feeding and satiety pathways in an attempt to clarify the possible mechanisms involved in the programming of food preferences.

https://doi.org/10.1017/S2040174415007187 Published online by Cambridge University Press

As mentioned above, fetal growth-restricted animals have a higher risk to develop obesity and the first studies to investigate the possible mechanisms responsible for this phenotype focused on the homeostatic control system. Nutritional restriction in early life (prenatal or perinatal) is associated with reduced satiety responses to leptin and impaired arcuate nucleus signaling responses to leptin,[37,55–57] as well as with increased responses to appetite stimulatory factors, such as ghrelin.[58] There is also association with increased expression of appetite (neuropeptide Y) versus satiety (pro-opiomelanocortin) neuropeptides[59–62] and programmed dysfunction of neuroprogenitor cell proliferation/differentiation.[63,64] According to Plagemann *et al.*,[61] cell counts were increased in SGA rats in the paraventricular, arcuate, and ventromedial nuclei, three hypothalamic regions involved in food intake regulation. Disruptions in leptin and insulin levels, which are produced not only maternally but in the placenta as well, could contribute to the dysregulation of the cell cycle in the hypothalamus.[63] In addition, another study that investigated protein deficiency during gestation and lactation observed an upregulation of hypothalamic intracellular signaling in the adult offspring of the low-protein group, particularly in the insulin and leptin intracellular transduction cascade (phophoinositide 3-kinase pathway).[65] Therefore, maternal undernutrition (by caloric restriction or low protein diet) can alter nutrient sensors, neuroendocrine levels and signaling, neurogenesis and/or neuropeptide levels of the offspring. These pathways can interact and impact appetite (for review see[66]).

In our studies we aimed at finding possible mechanisms related to the altered feeding behavior investigating especially to the mesocorticolimbic system. IUGR females submitted to the ASST exhibited increased tyrosine-hydroxylase (TH) content in the orbito-frontal cortex in response to sweet food intake. There is also a differential response of TH content in the NAcc after sweet food intake in both IUGR males and females.[49] In addition, we described diminished levels of dopamine-2 (D2) receptors in the NAcc of IUGR rats when compared to controls, which explains the conditioned place preference deficits in these animals.[67] In the same study, tissue was collected at baseline conditions (after 4 h fasting) or after 1 h of sweet food intake. At baseline, TH and phospoho-tyrosine hydroxylase (pTH) levels in the NAcc were higher in IUGR males compared to control males. However, in females, TH and pTH levels were increased after exposure to sweet food in IUGR compared with controls.[50] Together, our findings suggest that IUGR rats exhibit a preference for palatable foods and a different central response to palatable food cues, probably due to alterations in dopamine release in selected structures of the mesocorticolimbic dopaminergic pathway. Differently, a recent study that explored the gene expression of dopamine receptors (D1 and D2) in the ventral striatum of animals exposed to perinatal malnutrition observed an increase in gene expression of D1 receptors and no differences regarding D2 receptors. However, they used a different animal model based on perinatal protein restriction.[52] In this same study there was also a decrease in palatable diet consumption in both the control and malnourished groups after the application of D1 and D2 agonists; however, the anorexic effect of the D1 agonist was understated in malnourished animals.

Exploring the same system in an animal model of IUGR based on maternal protein restriction, Vucetic *et al.*[53] observed that their behavioral results were also accompanied by changes in dopamine expression. IUGR offspring had increased expression of dopamine-related genes [TH and dopamine reuptake transporter (DAT)] in brain regions related to reward processing (VTA, NAcc and PFC) and homeostatic control (hypothalamus), and increased content of TH and dopamine in the VTA and PFC, respectively. Thus, the basic mesocorticolimbic circuitry represented by VTA to NAcc and PFC connectivity is dysregulated in IUGR. According to these results, it seems that there is a net hyperdopaminergic tone, with TH overactivity and compensatory increases in DAT. Together with the mesocorticolimbic system alterations they also verified the opioid system and were able to find changes in IUGR rats that fit with the decreased sucrose preference observed in the behavioral tasks. A decreased expression of opioid genes was observed: preproenkephalin in the PFC and mu-opioid receptor in the NAcc.[54] Similarly, Kademian *et al.*[68] found that rats undernourished at perinatal age (day 14 of gestation until 50 days of age) had decreased mu-opioid receptor density (B_{max}) in the midbrain in adult life.

Therefore, the compilation of these results demonstrates that an imbalance between the hedonic versus homeostatic control systems may be associated with overeating in IUGR animals (especially palatable/rewarding foods), resulting in poor regulation of body weight in the long term.

Another possible mechanism involved in eating behavior changes in IUGR individuals is the functioning of the hypothalamic–pituitary–adrenal (HPA) axis. Studies suggest that early exposure to undernutrition programs HPA axis throughout lifespan. As cited above, IUGR is associated with higher levels of corticosterone in different ages, leading to chronic hyperactivity of this neuroendocrine axis.[39,40,69] There is also evidence showing that maternal food restriction leads to reduced glucocorticoid and mineralocorticoid receptor expressions in the hippocampus of IUGR newborns.[70] The chronic hyperactivity of the HPA axis may contribute to the programming of chronic diseases, as well as altered response to acute stress, which can influence feeding behavior and food choices.

Considering what was already experimentally demonstrated, a better characterization of the fetal programming of food preferences involves the assessment of *in vivo* functional changes during the exposure to palatable foods, as well as a deep investigation of other systems related to food preference such as the opioid system. It is also important to further explore the neurobiological aspects involved in food intake and preferences, that is how tissue's specifics changes in the sensitivity to metabolic signals (insulin, leptin and ghrelin) can modulate neurotransmitters' release and neuron's activity in areas related to reward, pleasure and decision making.

Another important question that needs to be addressed refers to the potential interventions that could modify this

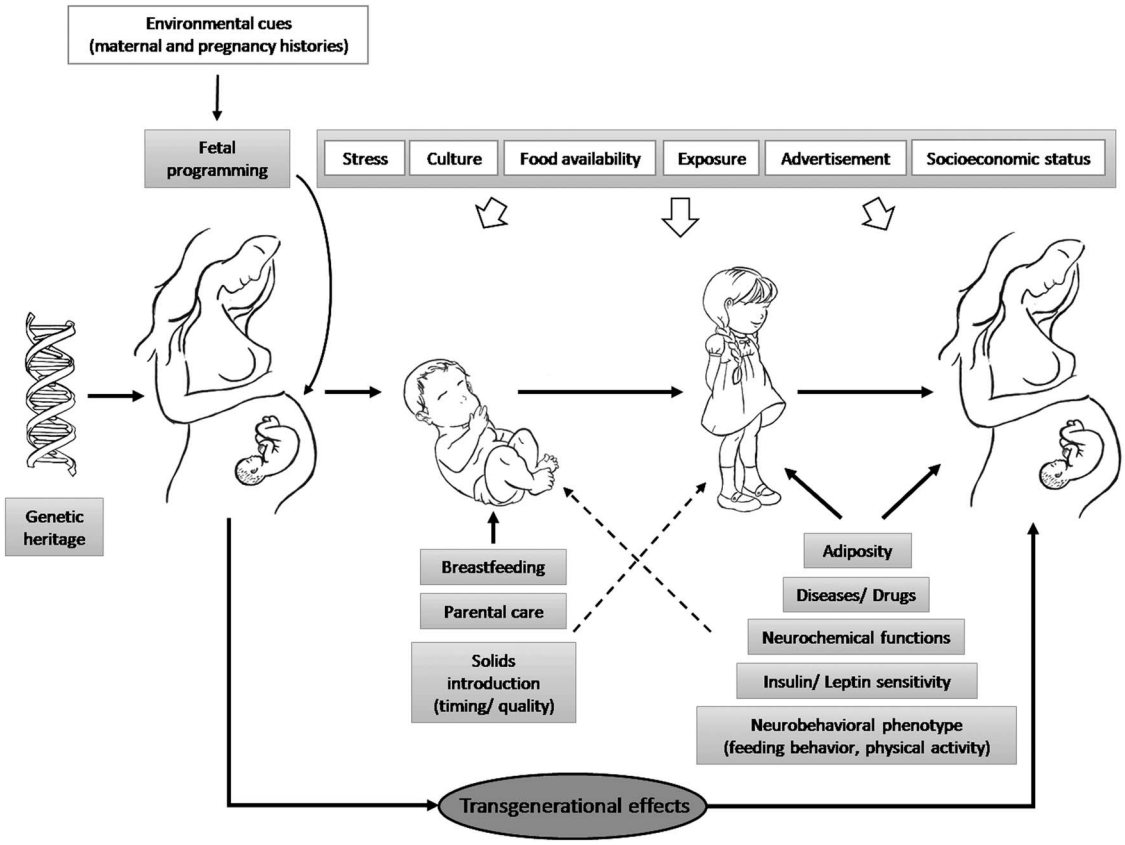

Fig. 1. Factors influencing food preferences over the life course. Genetic heritage affects flavor sensitivity. Events and exposures happening *in utero* program food preferences and influence the third generation through the oocytes already present in fetal life (transgenerational effects). During infancy, breastfeeding practice and duration, the quality and timing of the solids introduction, as well as the quality of parental care will influence the infant's feeding behavior, learning and preferences being established, having some influence (though smaller, dotted line) also during childhood. Adiposity, hormonal sensitivity and neurochemical functioning, exposure to diseases or drugs and temperament/behavior will affect food choices in children, having had also some effect in toddlers (dotted line). Stress, culture, food availability, exposures/learning, socioeconomic status and environmental cues such as media and advertisements from food industry will impact food choices over the life course. The notion that all these factors interact is essential for comprehending the diversity of phenotypes observed in the different studies, although many describe specific behaviors in IUGR individuals, which will vary according to the age tested and the tools used.

programmed food preference in IUGR offspring. This idea was explored in a recent study involving the consumption of n-3 polyunsaturated fatty acids (n-3 PUFAs) during infancy, in which authors show that n-3 PUFAs intake during infancy decreases a non-adaptive feeding behavior, namely food fussiness, in IUGR children. They suggest that n-3 PUFAs putatively acts by modulating inhibitory control and reward sensitivity through alterations in the dopamine system.[71] Therefore, they suggest that n-3 PUFAs may protect IUGR children from difficult feeding behaviors later on in childhood, but other studies need to be performed to elucidate the mechanisms involved and plan interventions. Similarly, the quality of maternal care seems to moderate the association between IUGR and emotional overeating in girls.[72] There is preliminary evidence suggesting that interventions improving this relationship may also benefit IUGR children.[73] Figure 1 delineates the factors affecting food choices over the life course.

Conclusions

From the reviewed clinical and experimental evidence, the fetal programming of food preferences is a consistent finding, replicated in different continents, despite the heterogeneity of the studied populations in terms of age, sex, economic development and IUGR cause. Therefore, through a persistent imbalance in food choices in everyday life, over the life course, this phenomena is likely to be a key player in the increased risk for obesity and its metabolic consequences demonstrated in these individuals.[74] Awareness about fetal programming effects in the clinical practice, as well as the better understanding of putative mechanisms and mediators, can have an important impact for preventive medicine in this vulnerable population.

Acknowledgement

None.

https://doi.org/10.1017/S2040174415007187 Published online by Cambridge University Press

Financial Support

Research Support Foundation of Rio Grande do Sul (FAPERGS), Coordination for the Improvement of Higher Education Personnel (Capes) and National Counsel of Technological and Scientific Development (CNPq).

Conflicts of Interest

None.

References

1. Barker DJ, Lampl M. Commentary: the meaning of thrift. *Int J Epidemiol*. 2013; 42, 1229–1230.
2. Vickers MH, Breier BH, McCarthy D, Gluckman PD. Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. *Am J Physiol*. 2003; 285, R271–R273.
3. Kaseva N, Wehkalampi K, Strang-Karlsson S, *et al*. Lower conditioning leisure-time physical activity in young adults born preterm at very low birth weight. *PLoS One*. 2012; 7, e32430.
4. Kajantie E, Strang-Karlsson S, Hovi P, *et al*. Adults born at very low birth weight exercise less than their peers born at term. *J Pediatr*. 2010; 157, 610–616.
5. El-Haddad MA, Desai M, Gayle D, Ross MG. In utero development of fetal thirst and appetite: potential for programming. *J Soc Gynecol Invest*. 2004; 11, 123–130.
6. Ross MG, Desai M. Developmental programming of offspring obesity, adipogenesis, and appetite. *Clin Obstet Gynecol*. 2013; 56, 529–536.
7. Portella AK, Silveira PP. Neurobehavioral determinants of nutritional security in fetal growth-restricted individuals. *Ann N Y Acad Sci*. 2014; 1331, 15–33.
8. Portella AK, Kajantie E, Hovi P, *et al*. Effects of in utero conditions on adult feeding preferences. *J Dev Orig Hlth Dis*. 2012; 3, 140–152.
9. Low YQ, Lacy K, Keast R. The role of sweet taste in satiation and satiety. *Nutrients*. 2014; 6, 3431–3450.
10. Lampure A, Deglaire A, Schlich P, *et al*. Liking for fat is associated with sociodemographic, psychological, lifestyle and health characteristics. *Br J Nutr*. 2014; 112, 1353–1363.
11. Legradi G, Lechan RM. The arcuate nucleus is the major source for neuropeptide Y-innervation of thyrotropin-releasing hormone neurons in the hypothalamic paraventricular nucleus. *Endocrinology*. 1998; 139, 3262–3270.
12. Beaulieu J, Champagne D, Drolet G. Enkephalin innervation of the paraventricular nucleus of the hypothalamus: distribution of fibers and origins of input. *J Chem Neuroanat*. 1996; 10, 79–92.
13. Marcus JN, Aschkenasi CJ, Lee CE, *et al*. Differential expression of orexin receptors 1 and 2 in the rat brain. *J Comp Neurol*. 2001; 435, 6–25.
14. Trivedi P, Yu H, MacNeil DJ, Van der Ploeg LH, Guan XM. Distribution of orexin receptor mRNA in the rat brain. *FEBS Lett*. 1998; 438, 71–75.
15. Zamir N, Skofitsch G, Jacobowitz DM. Distribution of immunoreactive melanin-concentrating hormone in the central nervous system of the rat. *Brain Res*. 1986; 373, 240–245.
16. Rodaros D, Caruana DA, Amir S, Stewart J. Corticotropin-releasing factor projections from limbic forebrain and paraventricular nucleus of the hypothalamus to the region of the ventral tegmental area. *Neuroscience*. 2007; 150, 8–13.
17. Sakanaka M, Magari S, Shibasaki T, Inoue N. Co-localization of corticotropin-releasing factor- and enkephalin-like immunoreactivities in nerve cells of the rat hypothalamus and adjacent areas. *Brain Res*. 1989; 487, 357–362.
18. Kampe J, Tschop MH, Hollis JH, Oldfield BJ. An anatomic basis for the communication of hypothalamic, cortical and mesolimbic circuitry in the regulation of energy balance. *Eur J Neurosci*. 2009; 30, 415–430.
19. Fadel J, Deutch AY. Anatomical substrates of orexin-dopamine interactions: lateral hypothalamic projections to the ventral tegmental area. *Neuroscience*. 2002; 111, 379–387.
20. Beckstead RM, Domesick VB, Nauta WJ. Efferent connections of the substantia nigra and ventral tegmental area in the rat. *Brain Res*. 1979; 175, 191–217.
21. Heimer L, Zahm DS, Churchill L, Kalivas PW, Wohltmann C. Specificity in the projection patterns of accumbal core and shell in the rat. *Neuroscience*. 1991; 41, 89–125.
22. Kita H, Oomura Y. Reciprocal connections between the lateral hypothalamus and the frontal complex in the rat: electrophysiological and anatomical observations. *Brain Res*. 1981; 213, 1–16.
23. Barbieri MA, Portella AK, Silveira PP, *et al*. Severe intrauterine growth restriction is associated with higher spontaneous carbohydrate intake in young women. *Pediatr Res*. 2009; 65, 215–220.
24. Stein AD, Rundle A, Wada N, Goldbohm RA, Lumey LH. Associations of gestational exposure to famine with energy balance and macronutrient density of the diet at age 58 years differ according to the reference population used. *J Nutr*. 2009; 139, 1555–1561.
25. Lussana F, Painter RC, Ocke MC, *et al*. Prenatal exposure to the Dutch famine is associated with a preference for fatty foods and a more atherogenic lipid profile. *Am J Clin Nutr*. 2008; 88, 1648–1652.
26. Perälä MM, Männistö S, Kaartinen NE, *et al*. Body size at birth is associated with food and nutrient intake in adulthood. *PLoS One*. 2012; 7, e46139.
27. Kaseva N, Wehkalampi K, Hemiö K, *et al*. Diet and nutrient intake in young adults born preterm at very low birth weight. *J Pediatr*. 2013; 163, 43–48.
28. Silveira PP, Agranonik M, Faras H, *et al*. Preliminary evidence for an impulsivity-based thrifty eating phenotype. *Pediatr Res*. 2012; 71, 293–298.
29. Migraine A, Nicklaus S, Patricia PP, *et al*. Effect of preterm birth and birth weight on eating behavior at 2 y of age. *Am J Clin Nutr*. 2013; 97, 1270–1277.
30. Oliveira A, de Lauzon-Guillain B, Jones L, *et al*. Birth weight and eating behaviors of young children. *J Pediatr*. 2015; 166, 59–65.
31. Crume TL, Scherzinger A, Stamm E, *et al*. The long-term impact of intrauterine growth restriction in a diverse U.S. cohort of children: the EPOCH study. *Obesity*. 2014; 22, 608–615.
32. Ayres C, Agranonik M, Portella AK, *et al*. Intrauterine growth restriction and the fetal programming of the hedonic response to sweet taste in newborn infants. *Int J Pediatr*. 2012; 2012, 657379.
33. Rotstein M, Stolar O, Uliel S, *et al*. Facial expression in response to smell and taste stimuli in small and appropriate for gestational age newborns. *J Child Neurol*. 2015; pii: 0883073815570153 [Epub ahead of print].
34. Laureano DP, Molle RD, Portella AK, Silveira PP. Facial expressions in small for gestational age newborns. *J Child Neurol*. 2015; pii: 0883073815592225 [Epub ahead of print].

35. Mucellini ABM, Manfro GG, Silveira PP. Tackling obesity: challenges ahead. *Lancet.* 2015; 386, 740.
36. Desai M, Gayle D, Babu J, Ross MG. Programmed obesity in intrauterine growth-restricted newborns: modulation by. *Am J Physiol Regul Integr Comp Physiol*. 2005; 288, R91–R96.
37. Desai M, Gayle D, Han G, Ross MG. Programmed hyperphagia due to reduced anorexigenic mechanisms in intrauterine growth-restricted offspring. *Reprod Sci*. 2007; 14, 329–337.
38. George LA, Zhang L, Tuersunjiang N, *et al*. Early maternal undernutrition programs increased feed intake, altered glucose metabolism and insulin secretion, and liver function in aged female offspring. *Am J Physiol Regul Integr Comp Physiol*. 2012; 302, R795–R804.
39. Dellschaft NS, Alexandre-Gouabau MC, Gardner DS, *et al*. Effect of pre- and postnatal growth and post-weaning activity on glucose metabolism in the offspring. *J Endocrinol*. 2015; 224, 171–182.
40. Ovilo C, Gonzalez-Bulnes A, Benitez R, *et al*. Prenatal programming in an obese swine model: sex-related effects of maternal energy restriction on morphology, metabolism and hypothalamic gene expression. *Br J Nutr*. 2014; 111, 735–746.
41. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia*. 1992; 35, 595–601.
42. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. 1992. *Int J Epidemiol*. 2013; 42, 1215–1222.
43. Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD. Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. *Am J Physiol Endocrinol Metab*. 2000; 279, E83–E87.
44. Vickers MH, Breier BH, McCarthy D, Gluckman PD. Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. *Am J Physiol Regul Integr Comp Physiol*. 2003; 285, R271–R273.
45. Bellinger L, Lilley C, Langley-Evans SC. Prenatal exposure to a maternal low-protein diet programmes a preference for high-fat foods in the young adult rat. *Br J Nutr*. 2004; 92, 513–520.
46. Bellinger L, Langley-Evans SC. Fetal programming of appetite by exposure to a maternal low-protein diet in the rat. *Clin Sci*. 2005; 109, 413–420.
47. Bellinger L, Sculley DV, Langley-Evans SC. Exposure to undernutrition in fetal life determines fat distribution, locomotor activity and food intake in ageing rats. *Int J Obes*. 2006; 30, 729–738.
48. Cunha Fda S, Dalle Molle R, Portella AK, *et al*. Both food restriction and high-fat diet during gestation induce low birth weight and altered physical activity in adult rat offspring: the 'Similarities in the Inequalities' model. *PLoS One*. 2015; 10, e0118586.
49. Alves MB, Dalle Molle R, Desai M, Ross MG, Silveira PP. Increased palatable food intake and response to food cues in intrauterine growth-restricted rats are related to tyrosine hydroxylase content in the orbitofrontal cortex and nucleus accumbens. *Behav Brain Res*. 2015; 287, 73–81.
50. Molle RD, Laureano DP, Alves MB, *et al*. Intrauterine growth restriction increases the preference for palatable foods and affects sensitivity to food rewards in male and female adult rats. *Brain Res*. 2015; 1618, 41–49.
51. da Silva AA, Borba TK, de Almeida Lira L, *et al*. Perinatal undernutrition stimulates seeking food reward. *Int J Dev Neurosci*. 2013; 31, 334–341.
52. de Melo Martimiano PH, da Silva GR, Coimbra VF, *et al*. Perinatal malnutrition stimulates motivation through reward and enhances drd receptor expression in the ventral striatum of adult mice. *Pharmacol Biochem Behav*. 2015; 134, 106–114.
53. Vucetic Z, Totoki K, Schoch H, *et al*. Early life protein restriction alters dopamine circuitry. *Neuroscience*. 2010; 168, 359–370.
54. Grissom NM, Reyes TM. Gestational overgrowth and undergrowth affect neurodevelopment: similarities and differences from behavior to epigenetics. *Int J Dev Neurosci*. 2013; 31, 406–414.
55. Shin BC, Dai Y, Thamotharan M, Gibson LC, Devaskar SU. Pre- and postnatal calorie restriction perturbs early hypothalamic neuropeptide and energy balance. *J Neurosci Res*. 2012; 90, 1169–1182.
56. Puglianiello A, Germani D, Cianfarani S. Exposure to uteroplacental insufficiency reduces the expression of signal transducer and activator of transcription 3 and proopiomelanocortin in the hypothalamus of newborn rats. *Pediatr Res*. 2009; 66, 208–211.
57. Delahaye F, Breton C, Risold PY, *et al*. Maternal perinatal undernutrition drastically reduces postnatal leptin surge and affects the development of arcuate nucleus proopiomelanocortin neurons in neonatal male rat pups. *Endocrinology*. 2008; 149, 470–475.
58. Yousheng J, Nguyen T, Desai M, Ross MG. Programmed alterations in hypothalamic neuronal orexigenic responses to ghrelin following gestational nutrient restriction. *Reprod Sci*. 2008; 15, 702–709.
59. Remmers F, Verhagen LA, Adan RA, Delemarre-van de Waal HA. Hypothalamic neuropeptide expression of juvenile and middle-aged rats after early postnatal food restriction. *Endocrinology*. 2008; 149, 3617–3625.
60. Garcia AP, Palou M, Priego T, *et al*. Moderate caloric restriction during gestation results in lower arcuate nucleus NPY- and alphaMSH-neurons and impairs hypothalamic response to fed/fasting conditions in weaned rats. *Diabetes Obes Metab*. 2010; 12, 403–413.
61. Plagemann A, Harder T, Rake A, *et al*. Hypothalamic nuclei are malformed in weanling offspring of low protein malnourished rat dams. *J Nutr*. 2000; 130, 2582–2589.
62. Fukami T, Sun X, Li T, Desai M, Ross MG. Mechanism of programmed obesity in intrauterine fetal growth restricted offspring: paradoxically enhanced appetite stimulation in fed and fasting states. *Reprod Sci*. 2012; 19, 423–430.
63. Desai M, Li T, Ross MG. Fetal hypothalamic neuroprogenitor cell culture: preferential differentiation paths induced by leptin and insulin. *Endocrinology*. 2011; 152, 3192–3201.
64. Desai M, Li T, Ross MG. Hypothalamic neurosphere progenitor cells in low birth-weight rat newborns: neurotrophic effects of leptin and insulin. *Brain Res*. 2011; 1378, 29–42.
65. Orozco-Solis R, Matos RJ, Guzman-Quevedo O, *et al*. Nutritional programming in the rat is linked to long-lasting changes in nutrient sensing and energy homeostasis in the hypothalamus. *PLoS One*. 2010; 5, e13537.
66. Ross MG, Desai M. Developmental programming of appetite/satiety. *Ann Nutr Metab*. 2014; 64(Suppl. 1), 36–44.
67. Smith JW, Fetsko LA, Xu R, Wang Y. Dopamine D2L receptor knockout mice display deficits in positive and negative reinforcing properties of morphine and in avoidance learning. *Neuroscience*. 2002; 113, 755–765.
68. Kademian S, Perez MF, Keller EA. Perinatal undernutrition: changes in brain opiate receptor density. *Nutr Neurosci*. 2002; 5, 53–57.
69. Vieau D, Sebaai N, Leonhardt M, *et al*. HPA axis programming by maternal undernutrition in the male rat offspring. *Psychoneuroendocrinology*. 2007; 32(Suppl. 1), S16–S20.

70. Lesage J, Blondeau B, Grino M, Breant B, Dupouy JP. Maternal undernutrition during late gestation induces fetal overexposure to glucocorticoids and intrauterine growth retardation, and disturbs the hypothalamo-pituitary adrenal axis in the newborn rat. *Endocrinology*. 2001; 142, 1692–1702.
71. Reis RS, Bernardi JR, Steiner M, *et al*. Poor infant inhibitory control predicts food fussiness in childhood – a possible protective role of n-3 PUFAs for vulnerable children. *Prostaglandins Leukot Essential Fatty Acids*. 2015; 97, 21–25.
72. Escobar RS, O'Donnell KA, Colalillo S, *et al*. Better quality of mother-child interaction at 4 years of age decreases emotional overeating in IUGR girls. *Appetite*. 2014; 81, 337–342.
73. Braga CL, Farias BL, Reis RS, Agranonik M, Silveira PP. Musical intervention and food preferences in girls born with lower birth weight. *Early Hum Dev*. 2015; http://dx.doi.org/10.1016/j.earlhumdev.2015.08.004.
74. Portella AK, Silveira PP. Parenting: roots of the sweet tooth. *Science*. 2014; 345, 1571–1572.